MUNI MED Department of Pediatric Neurology

Pediatric epileptology

Habilitation thesis
(Collection of published scholarly works with commentary)

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I hereby declare that I wrote this habilitation thesis on my own, using the relevant resources listed in the references.

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Signature

Commentary:

Pediatric epileptology is a very important branch of pediatric neurology. The classification of the epilepsies has changed significantly in recent years, pointing to experience we know from clinical practice: Is Rolandic epilepsy benign, indeed? Do idiopathic epilepsies always have a good prognosis? Is it only epileptiform discharges in the EEG that interfere with the neurodevelopment of a child with epilepsy? There are still many questions; advances in diagnostics, especially genetic, answer some of them. The genetics of epilepsies have made tremendous progress and elucidated the cause of epilepsy in many of our patients. It ended a very exhausting and stressing diagnostic oddyssey and relieved many patients and their families. It also showed us a new path that is a huge challenge for pediatric epileptologists and a promising outlook for the future - precision medicine strategy. Treating not only the symptoms of epilepsy, but also its cause sounds like the music of the future and we believe it will become more and more real.

The author's work is divided into several parts, which are interwoven with her own scientific results and observations.

The first part deals with the classification of seizure types and epilepsies.

The second part focuses on the description of important epileptic syndromes and outlines the proposal of the forthcoming ILAE Classification of Epileptic Syndromes.

The last part is focused on the genetic causes of epilepsy and concludes the work on linking genetics and phenotype to "new genetic epileptic syndromes" with the possibility of applying precision medicine strategy.

Where relevant, chapters are accompanied by commentaries introducing the topic of each publication, describing the current state of knowledge and how the author has contributed to knowledge in this field.

The work is based on research activities at the authors' workplaces, the Department of Pediatric Neurology, Faculty of Medicine, Masaryk University and University Hospital Brno.

The work is concluded with a collection of author´s published scholarly works with commentary.

Content:

Acknowledgments:

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Abbreviations:

ACE – angiotensin converting enzyme

ACTH – adrenocorticotropin hormone

ADHD – Attention deficit hyperactivity disorder

ALDH7A1 - aldehyde Dehydrogenase 7 Family Member A1

ALG13 - UDP-N-Acetylglucosaminyltransferase Subunit

ARX - aristaless-related homeobox

ASS – acute symptomatic seizure

BDZ - benzodiazepine

BRD2 - bromodomain containing 2

CACNA1A - calcium voltage-gated channel subunit alpha1 A

CACNB4 - voltage-dependent L-type calcium channel subunit beta-4

CAE – childhood absence epilepsy

CBZ - carbamazepine

CDKL5 - cyclin-dependent kinase-like 5

CHD2 - chromodomain DNA helicase protein 2

CLB - clobazame

CLCN2 - chloride voltage-gated channel 2

CLZ - clobazame

CNS – central nervous system

CNV – copy number variant

COE-G – childhood occipital epilepsy - Gastaut

CSF – cerebrospinal fluid

CSWS – cerebral salt wasting syndrome

CTS – centrotemporal spike

DBS – deep brain stimulation

DEE – developmental and epileptic encephalopathy

DNET – dysembryoplastic neuroepithelial tumor

DNM1 - Dynamin 1

DS – Dravet syndrome

DSAP – Dystonia severity action plan

EFMR – epilepsy related to females with mental retardation

EEG - electoencephalogrphy

EFHC1- EF-hand domain containing 1

ELP4 – elongator protein 4

EMG - electromyography

ERBB4 - Erb-B2 receptor tyrosine kinase 4

ESES – electrical status epilepticus in sleep

ESM - ethosuximide

FBM - felbamate

FBTCS – focal to bilateral tonic-clonic seizure

FOXG1 - forkhead box G1

GABRA1 - gamma-aminobutyric acid type A receptor subunit alpha1

GABRB2 - gamma-aminobutyric acid type A receptor subunit beta2

GABRB3 - gamma-aminobutyric acid type A receptor subunit beta3

GABRG2 - gamma-aminobutyric acid type A receptor subunit gamma2

GEE – genetic generalized epilepsy

GLUT1 – glucose transporter 1

GNAO1 – G-protein subunit alpha O1

GPi-DBS – globus pallidus internus – deep brain stimulation

GPR56 – G-protein-coupled receptor

GRIN2A - glutamate ionotropic receptor NMDA type subunit 2A

GTCS – generalized tonic-clonic seizure

ICK - intestinal cell kinase

ICU – intensive care unit

IGE – idiopathic generalized epilepsy

ILAE – Intenrational League Against Epilepsy

IQ – intelligence quocient

IS – infantile spasms

JAE – Juvenile absence epilepsy

JME – Juvenile myoclonic epilepsy

KCNA2 - potassium voltage-gated channel subfamily A member 2

KCNB1 - potassium voltage-gated channel subfamily B member 2

KCNQ2 - potassium voltage-gated channel subfamily Q member 2

KCNQ3 - potassium voltage-gated channel subfamily Q member 3

LCM - lacosamide

LGG – low-grade glioma

LGS – Lennox-Gastaut syndrome

MAE – Myoclonic-atonic epilepsy

MAG12 - membrane associated guanylate kinase

MEI – Myoclonic epilepsy in infancy

MRI – magnetic resonance imaging

mTOR - mammalian target of rapamycin

MTS – mesiotemporal sclerosis

NGS – next-generation sequencing

NREM – non-rapid eye movement

OXC - oxcarbazepine

PB - phenobarbital

PER - perampanel

PHT - phenytoin

PRES – Posterior reversible encephalopathy snydrome

PRRT2 - proline-rich transmembrane protein 2

RFN - rufinamide

S-B – suppresion-burst

SCB – sodium-channel blockers

SCN1A - sodium voltage-gated channel alpha subunit 1

SCN1B - sodium voltage-gated channel beta subunit 1

SCN2A - sodium voltage-gated channel alpha subunit 2

SCN8A - sodium voltage-gated channel alpha subunit 8

SI – spike index

SIADH - syndrome of inappropriate antidiuretic hormone

SIK1 - saltiInducible kinase 1

SLC2A1 - solute carrier family 2 member 1

SLC25A22 - solute carrier family 52 member 22

SLC4A22 - solute carrier family 4 member 22

SMEI – Severe myoclonic epilepsy of infancy

SPTAN1 - spectrin alpha, non-erythrocytic 1

SSRI - selective serotonin reuptake inhibitors

STM - sulthiame

STXBP1 - syntaxin-binding protein 1

SWA – slow-wave activity

TPM - topiramate

TSC1 – tuberous sclerosis complex 1

TSC2 - tuberous sclerosis complex 2

VNS – vagal nerve stimulation

WES – whole-exome sequencing

WGS – whole-genome sequencing

WS – West syndrome

ZDHHC9 - zinc finger DHHC-type palmitoyltransferase 9

ZNS - zonisamide

1 Introduction and background

1.1 Incidence and prevalence of epilepsy:

Epilepsy is one of the most common chronic neurological diseases in children. The incidence of epilepsy in childhood is highest in the first year of age, estimated at 144 / 100,000 in children aged 0-1 years and 58 / 100,000 in children aged 1-10 years (1). The cumulative incidence (total proportion of children with epilepsy aged 0-10 years) is reported to be 0.66% (1). Graphically, the results are shown in Fig. 1. A systematic review and meta-analysis of 222 international studies on epilepsy incidence and prevalence reported a point prevalence of epilepsy of 6.38 per 1,000 persons (95% CI 5.57-7.30), a pooled lifetime prevalence of 7.6 per 1,000 and an incidence rate of 61.44 per 100,000 patients / year (95% CI 50.75 - 74.38) (2).

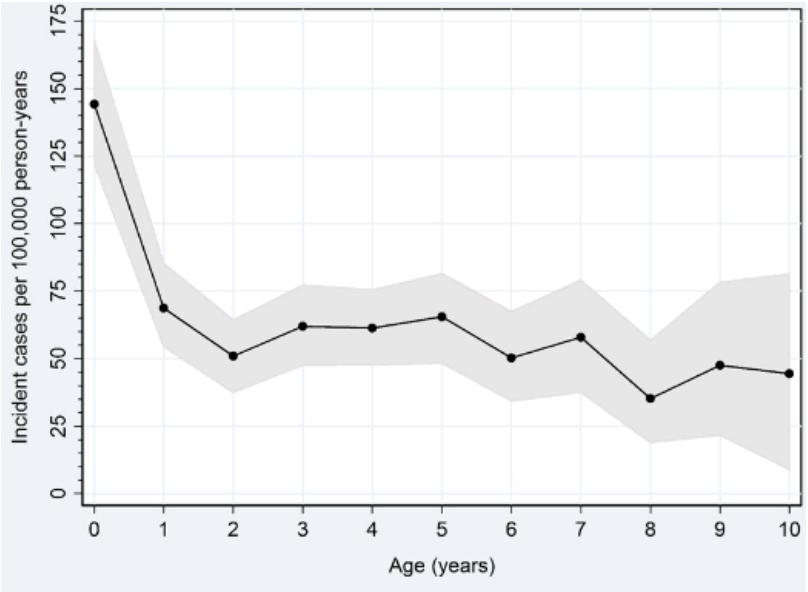

Fig. 1: Incidence of epilepsy in children in the first 10 years of age (1).

1.2 Epileptic seizure

In 2005, the International League Against Epilepsy (ILAE) formulated a conceptual definition of seizures and epilepsy. According to this definition, an epileptic seizure is defined as a transient occurrence of symptoms resulting from abnormal excessive or synchronous (epileptic) neuronal activity in the brain (3). According to the new 2017 ILAE Classification of seizure types (4), seizures are divided into focal, generalized and seizures of unknown origin - all these

groups are further divided into the category of motor seizures, or seizures without motor manifestations (see Fig. 2).

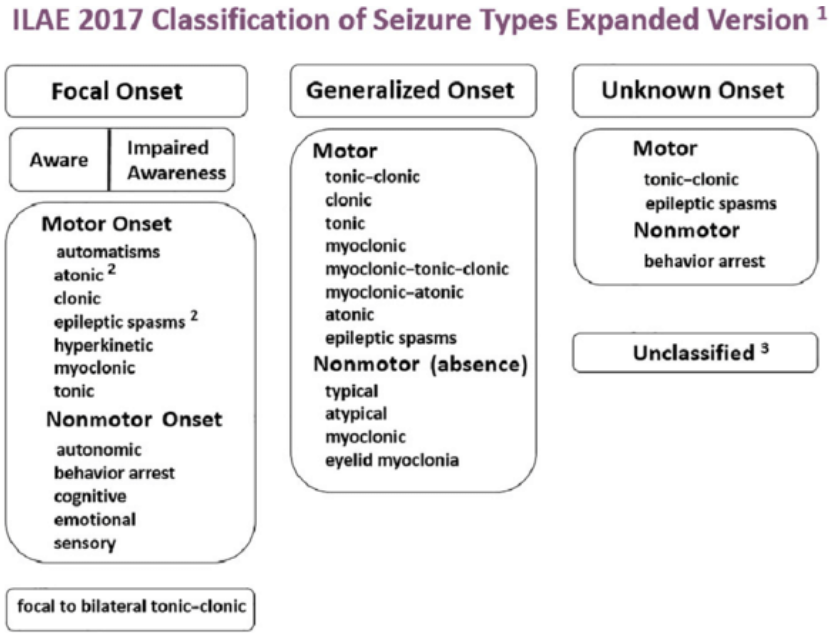

Fig. 2: ILAE 2017 Classification of seizure types (4)

1.2.1 Focal epileptic seizures

In focal seizures, the initial clinical manifestations and / or EEG changes suggest the onset in part of one cerebral hemisphere. Localization can be very discrete or widely distributed. Focal seizures can begin in subcortical structures. For each type of seizure, the ictal onset is given and unchanged, and there are preferential propagation patterns that can extend into the contralateral hemisphere (5). A state of awareness can be classified for focal seizures. An aware seizure means that the affected person is aware of himself / herself and the environment throughout the course of the course, even though he is, for example, immobile or aphasic. A seizure with impaired awareness means that consciousness is not maintained during the seizure. Focal seizures, with or without impaired awareness, are further subdivided into motor or non-motor. Furthermore, the individual groups are specified, as shown schematically in Fig. 2. The assignment of a certain term is decided by the first predominant symptom or manifestation of the seizure (5).

Focal motor seizures: are characterized by the dominance of motor manifestations. For some, these are unnatural movements and body positions different from physiological movements for their unnatural speed, chronology or posture (**focal clonic, myoclonic, tonic,** etc.). In other seizures, it is a complex motor activity similar to physiological movement patterns, but which occurs in an inadequate situation (eg automatisms).

Focal motor seizures with automatisms are characterized by the presence of unconscious movements - licking lips, clapping, swallowing, scratching, playing with clothes or a blanket, etc.

Focal atonic seizures are manifested by a short (250ms-1s) and sudden loss or decrease in muscle tone of the head, body, jaws and limbs without previous myoclonic or tonic manifestations.

Hyperkinetic seizures are characterized by marked physical agitation or the occurrence of movements resembling pedaling a bicycle.

Cognitive seizures express a disorder of speech or other cognitive functions or, conversely, describe positive symptoms reported by a patient, such as déjà vu, hallucinations, illusions, or feelings of distorted perception.

Emotional seizures express subjectively reported anxiety, fear, joy, or other emotions as the predominant symptom reported at the onset of the seizure, but also the situation around the observed emotional expression in a patient without subjectively reported emotions.

In a seizure with behavioral arrest, the disappearance of the patient's activity is the predominant symptom (5).

The 2010 ILAE Revision of the classification (6) and the 2017 ILAE Classification of seizure types (4) also include **epileptic spasms**; first in the group of seizures of unknown origin (6), then according to the new classification either in the group of focal seizures, generalized or with unknown origin (4). Their correct classification requires detailed analysis of the video-EEG recording. Because epileptic spasms may continue beyond the age of infancy or even occur de novo outside this age, it is no longer recommended to use the term infantile spasms as before.

If a focal seizure spreads to both hemispheres and a tonic-clonic seizure develops, the term "*focal to bilateral tonic-clonic seizure - FBTCS*" is used (4).

1.2.2 Generalised epileptic seizures

Generalized seizures are characterized by the fact that the first clinical changes indicate the involvement of both hemispheres (EEG patterns are bilateral from the beginning). They are also divided into motor seizures or non-motor seizures (= absences). Generalized seizure manifestations can be asymmetric, which sometimes makes it difficult to distinguish them from focal seizures.

1.2.2.1 Generalised motor seizures

Tonic-clonic (GTCS): are characterised by bilateral symmetrical tonic contraction, then bilateral clonic contractions of somatic muscles usually associated with autonomic phenomena. Examples of GTCSs in children include most febrile seizures and GTCSs in idiopathic (=genetic) eplepsies (IGEs, GGEs), such as juvenile myoclonic epilepsy (JME). Focal epilepsies can manifest with focal seizures evolving to bilateral tonic-clonic seizures (FBTCS). Investigations of symptoms and precipitating factors immediately before the onset of a GTCS is a crucial part of the history taking, with significant diagnostic and management implications.

Ictal EEG: Rhythm at ≥ 10 cycles/s decreasing in frequency and increasing in amplitude during tonic phase. Interrupted by slow waves during clonic phase.

Clonic: manifest by bilateral rhythmic clonic convulsions only. Each clonic event lasts <100ms at a rate of 1-5Hz. They should be distinguished from myoclonic seizures; clonic seizures are rhythmic at 1-5Hz, whereas myoclonic seizures are singular or irregular recurrent events.

Ictal EEG: each clonic convulsion corresponds to a generalised discharge of spike and multiple spikes or, more rarely, a mixture of rapid rhythms and slow waves.

Tonic: convulsive attacks of sustained muscular contractions only, without clonic component. They are of longer duration than myoclonic jerks and spasms (>2 – 10s).

Ictal EEG: low-voltage, fast activity or a fast rhythm 9-10 cycles/s, decreasing in frequency and increasing in amplitude.

Myoclonic: myoclonus is termed epileptic when it occurs in combination with cortical epileptiform discharges. Another possible definition is that myoclonus is epileptic when generated in the cortex, and non-epileptic, when generated in subcortical structures. Panayitopoulos proposes the following definition: epileptic myoclonus is a transient (<100 ms)

involuntary single or multiple muscle jerk due to abnormal excessive synchronous neuronal activity in the brain (7). Myoclonic seizures are briefer than tonic seizures and epileptic spasms.

Ictal EEG: polyspike and wave or sometimes spike and wave or sharp and slow wave.

Atonic: a sudden loss or diminution of muscle tone without an apparent preceding myoclonic or tonic event, lasting approximately 1 or 2 s, involving the head, trunk, jaw or limb musculature.

Ictal EEG: polyspikes and wave or flattening or low-voltage fast activity.

Epileptic spasms: seizures that can be generalised, focal, or of unclear onset. Epileptic spasms are sudden and brief bilateral tonic contractions of the axial and proximal limb muscles with abrupt onset and termination. They usually last for around 1 s and thus they are of longer duration than myoclonic jerks but of shorter duration than tonic seizures. The most common and characteristic form of epileptic spasm is with West syndrome (WS) but epileptic spasm may also occur in older children with epileptic encephalopathies. They are usually symmetrical and may involve widespread muscle groups or only the neck, abdomen or shoulders. Lateralising features may occur. Subtle spasms may occur as episodes of facial grimacing or isolated eye movements. The end of the attack is often followed by a cry or laughter. Epileptic spasms usually occur in clusters, often on awakening (7).

Ictal EEG: is heterogenous; a high amplitude, biphasic, slow wave or spike and wave activity may occur.

The new ILAE 2017 Classification of seizure types also recognizes the inclusion of seizure combinations: **myoclonic-atonic** and **myoclonic-tonic-clonic** as new types (4).

1.2.2.2 Generalized non-motor seizures

Typical absence seizures: generalized epileptic seizures of abrupt onset and abrupt termination, clinically manifesting as impairment of consciousness often associated with other concomitant symptoms, such as myoclonia, automatisms or autonomic distrubances. In 90% of patients, they are precipitated by hyperventilation. Other specific modes of precipitation include photic, pattern, video games and thinking.

Ictal EEG: generalized spike-slow wave discharges of 3 – 4 Hz. Typical absence seizures are present in childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE), mild can be seen in juvenile myoclonic epilepsy (JME) (7).

Atypical absence seizures: clinical symptoms of mild-to-severe impairment of consciousness, often significant changes in tone with hypotonia and atonia, mild tonic or autonomic alterations. Their duration ranges from 5-10s to minutes. Atypical absence seizures occur in the context of severe epileptic encephalopathies, typically in Lennox-Gastaut syndrome (LGS), myoclonic-atonic epilepsy (MAE) etc.

Ictal EEG: slows generalised spike-wave discharegs (<2.5Hz). These are hererogenous, often assymetrical.

Absences with eyelid myoclonias could be placed in a group of generalized seizures with motor manifestations. Because eyelid myoclonias are the most prominent clinical feature of these seizures, they are placed in the category of absences.

1.2.3 Provoked vs. unprovoked seizures

Seizures can be divided into unprovoked, occurring in the absence of precipitating factors and provoked – acute symptomatic seizures (ASSs) as explained below.

At this point, it is important to highlight the issue of reflex seizures, which by definition are ranked among the unprovoked. These are, for example, seizures that occur in response to photo stimuli and are therefore provoked. However, because there is a clear trend to respond to these stimuli with repeated seizures, there is an abnormal permanent predisposition to them, and therefore the occurence of reflex seizures meets the conceptual definition of epilepsy (7).

Provoked seizures - acute symptomatic seizures (ASSs) occur in close temporal connection with the ongoing CNS structural, toxic, metabolic or inflammatory insult. ASSs have higher early mortality, which depends on their cause. However, they have lower risk of further unprovoked seizures and the development of epilepsy (4).

The causes of ASSs are for example as follows (8):

Hypoglycaemia

In hypoglycemia, we can often see focal seizures that may divert our attention to the search for the structural cause of the seizures. In the case of the development of any ASS, it is necessary to consider the possibility of hypoglycemia.

Hypocalcaemia

The level of ionized calcium is crucial, which depends on the blood pH and decreases during alkalosis (binding to albumin). Therefore, we must be careful with the correction of metabolic acidosis in patients with limit values of ionized calcium.

Hypomagnesaemia

Diarrhea, insufficient income, malabsorption are the main causes of this condition.

Hyponatremia

Hyponatremia can occur in cardiac or renal edema or iatrogenically in hyperhydration. It can also have intracranial causes after head injuries or neurosurgical procedures - the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting syndrome (CSWS), the mechanism of which is inadequate renal sodium loss accompanied by hypovolemia. CSWS increases the production of brain natriuretic peptide, leading to increased sodium excretion and renal loss of sodium and water. This produces a large volume of diluted urine and reduces the extracellular volume of water. In SIADH, fluid retention and dilution hyponatremia occur, so the volume of the extracellular fluid is normal, hypervolemia develops, and highly concentrated urine is formed with a small volume. The cause may be an injury, infection, stroke, drugs (tricyclic antidepressants, carbamazepine, ACE inhibitors, vincristine, etc.). Hyponatremia leads to the development of cerebral edema. With hyponatremia below 125 mmol/l, gastrointestinal symptoms (nausea, vomiting) appear, and when sodium falls below 120 mmol/l, mild cognitive dysfunction is added. More severe encephalopathy with ASSs, delirium and coma occurs when sodium drops below 120 mmol/l.

Cerebral hypoxia and anoxia

This condition can occur for a number of reasons - heart and circulation failure in myocardial infarction, arrhythmia, bleeding, septic shock, etc. In diffuse hypoxia, the hippocampus and

cerebellum are affected first, then the cerebral cortex, the most resistant is the brainstem. Short-term hypoxia can lead to the development of syncope, which can also be convulsive, then it acts as an epileptic seizure.

Drug causes

The combination of tramadol with SSRIs, for example, or some chemotherapeutics, which we often encounter in pediatric oncology patients (methotrexate, ifosfamide), has a proconvulsant effect.

Withdrawal syndrome

After the withdrawal of barbiturates, opiates or benzodiazepines, especially after a rapid action.

Brain tumor

Supratentorial tumors in children are less common, and even in this location the risk of developing seizures is relatively low compared to adult patients. Epileptic seizure as an initial symptom has been described in 15% of children with supratentorial tumor localization (8). Only 1% of children after the first epileptic seizure were diagnosed with a brain tumor as the underlying cause. Brain tumors in children occur predominantly in the posterior fossa, their growth is rapid and they are highly malignant. Such tumors often have symptoms other than seizures, based on their location and the extent of brain tissue involvement. ASSs in these tumors are caused mainly by decompensation of intracranial pressure, which is caused by rapid tumor growth and collateral edema. In contrast, slow-growing tumors such as dysembryoplastic neuroepithelial tumor (DNET) or low-grade gliomas (LGGs) are associated with a risk of seizures and the development of epilepsy. DNET is often associated with a malformation of cortical development and epileptogenicity is ensured by cortical dysplasia in its surroundings. Epileptic seizures in these children can be the first manifestation of the disease. Children are treated for epilepsy and can be candidates for epileptosurgery.

Stroke

In general, stroke is rare in children. ASSs in this condition occur in 4.2-6.1% of cases. Most of them take place within 24 hours after the onset of clinical symptoms (9). They are slightly more common in hemmorhagic stroke. In cerebral venous thrombosis, ASS occurs in up to 40%

of cases (8). It is necessary to perform brain MRI with venography in these pateints and carefully search for cerebral venous thrombosis.

CNS infections

As ASSs are concerned, brain abscesses are especially important. As many as a quarter of patients with a brain abscess manifest with ASS (8).

Posterior Reversible Encephalopathy Syndrome (PRES)

As mentioned above, ASSs also occur, for example, in PRES syndrome, which is a clinico-radiological syndrome. This is defined as transient cerebral vasogenic edema, which occurs preferentially in the posterior cerebral circulation. It is clinically characterized by headaches, seizures, impaired consciousness, visual and other focal neurological symptoms (10). The radiological finding of vasogenic edema in the posterior cerebral circulation is characteristic, but other areas may also be affected, especially the basal ganglia, brainstem and white matter (Fig. 3). The pathophysiology of the syndrome is unclear. Arterial hypertension and endothelial dysfunction, which lead to a blood-brain barrier disorder and the development of vasogenic brain tissue edema, are thought to occur (10). Moderate to severe hypertension can be traced in up to 75% of patients (11). In pediatrics, this syndrome is most commonly encountered in oncology patients, especially in children with hematological malignancies during the protocol treatment.

The author studied PRES in children treated at the Department of Pediatric Oncology of the Faculty of Medicine, Masaryk University and University Hospital Brno in the years 2008-2018 and evaluated a group of 21 patients with this diagnosis (12). ASSs were identified in 17 of 21 patients (80.9%), 4 of 21 patients (19.0%) had seizures even after the acute period, and epilepsy was present in 2 of 21 children (9.5%) at one-year follow-up. Interestingly, both of these patients had glial changes on the brain MRI. These two patients were discussed from the point of pathophysiology. Were there other factors in addition to vasogenic edema at PRES onset? Vasogenic edema should be reversible and possibly other factors that worsened the patients´ prognosis were involved. The key finding was that PRES is mainly reversible with a good prognosis and seizures in this syndrome are mostly acute symptomatic (12).

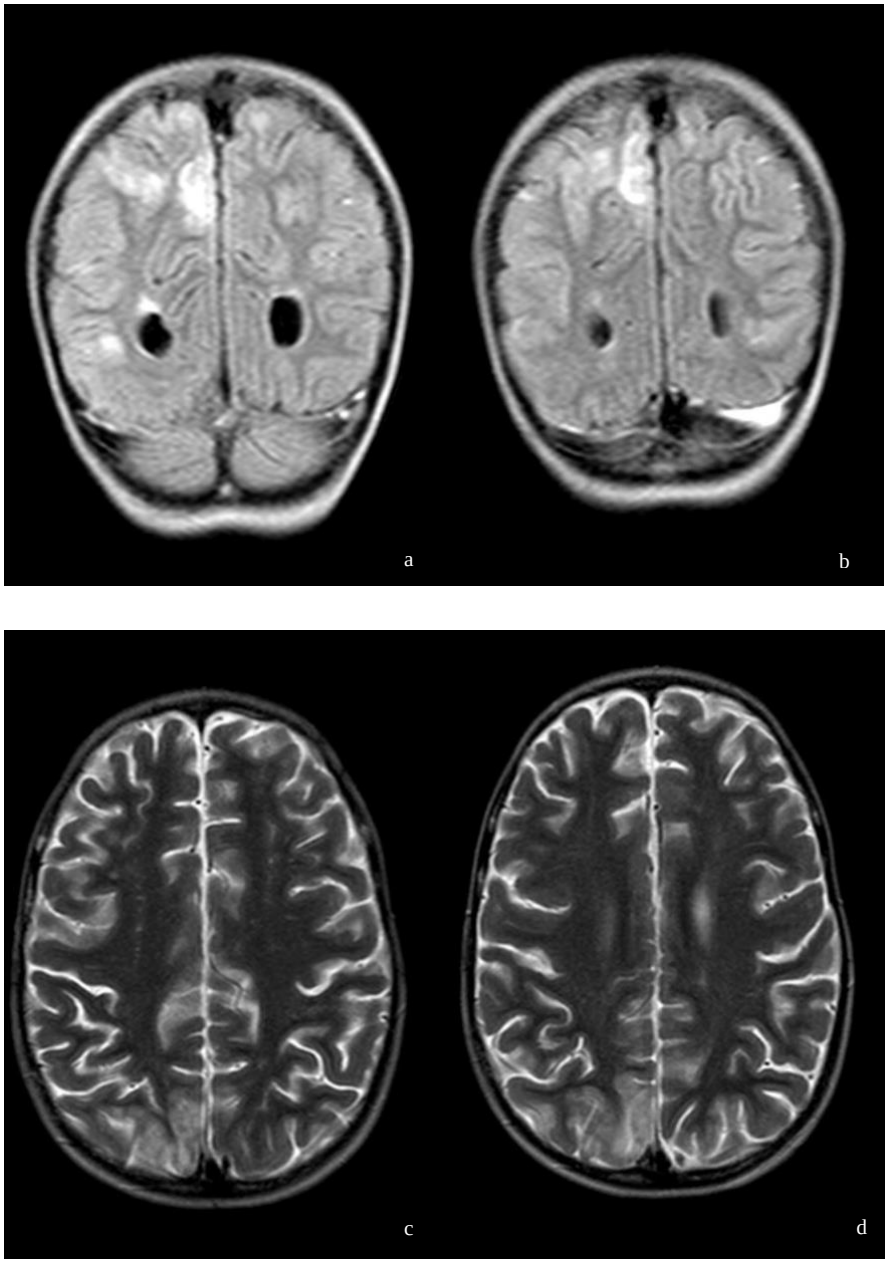

Fig. 3: MRI at PRES onset showing FLAIR (a,b) and T2-weightened (c,d) subcortical hyperintensities in occipital regions with right predominance.

Images from the archive of the Department of Pediatric Radiology, Faculty of Medicine, Masaryk University, University Hospital Brno.

Annex 1

1.3 Epilepsy

Epilepsy was defined in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (3). In 2014, the ILAE newly proposed an amendment to the conceptual definition of epilepsy for practical clinical needs (13):

Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring >24 h apart

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no antiseizure medication for the last 5 years (13).

Epilepsy is a very heterogeneous group of diseases and their correct classification, including the determination of etiology, has a major impact on treatment and prognosis (3). The current ILAE 2017 Classification of the epilepsies is multi-level and, where possible, should be set at all three levels (14). See Fig. 4.

The first level is the seizure type classification, as discussed in the previous chapter. Classifications of seizure type and epilepsy also take into account the results of examinations such as EEG and imaging methods, along with others to reveal the etiology of epilepsy.

The second level is the determination of the type of epilepsy - see the 2014 definition of epilepsy (13). Thus, we distinguish between focal and generalized epilepsy; since 2017, two new groups have been added: combined generalized and focal epilepsy and epilepsy of an unknown origin (14).

A patient with **generalized epilepsy** typically has generalized discharges of spike and wave complexes in the EEG. These patients may have different types of generalized seizures: absence, myoclonic, atonic, tonic, tonic-clonic, etc. The diagnosis is conditioned by a typical

clinical manifestation and EEG findings. Caution should be exercised if the patient has a history of generalized tonic-clonic seizures and a negative EEG. The diagnosis may be supported by, for example, the occurrence of myoclonic jerks or a relevant family history (14).

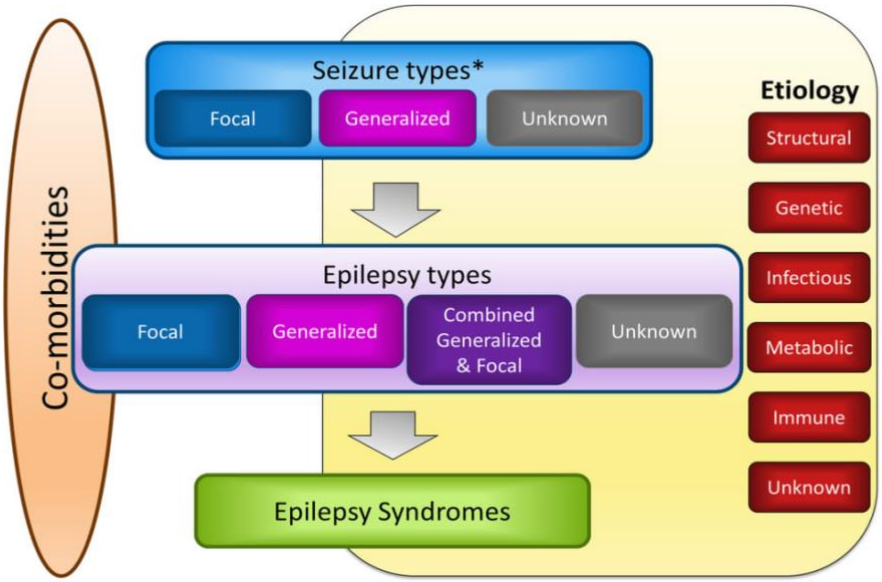

Fig. 4: 2017 ILAE Classification of the epilepsies (14)

Focal epilepsy can be unifocal or multifocal, or seizures affect one hemisphere, as described in detail in the previous chapter. In the EEG, we typically find focal epileptiform discharges and the diagnosis can be based on a clinical picture supported by the EEG finding.

A new group of **combined generalized and focal epilepsy**, where one patient may experience both focal and generalized seizures, is essential especially for epileptic encephalopathies. Typically this type of epilepsy can be found in Lennox-Gastaut syndrome or Dravet syndrome (14).

Epilepsy of an unknown type indicates a situation where the patient has epilepsy, but we are unable to determine whether it is focal or generalized because there is a lack of information about the type of seizures. Likewise, the EEG does not provide enough information or is not available at all.

The third level is the determination of epileptic syndrome, as discussed below.

There are several major changes in the new classification of epilepsy compared to the 1989 ILAE Classification (15):

Idiopathic generalized epilepsy (IGE): this is a very well-defined and widely used term for a group of diseases that include Childhood absence epilepsy (CAE), Juvenile absence apilepsy (JAE), Juvenile myoclonic epilepsy (JME), and Generalized tonic-clonic seizures alone. The last group used to be called GTCS on awakening. The circadian rhythm dependence is not always present, thus the syndrome´s name has been changed. Recently, the name of these epileptic syndromes has been changed to Genetic generalized epilepsy (GGE). This name has been supported by clinical research on the inheritance of these syndromes in twin and familial studies. This does not mean that a pathogenic sequence variant or genetic cause in general explains the etiology of the disease in patients with GGE. Therefore, it is still possible to use both IGE and GGE terms (14).

The term "idiopathic" has also been used to indicate that it is a highly pharmacoresponsive syndrome, often remitting in age and essentially "benign." Concomitant cognitive and behavioral changes in patients with these epileptic syndromes have often not been reported (14). The author studied a group of 46 patients with JAE followed up at the Center for Epilepsy Brno in the years 2006-2011 (16) and found that almost half of the patients had a high level of drug resistance with ongoing seizures. On average, patients in this cohort took 4-6 antiseizure drugs. This is an example of an epileptic syndrome generally considered to be a syndrome with a very good prognosis, but the results did not support this claim.

Annex 2

A similar question also arose in the group of „benign focal epilepsies“, where Rolandic eplepsy (Self-limited epilepsy with centrotemporal spikes) is a typical example. This syndrome was considered as benign for a long time, as the name suggested (formerly Benign childhood epilepsy with centrotemporal spikes – BCECTS). The truth is that most patients with this syndrome have a very good prognosis, but the accompanying cognitive and behavioral changes in these children cannot be neglected, and this syndrome is typically associated with Attention Deficit Hyperactivity Disorder (ADHD) (17–19). Even before the announcement of the new ILAE 2017 Classification of the epilepsies in 2017 (14), the author prepared her dissertation on

the topic "The influence of EEG-detected nocturnal centrotemporal discharges on the expression of on core symptoms of ADHD in children with BCECTS" (20). The work evaluated 32 children aged 6-11 years treated at the Department of Pediatric Neurology, Faculty of Medicine, Masaryk University and University Hospital Brno, with a diagnosis of Rolandic epilepsy. ADHD was diagnosed in 65.8% of them. Patients with greater activation of epileptiform discharges in sleep also had a higher rate of attention deficit and impulsivity. The influence of nocturnal epileptiform discharges on the development of cognitive functions in the critical period of development of neuropsychological functions was extensively discussed in the work.

The ILAE 2017 Classification of the epilepsies leaves the labeling of "benign focal epilepsies" as benign. The renaming this group to "self-limited focal epilepsies" is somewhat more appropriate, reflects their age and does not emphasize the benign course, which may not always be a condition. Other self-limited focal childhood epilepsy is Panayitopoulos syndrome and Self-limited focal occipital epilepsy of Gastaut. Self-limited epilepsis of the frontal lobe, temporal lobe or parietal lobe have been described with beginning in adolescence or even in adulthood (14).

Annex 3

1.4 Epileptic syndromes

An epileptic syndrome is a condition characterized by epileptic seizures in which a consistent cluster of clinical, EEG and investigative features has specific etiological, management and prognostic implications. An epileptic syndrome may have one or more etiologies. When a single etiology is associated with a consistent epilepsy phenotype, the etiology, for example a genetic or structural lesion, may best define the syndrome rather than a single clinical feature or eponym. The definition would allow hippocampal sclerosis with focal seizures, hypothalamic hamartoma with gelastic seizures, and CDKL5 developmental and epileptic encephalopathy to all be classified as epileptic syndrome (21).

Neonatal
benign familial and non-familial neonatal seizures (BFNS, BNFNS)
early myoclonic encephalopathy (EME)
early infantile epileptic encephalopathy (EIEE)
Infantile
Infantile spasms syndrome (West syndrome - WS)
Lennox-Gastaut syndrome (LGS)
epilepsy of infancy with migrating focal seizures
myoclonic-atonic epilepsy (MAE)
myoclonic epilepsy in infancy (MEI)
Dravet syndrome (previously severe myoclonic epilepsy in infancy SMEI)
febrile seizures +
Childhood
childhood absence epilepsy (CAE)
Epilepsy with myoclonic absences (EMA)
self-limited focal epilepsy with centrotemporal spikes – Rolandic epilepsy
Panayitopoulos syndrome (PS)
Childhood occipital epilepsy of Gastaut (COE-G)
Encephalopathy related to status epilepticus during slow sleep (ESES) incl. Landau-Kleffner syndrome (LKS)
Adolescence
juvenile absence epilepsy (JAE)
epilepsy with absences with eyelid myoclonia
juvenile myoclonic epilepsy (JME)
generalised tonic-clonic seizures only
Others
Rasmussen syndrome
new-onset refractory status epilepticus/ febrile infection related epilepsy syndrome (NORSE/FIRES)
photosensitive epilepsy
reading epilepsy
progressive myoclonic epilepsy (PME)
frontal lobe epilepsy (FLE)
temporal lobe epilepsy (TLE) mesiotemproal limbic epilepsy syndrome (MTLE)
parietal lobe epilepsy
occipital lobe epilepsy
hemiplegia/hemiconvulsions syndrome (HHS)

Tab. 1: Epileptic syndromes divided by age at onset; frequently used in pediatric neurology practice (taken from (21)).

A number of epileptic syndromes are currently described, but their formal classification has not yet been issued by the ILAE.

Tab.1 summarizes the overview of the most important and most common age-related epileptic syndromes used in pediatric neurological practice.

The next part will be devoted to selected clinically important age-related epileptic syndromes – *adopted and modified from (7) and (21):*

All EEG graphs are from the archive of the Department of Pediatric Neurology, Faculty of Medicine, Masaryk University, University Hospital Brno.

1.4.1 Epilepsy syndromes of neonatal and infantile period

1.4.1.1 Benign familial and non-familial neonatal seizures

Patients have typically neonatal onset of seizures, usually on the second or third day of life, and spontaneous remission by 6 months of age. Seizures are focal with different motor manifestations, mainly clonic, never tonic. They are often lateralised, starting on one side then affecting the other side.

EEG findings: interictal EEG is normal, discontinuous with focal or multifocal abnormalities or with *theta pointu alternant* pattern. The ictal pattern is characterised by a generalized flattening of the background activity followed by focal or bilateral spikes or slow waves lasting as long as the clinical manifestation.

Etiology: The linkage studies led to the identification of mutations in the voltage-gated potassium channel genes KCNQ2 and KCNQ3 (22, 23). Spectrum of phenotypes associated with KCNQ2 and KCNQ3 mutations and gene variants have been also associated to different epileptic phenotypes, from self-limited to drug-resistant epilepsy associated with developmental delay. More recently the phenotype of KCNQ2-related developmental and epileptic encephalopathy has been distinguished into two clinical phenotypes due to the different impact of the mutation on the channel functionality (gain or loss of function) (24). Variants that cause the loss of function cause the neonatal onset epileptic encephalopathy, while variants that cause a gain of function of the potassium channel cause a developmental and epileptic encephalopathy (DEE) with an infantile onset with epileptic spasms followed by drug-

resistant focal epilepsy and the occurence of non-epileptic myoclonus during the first months of life (24).

Treatment: This type of epilepsy syndrome is characterised by good prognosis, seizures are self-limited independently from the treatment. Nevertheless, seizures may be difficult to control in the neonatal period, then we use PB or BDZ. Currently, the use of sodium-channel blocker, such as CBZ and PHT, is preffered (21).

1.4.1.2 Early severe neonatal and infantile epilepsies - Early myoclonic encephalopathy (EME) and Ohtahara syndrome - Early infantile epileptic encephalopathy (EIEE)

ILAE described two age-dependent electroclinical syndromes characterised by encephalopathy which occur in the neonatal period (6): Early myoclonic encephalopathy (EME) and Ohtahara syndrome, also known as Early infantile epileptic encephalopathy (EIEE). Each of these syndromes are characterised by a specific clinical seizure type, clinical signs of encephalopathy and a suppression-burst (S-B) pattern on the EEG (Fig. 5 and 6). Detailed comparison between EME and EIEE is shown in Tab. 2.

Etiology: Two etiologic factors in EME received the most attention: genetic disorders or inborn errors of metabolism. Kojima et al. (25) recently summarized reported genetic causes of EME to include involvement of KCNQ2, ERBB4, SIK1, SLC4A22, and GABRB2. The most commonly reported inborn error of metabolism connected wth EME is nonketotic hyperglycinemia (26). Other reported metabolic disorders include hyerglycinemia, D-glyceric acidemia, methylmalonic acidemia, hyperammonemia, and propionic acidemia (21).

Although genetic factors have been most recently extensively investigated in EIEE, structural brain abnormalities still represent the most important etiologic factor in EIEE, making detailed neuroimaging critical component of the evaluation of these infants (21). Several authors reported cases of EIEE associated with mitochondrial chain deficiency (27,28). In a recent review, Pearl et al. (29) listed genes which have been associated with EIEE: CDKL5, SLC25A22, STXBP1, KCNQ2 and SCN2A.

Treatment: Due to the high degree of farmacoresistance, therapy is usually unsuccessful. If infants survive, transition to West syndrome is possible.

	EME	EIEE
predominant seizure type	erratic myoclonus	tonic spasms
other possible seizure type	generalized myoclonus, focal seizures, tonic spasms (late)	focal seizures, generalized myoclonus (rare), no erratic myoclonus
neurological examination	abnormal, hypotonia	abnormal, lateralized in case of brain structural abnormalities
EEG features	S-B with short paroxysmal bursts and longer period of suppression, S-B enhanced in sleep	S-B with longer periods of bursts and shorter periods of suppression
evolution	West syndrome	West syndrom or EEG and epilepsy improvement
etiology	metabolic disorders; genetic	CNS structural abnormalities; genetic
prognosis	early death or progressive deterioration of survivors	mental retardation, severe neurological impairment, variable epilepsy outcome

Tab. 2: Clinical features of EME vs. EIEE (21)

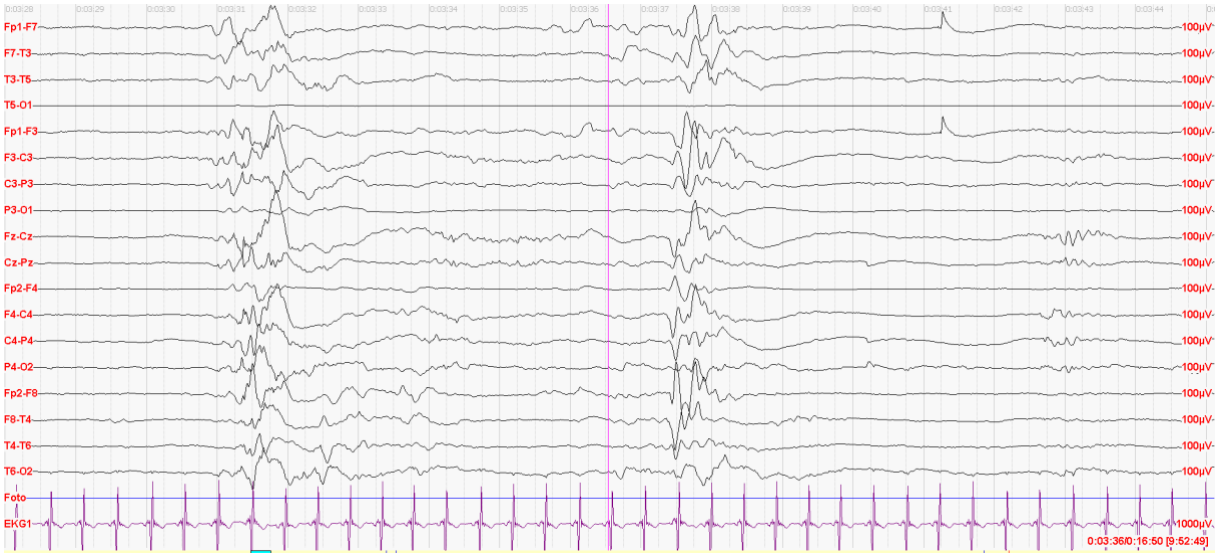

Fig. 5: ***Early myoclonic encephalopathy:*** *Suppression-bursts EEG pattern with myoclonic jerks associated to the bursts in a neonate with non-ketotic hyperglycinemia.*

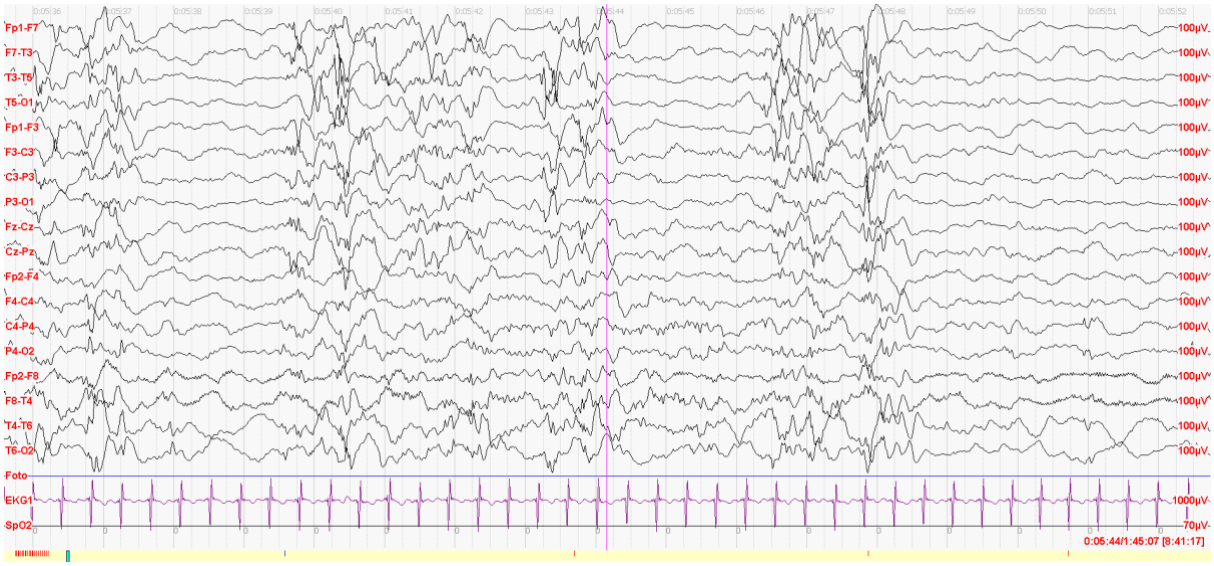

Fig. 6: ***Early infantile epileptic encephalopathy (Ohtahara syndrome):*** *Suppression-bursts EEG pattern with left-sided accentation in a 3-month-old child with extensive malformation of the cortical development (focal cortical dysplasia) predominantly in the left temporo-parietal region.*

1.4.1.3 Infantile spasms syndrome (IS; West syndrome)

The development of this syndrome is most common in the first year of age, around 3 to 4 months of age, then it is called West syndrome. The syndrome is characterized by the occurence of epileptic spasms and hypsarhytmia on EEG (Fig. 7-11) frequently associated with modification of behavior or cognitive decline.

Etiology: Etiology of IS is classified as structural, genetic, infectious, metabolic, immune, or unknown (4). Genetic etiology represents about 25% of IS (30). Several chromosomal abnormalities have been reported in about a fourth of spasms of genetic etiology and the most frequent are trisomy 21, XXY, 17p13.3 microdeletion, and 1p36 del (31,32). Moreover, mutations in X-linked genes have been described such as CDKL5, particularly in female, and ARX, usually in male patients (33). Other gene mutation (SCN1A, MAG12, CACNA1A) have also been reported (34). IS can also be the first manifestation of tuberous sclerosis with mutation in TSC1 or TSC2 gene. In about 20% of IS, the underlying cause is unknown (21).

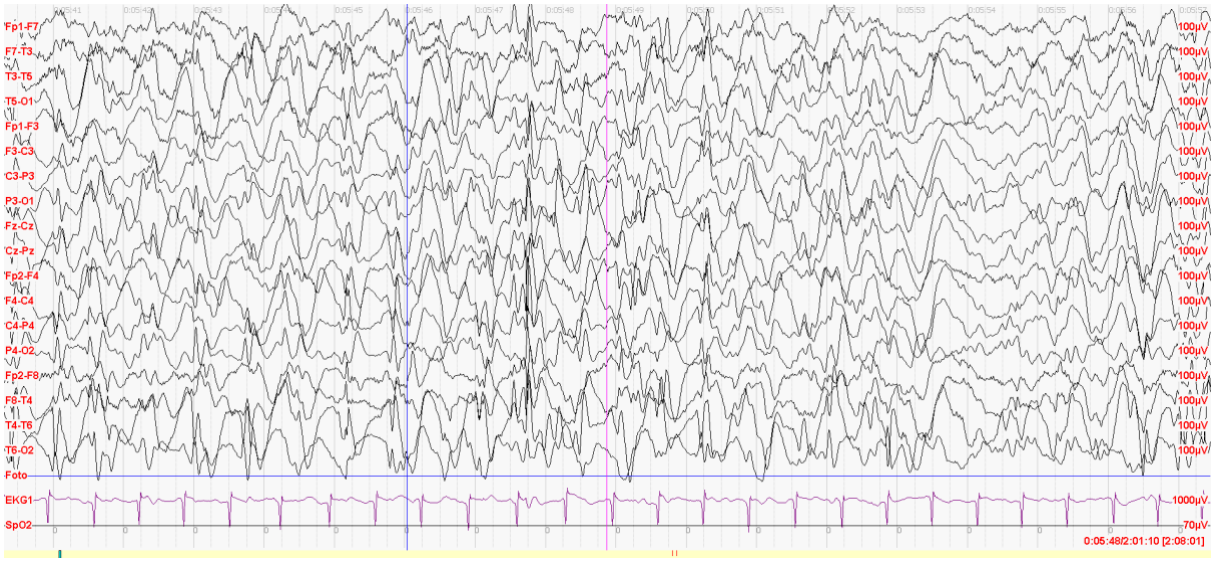

Fig. 7: ***West syndrome:*** *High-amplitude slow waves intermingled with spikes with asynchronous occurence – the EEG pattern of hypsarrhythmia in a 5-month-old child with West syndrome of unknown etiology.*

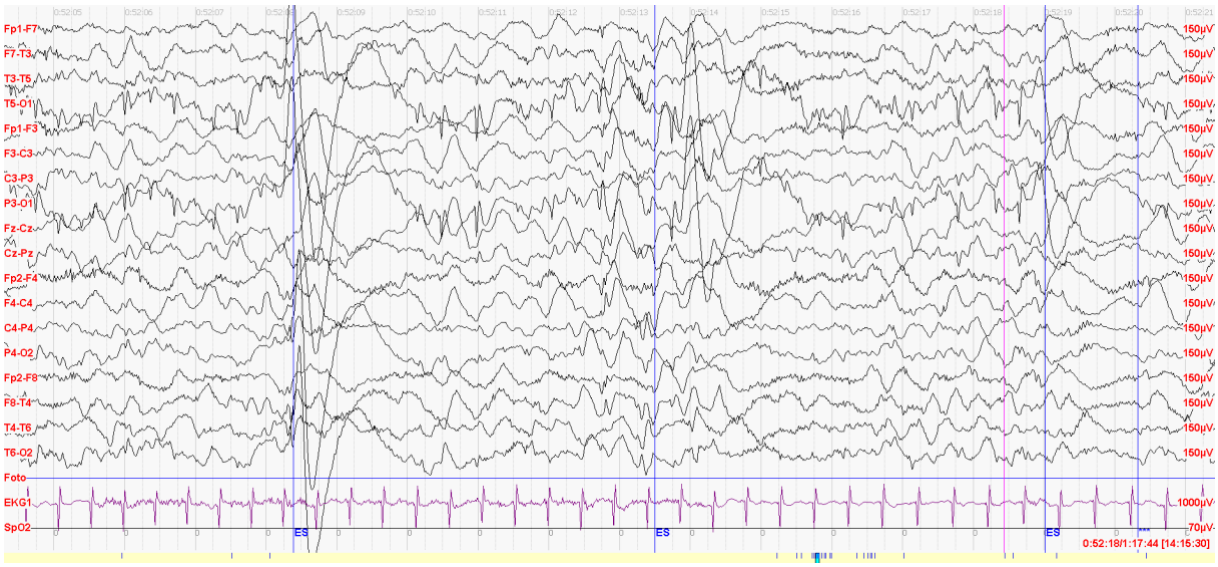

Fig.8: ***West syndrome:*** *Ictal pattern of epileptic spasms in a 4-month-old child with CACNA1A-related DEE. The ictal pattern is an asynchronous high amplitude diffuse slow wave.*

Treatment: Hormonal treatment (ACTH or corticosteroids) and vigabatrin (VGB) are now considered as two standard first line therapies. Earlier the diagnosis and earlier the treatment,

better the developmental outcome (35). Conventional antiseizure medication is less efficient than standard therapy, VPA, TPM, or ZNS are frequently used.

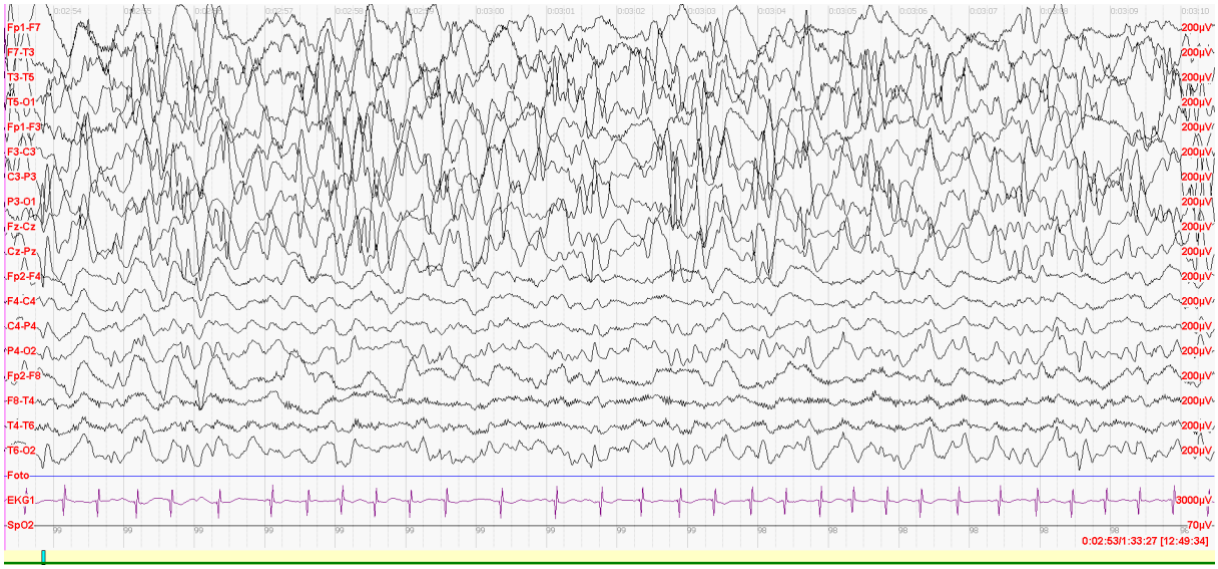

Fig. 9: ***West syndrome:*** *Left-sided hemihypsarrhythmia in an 8-month-old girl with severe perinatal hypoxic-ischemic encephalopathy.*

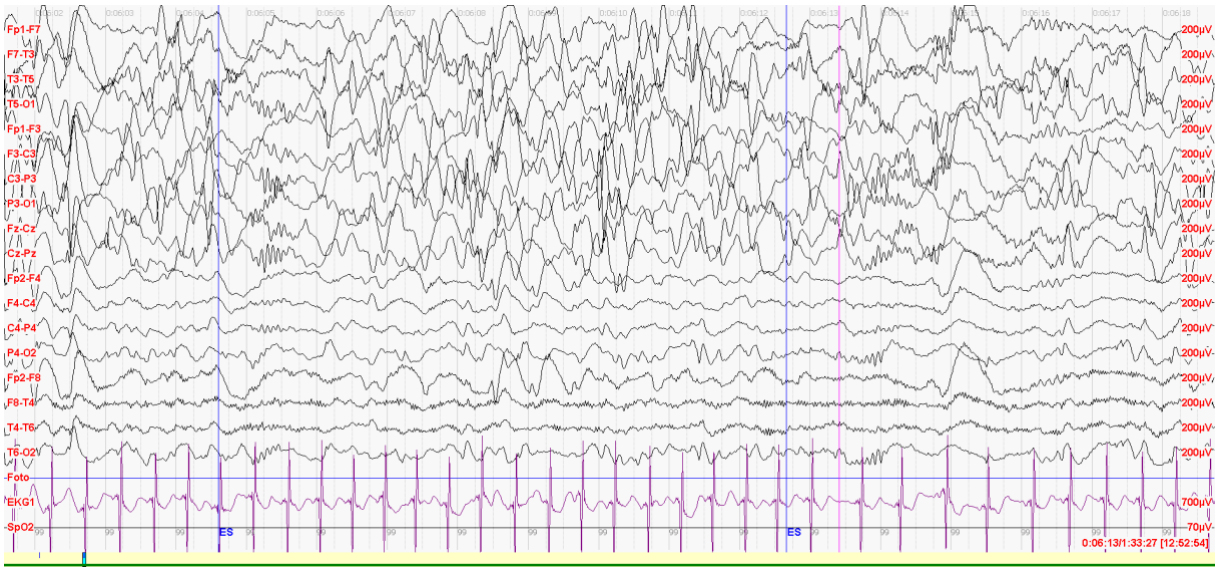

Fig. 10: ***West syndrome:*** *Ictal pattern of epileptic spasms in an 8-month-old girl with severe hypoxic-ischemic perinatal encephalpathy. Hemihypsarrhythmia is interrupted by a high amplitude asynchronous slow wave in the lefte hemisphere.*

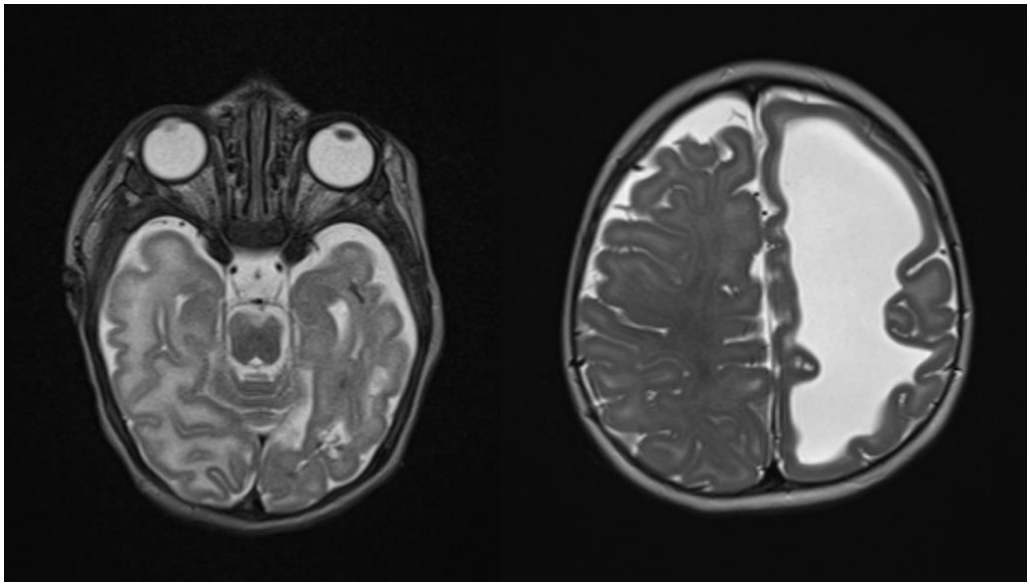

Fig. 11: ***Perinatal hypoxic-ischemic encephalopathy with West syndrome:*** *Brain MRI in a girl with severe hypoxic-ischemic perinatal encephalopathy. T2W axial in 2,5months of age (on the left) and T2W axial in 8 months of age.*

Images from the archive of the Department of Pediatric Radiology, Faculty of Medicine, Masaryk University, University Hospital Brno.

1.4.1.4 Dravet syndrome (DS; previously Severe Myoclonic Epilepsy in Infancy - SMEI)

Dravet syndrome was first described in 1978 by Professor Charlotte Dravet in France (36). The development of epileptic seizures typically begins in infancy with a peak around 5 months in still normally developing children. The incidence is reported as 1:30,000 children (7), boys are more often affected in a 2: 1 ratio (7). The following types of seizures occur: generalized tonic-clonic seizures (or often lateralized alternating seizures), myoclonic seizures, atypical absences and focal seizures with impaired awareness. Status epilepticus is very common, especially in the initial period, mainly in febrile seizures.

The clinical course of DS can be divided in three stages: a "febrile phase", in the first year of life, then a "catastrophic phase", of variable duration, and a "sequel phase" (21).

Etiology: In accordance with the ILAE 2017 Classification of the epilepsies, DS ranks etiologically among epilepsies on a genetic basis. The vast majority of patients carry a mutation in the sodium channel alpha1 subunit gene (SCN1A gene), this mutation occurs in 70-80% of patients (37). There is a reduction in the excitability of GABAergic interneurons in the

neocortex and hippocampus (38), which results in a reduction in discharges in these inhibitory interneurons. This will increase the excitability in the neural network and development SCN1A-DEE. There is a certain variability in these patients in the clinical picture, we speak of DS-spectrum (37).

Approximately 5% of patients carry a mutation in the PCDH19 gene with X-linked inheritance (39). It is a gene encoding protocadherin 19, the function of which has not yet been fully elucidated, but its involvement in neural networks is thought to be involved. The mutation causes Epilepsy limited to females with mental retardation (EFMR). A characteristic feature here is a lower incidence of epileptic states and myoclonic seizures rarely occur. In 45% of patients, mental retardation is only mild, autistic features are common. Mutations in the GABARG2 (40) and SCN1B (41) genes have rarely been identified.

Treatment: Therapeutic options are relatively rich, but their effect is limited by high drug resistance. The drugs of first choice are VPA and BDZ (42), especially CLB. Stiripentol (STP) is indicated if these do not work. STP is classified as an orphan-drug in DS therapy and is approved as adjunctive therapy to VPA + CLB. DS therapy has been approved in Europe since 2007. Other therapeutic options are TPM (43) and LEV (effective mainly for myoclonic seizures (44)), which can be used as adjunctive drugs. LTG, CBZ, VGB and high doses of PB may worsen seizures and should be avoided. Last but not least, it is necessary to mention the ketogenic diet, which has a relatively high effectiveness in the treatment of DS in comparison with other epileptic encephalopathies (45). Vagal nerve stimulation (VNS) also shows favorable results in DS therapy (46).

1.4.1.5 Myoclonic epilepsies in infancy and early childhood

1.4.1.5.1 Myoclonic epilepsy in infancy (MEI)

MEI is characterized by brief and generalized myoclonic seizures without other seizure types, in the first three years of life in cognitively normal infants.

The age of onset is usually between 4 months and 3 years, myoclonic seizures are initially often rare, involving the upper limb and the head. Later, their frequency increases up to several times a day.

Etiology: the genetic contribution to MEI is unclear.

Treatment: VPA can lead to seizure freedom in 82.9% of patients and is considered as the first choice treatment (47). If myoclonic seizures are not completely controlled by VPA, other options can be chosen: CLB, CLZ, ESM, LTG (7).

1.4.1.5.2 Epilepsy with myoclonic-atonic seizures (MAE)

MAE is a childhood nonlesional generalized epilepsy with multiple seizure types, including myoclonic-atonic seizures, absence, atonic, GTCS, and tonic seizures, and with onset between 7 months and 6 years of age.

Myoclonic-atonic seizures are characterized by brief, massive or axial, symmetrical jerks, involving the neck, shoulders, arms and legs, often resulting in head nodding, abduction of arms and flexion of the legs at the knees. Each jerk is immediately followed by an abrupt loss of muscle tone that contributes causing the drop to the floor. Falls in MAE can also result from purely myoclonic or atonic seizures. The EEG of myoclonic-atonic seizure shows bursts of spike/polyspike and wave complexes at 2 to 4 Hz (Fig. 12 and 13). EMG recordings show that the myoclonic potential is usually followed by an EMG silence lasting up to 500ms. The interictal EEG can be normal at onset. Bursts of 3Hz spike-waves may occur without apparent clinical manifestations and may be activated by sleep. The most suggestive finding is the 4 to 7 Hz theta rhythm with parietal predominance and the occipital 4-Hz rhythm which is constantly blocked by eye opening (21).

Etiology: Genetic factors play an important role, dominant mutations have been demonstrated in the SLC2A1 (GLUT1-deficit) (48), SCN2A (49), GABRB3 (50), and SPTAN1 genes (51).

Treatment: Treatment of myoclonic seizures is primarily with VPA, ESM and BDZ. LTG can be effective especially in associated GTCSs. Other drugs, such as LEV, TPM and STM can be effective. The ketogenic diet can be very effective. If a mutation on SCL2A1 has been found, then the ketogenic diet should be used as the first-line treatment and maintained even with seizure freedom (21).

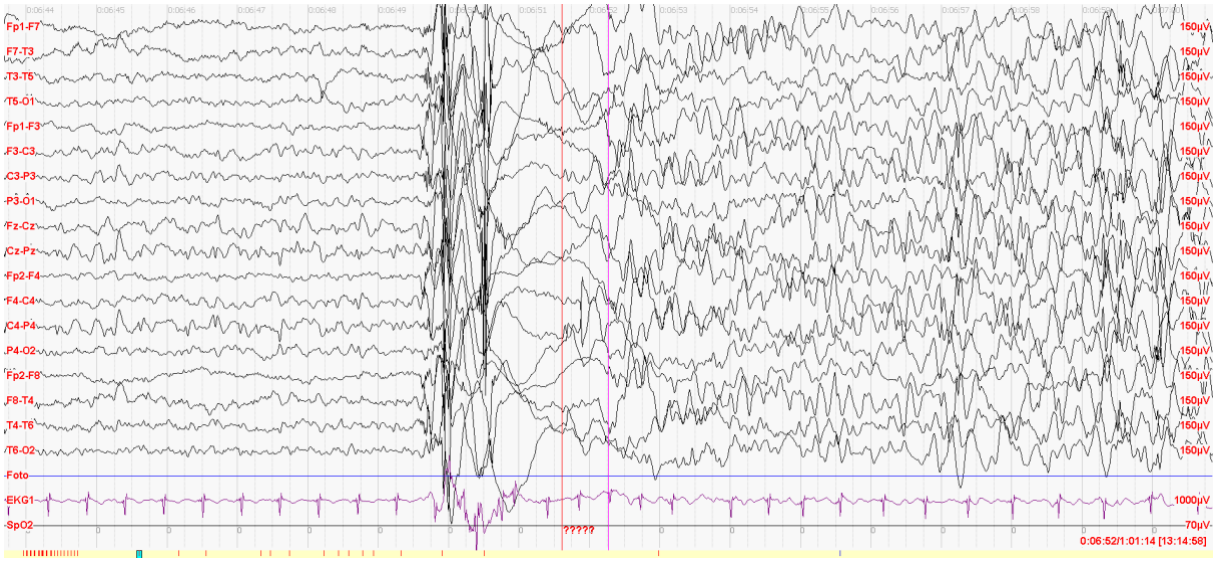

Fig.12: ***Myoclonic-atonic epilepsy:*** *Ictal recording in a 3-year-old boy with myoclonic-atonic epilepsy. A myoclonic jerk is correlated with a brief and diffuse spike and wave discharge. Pre-ictal background aktivity is normal. .*

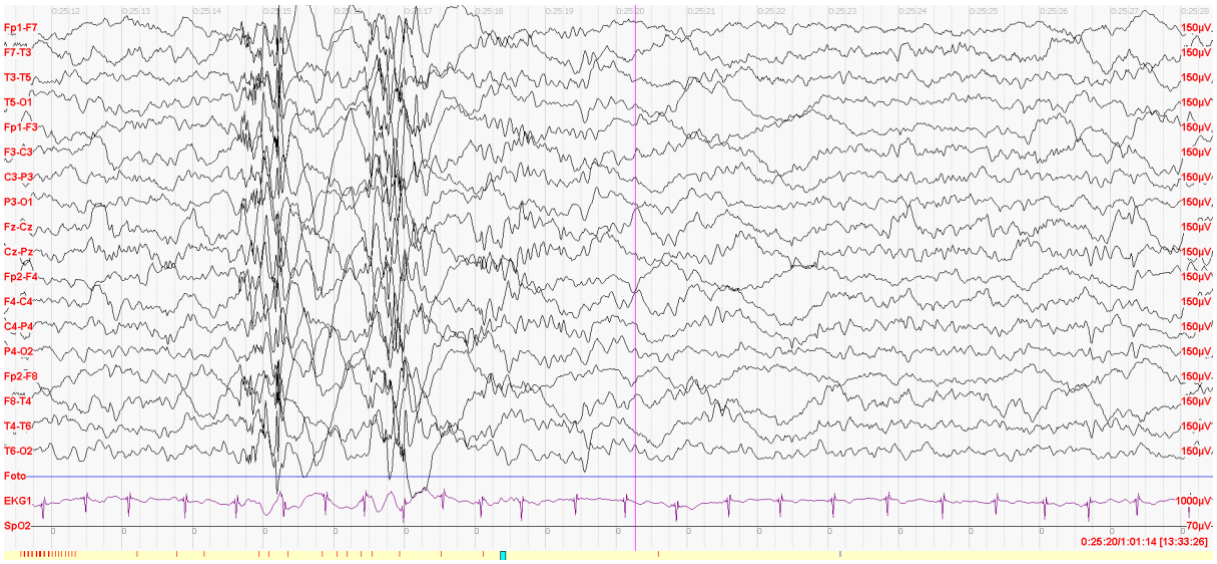

Fig.13: ***Myoclonic-atonic epilepsy.*** *Sleep EEG in a 3-year-old boy with MAE of unknown etiology. Generalized polyspike wave complexes in NREM II sleep.*

1.4.1.6 Lennox-Gastaut syndrome (LGS)

The LGS remains one of the most severe epileptic encephalopathies with high seizure frequency, progressive cognitive impairment and drug resistence. In the 2017 ILAE

Classification of the epilepsies, LGS is classified in the new group of combined generalized and focal epilepsies, because patients have both focal and generalized seizures (14). The typical LGS is desribed according to the following symptomatic triad:

1) EEG abnormalities: bursts of diffuse slow spike-wave during wakefullness (Fig. 14) and bursts of fast rhythmic waves and slow polyspikes and above all generalized fast rhythms at about 10 Hz during sleep (Fig. 15)
2) Epileptic seizures: axial tonic (Fig. 16), atonic (Fig. 17), atypical absence (Fig. 18)
3) Slowing of intellectual growth and associated personality disorders

Etiology: Several common etiologies of LGS have been described: perinatal hypoxic encephalopathy, cerebrovascular disorders or cerebromeningeal infections. LGS is also caused by malformations of cortical development or chromosomal disorders. In tuberous sclerosis, the LGS can occur with or without previous WS (52). Exome studies or case reports of patients with LGS have shown the role of other gene mutations such as GABRB3, ALG13, SCN8A, STXBP1, DNM1, FOXG1, CHD2 (53–55).

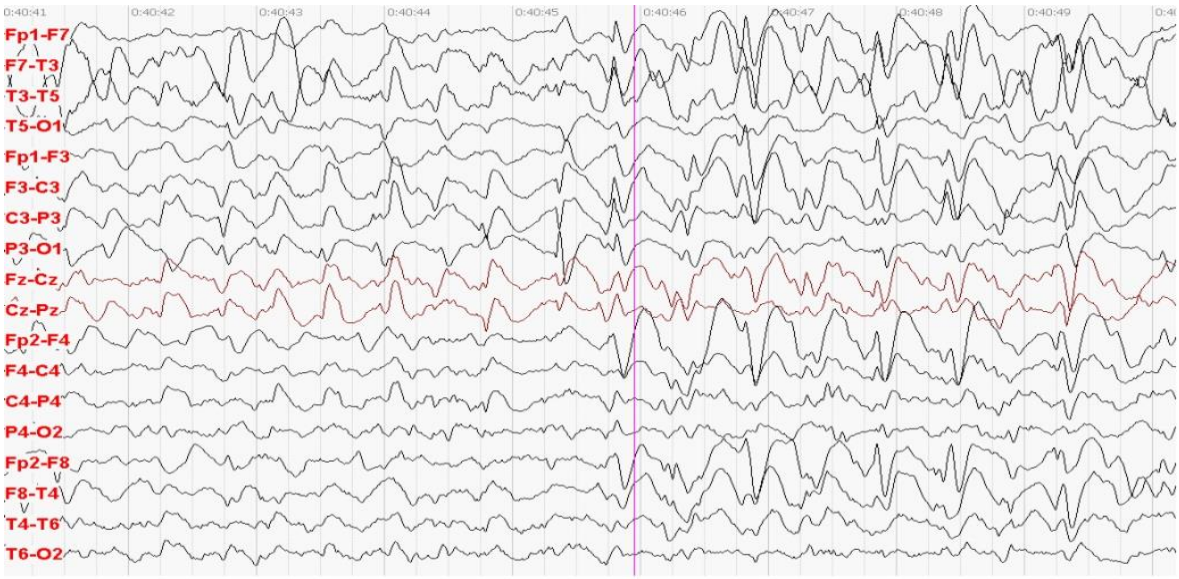

Fig. 14: ***Lennox-Gastaut syndrome:*** *Interictal EEG in a 15-year-old patient with Lennox-Gastaut syndrome of unknown etiology. Bifrontal bursts of slow spike-waves.*

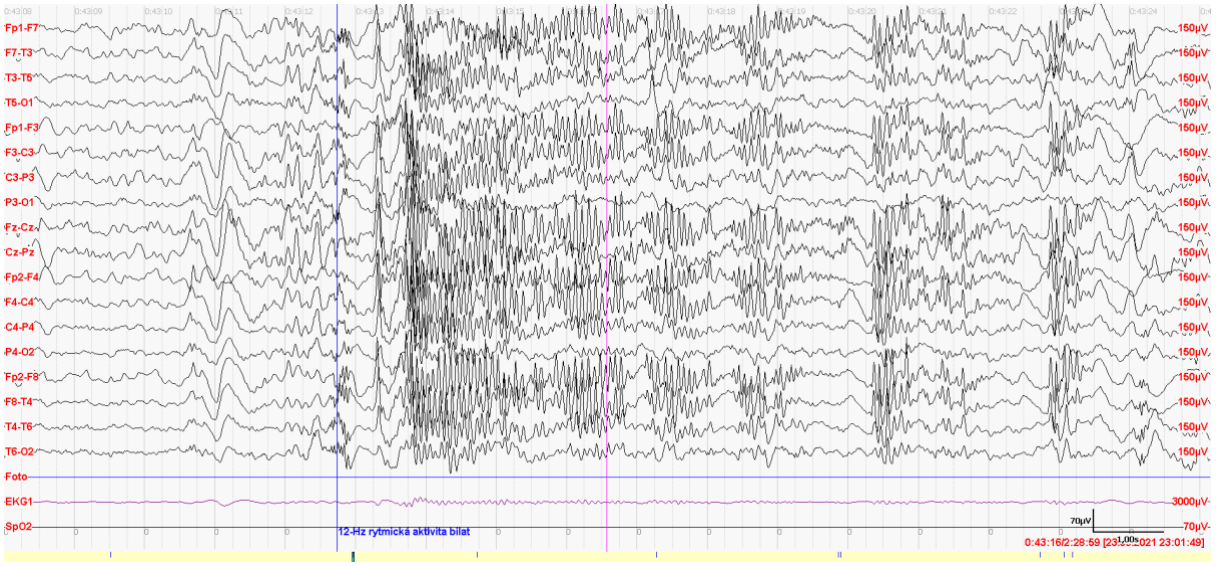

Fig. 15: ***Lennox-Gastaut syndrome:*** *Interictal sleep EEG in a 15-year-old patient with Lennox-Gastaut syndrome of unknown etiology. Generalized 12-Hz rhythmic activity with anterior dominance.*

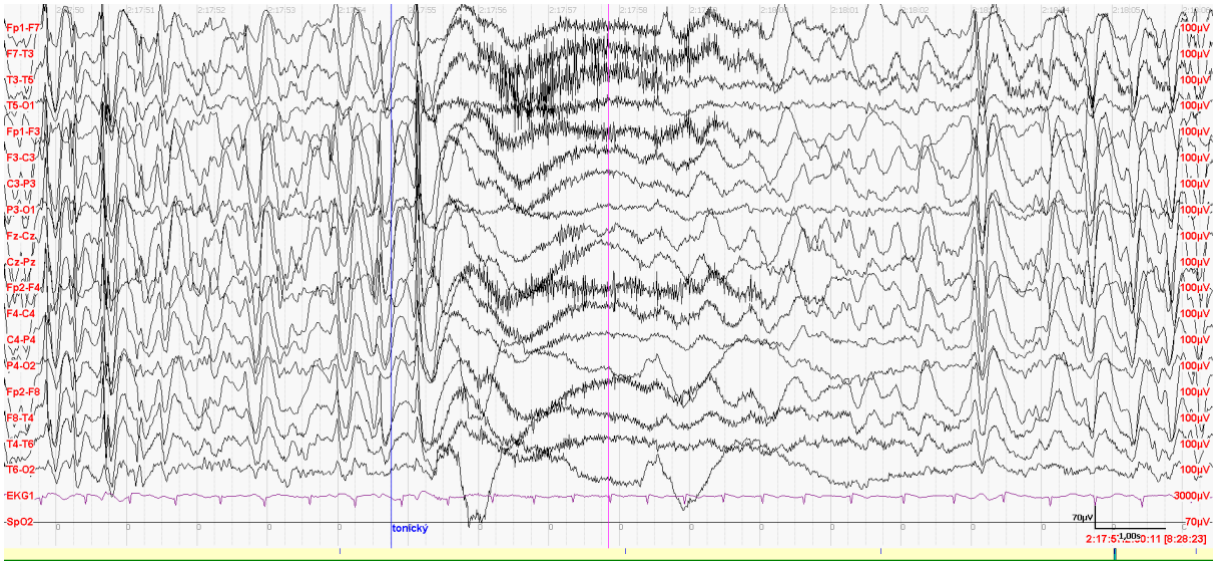

Fig. 16: ***Lennox-Gastaut syndrome:*** *Ictal EEG in a patient with Lennox-Gastaut syndrome of unknown etiology. Tonic axorhizomelic seizure with an initially high-amplitude complex, followed by low-voltage activity with fast rhythms.The discharge ends with slow delta waves with anterior dominance.*

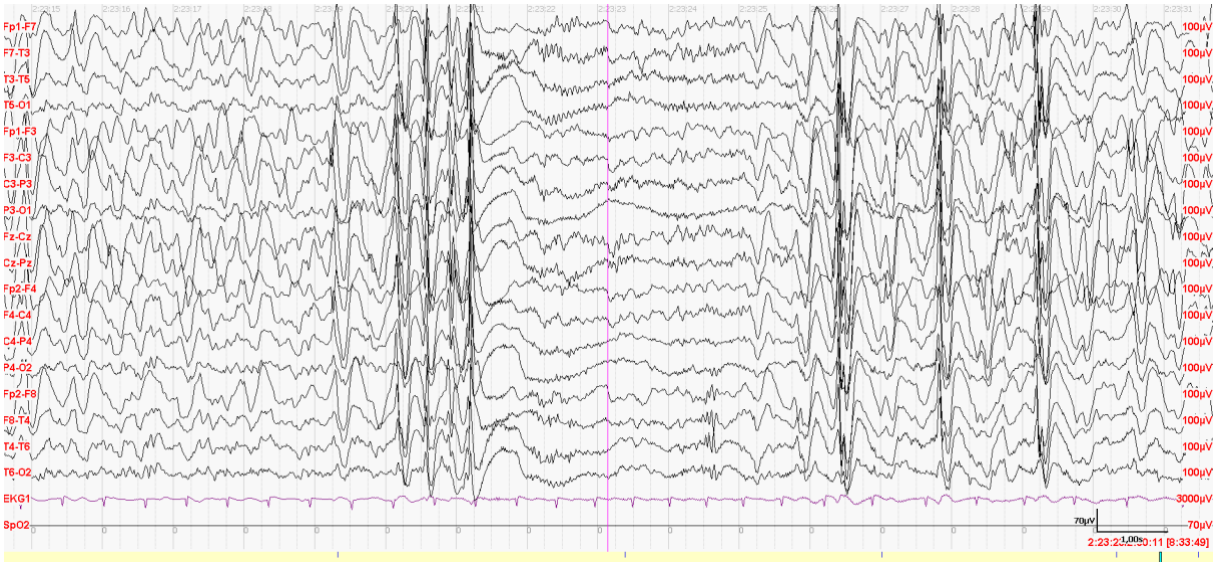

Fig. 17: ***Lennox-Gastaut syndrome:*** *Ictal EEG in a 15-year-old patient with Lennox-Gastaut syndrome of unknown etiology. Atonic seizure with ictal EEG correlate of brief generalized 3Hz spike/polyspike and slow wave complex. Atonic seizure is associated with the slow wave.*

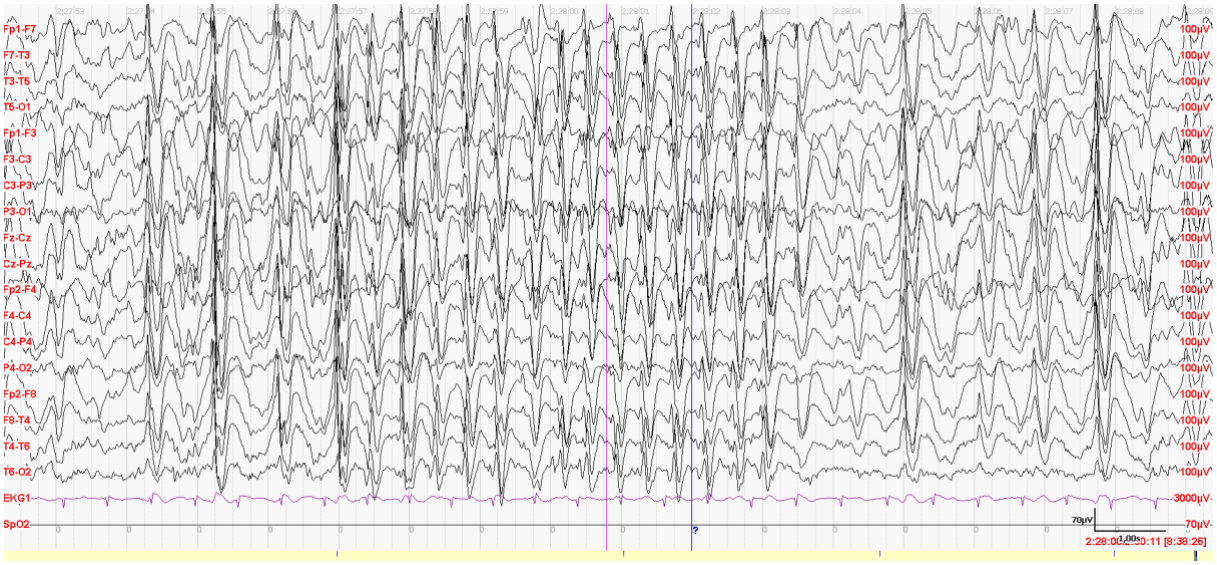

Fig. 18: ***Lennox-Gastaut syndrome:*** *Ictal EEG in a 15-year-old patient with Lennox-Gastaut syndrome of unknown etiology. Atypical absence seizure with ictal correlate of fluctuating generalized slow (1,5-2,5Hz) spike and wave complexes.*

Treatment: The LGS is one of the most pharmacoresistant epileptic syndromes. It is currently acknowledged that antiepileptic drug polytherapy is the most appropriate treatment due to the

severity of this type of epilepsy and to the wide range of seizure types with varying reaction to the different molecules. VPA is the first line treatment for LGS and especially in combination with LTG (56). VPA can also be combined with TPM, CLB, felbamate (FBM), LEV, rufinamide (RFN), ZNS. Two antiseizure drugs have special status as "orphan drugs" in the LGS: FBM and RFN. VNS can be very effective in patients with LGS with more than 50% responders in this group of patients. VNS can also improve cognitive skills, alertness, behavior, and sometimes intellectual ability and mood control (57). Another possibility of palliative surgical treatment in patients with LGS is corpus callosotomy. Callosotomy has been discussed in a large number of publications and clinical improvement was observed in 50 to 90% of subjects with more than 50% decrease in seizure frequency. It is particularly effective in reducing falls during atonic and tonic seizures (58). Deep brain stimulation of the centromedian nucleus of the thalamus has brought favorable results in LGS subjects (59).

1.4.2 Epilepsy syndromes of childhood period

1.4.2.1 Self-limited focal epilepsies in childhood

Self-limited focal epilepsies affect 25% of children with non-febrile seizures. They comprise three identifiable electroclinical syndromes recognized by the ILAE: Rolandic epilepsy, Panayitopoulos syndrome (PS) and the idiopathic childhood occipital epilepsy of Gastaut (ICOE-G) including the idiopathic photosensitive occipital lobe epilepsy.

1.4.2.1.1 Rolandic epilepsy (self-limited epilepsy with centro-temporal spikes)

Children develop infrequent focal seizures consisting of unilateral facial sensorimotor symptoms, oropharyngolaryngeal manifestations, speech arrest, and hypersalivation (7). Rolandic seizures are usually brief lasting for 1-3 minutes. 75% of seizures occur during NREM sleep, mainly at sleep onest or just before awakening.

EEG: Centrotemporal spikes (CTSs) are the hallmark of this epileptic syndrome. They are mainly localised in the C3 and C4 electrodes. CTSs are often bilateral activated by drowsiness and NREM sleep (Fig. 19).

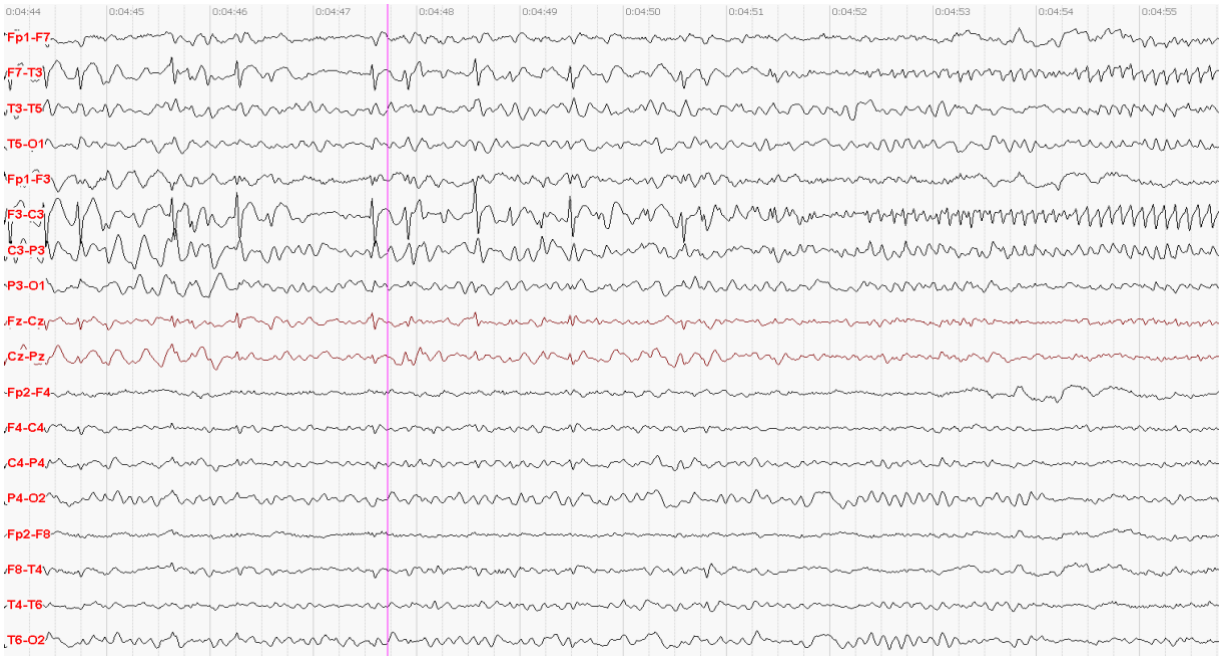

Fig.19: ***Self-limited epilepsy with centrotemporal spikes:*** *Left-sided centrotemporal spike and wave complexes in a 6-year-old child with Rolandic epilepsy, ictal onset of a typical rolandic focal motor seizure in the second part of the graph in the same region.*

CTSs and their impact on the neuropsychological profile of patients: Although Rolandic epilepsy used to be described as a "benign" epilepsy syndrome, many studies have revealed that a significant number of patients have some degree of neuropsychological impairment. Despite a favourable seizure outcome and normal intelligence, children with Rolandic epilepsy often have difficulties in various domains of neuropsychological functioning, such as behaviour (60), language (61,62), cognition (18,61,63), attention (17,19), and memory (19), which may lead to learning difficulties (62,64). A prominent comorbidity in children with Rolandic epilepsy is attention-deficit/hyperactivity disorder (ADHD) (17–19). The prevalence of ADHD in the general population is 3% to 7% (65); it is 31% in children with this type of epileptic syndrome (18).

Despite studies demonstrating the genetic basis of Rolandic epilepsy, the development of symptoms of this epilepsy syndrome and typical EEG discharges are age related and time limited. The prerequisite is thus the existence of a developmental window during which permissive factors appear that cause changes in the processes of the aging of affected brain areas. This developmental window is associated with cortical functional activity that can be

defined on the basis of regional cerebral blood flow (66) and local metabolic changes (67,68). At birth, the regional cortical cerebral blood flow is lower than in adults. After birth, it increases up to 5-6 years of age to values which are about 50-85% higher than in adults. It then decreases again and reaches adult values between 5-19 years (69). The time required to reach adult values varies depending on the area of the cortex. The shortest is in the primary cortex and the longest in associate cortical areas. The metabolic profile measured by glucose utilization is almost identical: low at birth, rising to 4 years of age when the child's brain consumes up to twice as much glucose as an adult, and then decreasing and reaching adult values at the age of 16-18. These changes correlate with an initial overproduction and subsequent elimination of excessive neurons, synapses, and dendrites, which can be seen in the developing brain (69). Early development of epilepsy can have long-term effects on the developing brain. The vulnerability of the developing brain emerges from impaired developmental processes such as synaptogenesis, dendritic branching, neural migration, and differentiation, rather than from neuronal death, which dominates in the case of development of seizures in adults when the brain is already matured (70). For this reason, it is possible to see more global autistic regression with more severe speech deficits in children with early development of ESES than in children with LKS with relatively later development where isolated speech regression is observed. Very different impacts of epilepsy can therefore be expected depending on the degree of the brain maturity when epilepsy becomes active. In a study (20), the author demonstrated that children with earlier seizure onset had lower IQs. In other neuropsychological testing, she found statistically significantly higher attention deficit and impulsivity in children with earlier onset of seizures. The results are supported by another study of 25 children with Rolandic epilepsy that proved that the early onset of seizures leads to worse results in neuropsychological testing of cognitive functions (71). Another study of 33 children with Rolandic epilepsy demonstrated that the patients with an average epilepsy onset at around 8 years were at higher risk of neuropsychological problems (64). In self-limited focal epilepsies, Rolandic epilepsy included, sleep increases the frequency of epileptiform discharges and the discharges remain high during the first phase of NREM sleep. During REM sleep, the frequency decreases; this decrease can also be observed in other NREM sleep cycles (64). The atypical development of Rolandic epilepsy to "Rolandic epilepsy plus" conditions shows that ongoing nocturnal epileptiform activity causes neuropsychological deficit and the level of severity depends on the rate of awake and sleep pathology (72). Night epileptiform discharges intervening during brain development may lead to the impaired development of neural networks involved in various neurocognitive functions. If these sleep discharges last for a certain time, they can lead to extensive

synaptogenesis with excess growth of the axons that ensure contact with the target cells. This interferes with the process of branching of neuronal processes, thus maintaining connections that should be eliminated. The affected neural network replaces the normal functional neuronal network at the cortical level and frequent epileptiform discharges encourage it to further growth so that it cannot be recovered (73). Slow wave activity (SWA) is the fundamental characteristic of NREM sleep on scalp EEG. Its neural correlate is the slow oscillation of membrane potentials of cortical neurons between depolarization and hyperpolarization. If these oscillations are synchronized and the majority of cortical neurons in a certain area are affected, they are detectable as slow waves on scalp EEG. The local increase in SWA during NREM sleep and the decrease in other phases of sleep is important for the plasticity of learning processes and synaptic homeostasis (74,75). The normal reduction of SWA during sleep is absent in patients with ESES. The interference of epileptiform discharges with normal sleep SWA may explain the cognitive deterioration in these patients (75).

In the author´s study (20), the results of detailed neuropsychological testing showed that the occurrence of discharges in total NREM sleep led to higher attention deficit and impulsivity in patients, but without proven statistical significance. The influence of epileptiform discharges in children with centrotemporal EEG pathology was examined in several studies (63,64,71). These studies found a significant negative impact of epileptiform discharge activation in patients with Rolandic epilepsy on their neuropsychological profiles.

Annex 3

Etiology: Rolandic epilepsy is genetically determined but the genetic factors are complex. The first clue to the epileptic cause of Rolandic epilepsy has led to pathogenic variants in the ELP4 gene (76), but other variants also appear in other locations: KCNQ2, KCNQ3 (77), GRIN2A (78), GABRG2 (79) or ZDHHC9 (80). Still, recent studies have yielded genetic and phenotypic heterogeneties supporting polygenic and complex inheritance pattern.

Treatment: In general, patients with infrequent, mild or nocturnal seizures may not need the antiseizure medication. STM, VPA or LEV can be used in specific cases. Sometimes we observe aggravation after CBZ or LTG administration (21).

1.4.2.1.2 Panayitopoulos syndrome

It is a common childhood-related idiopathic benign susceptibility to autonomic seizures and autonomic status epilepticus. Seizures comprise an unusual constelation of autonomic, mainly emetic symptoms, behavioral changes, unilateral deviation of the eyes etc. Autonomic status epilepticus can be observed.

EEG: Interictal EEG shows great variability in functional focal spikes at various electrode locations. Spikes are usually of high amplitude similar to CTSs. Two-thirds of patients have at least one EEG with occipital localisation of spikes (Fig. 20), the other one third never show occipital spikes.

Etiology: PS can be genetically determined although conventional genetic influences may be less important.

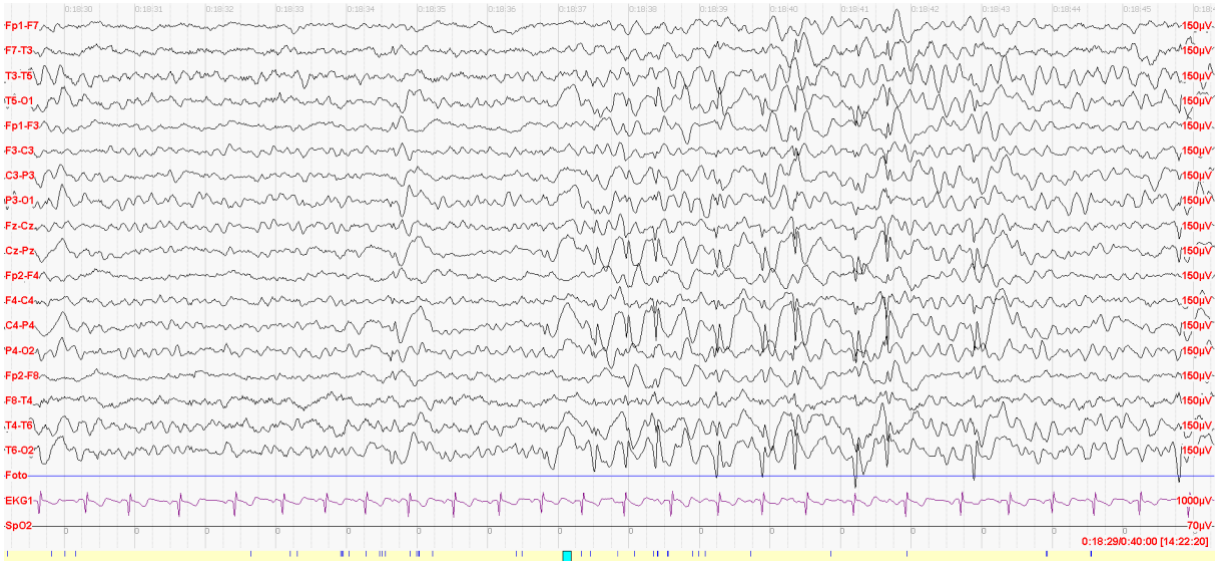

Fig. 20: ***Panayitopoulos syndrome:*** *Interictal EEG in a 7-year-old girl with Panayitopoulos syndrome: frequent spike and wave complexes in temporo-occipital regions with right sided amplitude dominance.*

Treatment: Prophylactic treatment with antiseizure mediacation is not reccomended, there is no increased risk of subsequent epilepsy or neurological deficit. Prophylaxis can be desired in multiple seizure reccurences. Most authors prefer CBZ or VPA. LEV can be used succesfully.

1.4.2.1.3 Childhood occipital epilepsy of Gastaut (COE-G)

Sizures are occipital and primarily manifest with elementary visual hallucinations, blindness or both. Postictal headache indistinguishable from migraine headache occurs in half of the patients.

EEG: The interictal EEG shows mostly occipital epileptiform discharges, which are usually bilateral and synchronous. They are activated in both occipital regions by the elimination of fixation and central vision.

Treatment: Patients often suffer from frequent seizures, and prophylactic treatment with CBZ is likely to be mandatory.

1.4.2.2 Encephalopathy related to status epilepticus during slow sleep (ESES) including Landau-Kleffner syndrome

The first description of subclinical status epilepticus induced by sleep in children dates back to 1971 (81). In 1978 Kellerman et al. first documented that patients with acquired epileptic aphasia or Landau-Kleffner syndrome (LKS) had an extreme activation of spike and wave discharges during slow sleep consistent with ESES (82). Actually, LKS is now considered a clinical variant of a subtype of ESES (83) (Fig. 22).

ESES syndrome is typically characterized by: focal and generalized seizures (clonic, tonic-clonic, absences), neurological deterioration, involving cognitive, behavioral and motor domains, typical EEG finding of electrical status epilepticus during sleep, defined as the appearance at sleep onset of a pattern of diffuse spike-and-waves occuring in up to 85% of slow sleep (Fig. 21).

Etiology: ESES is often seen in patients with important perinatal insults, hydrocephalus, malformations of cortical development and structural etiology in general. ESES has been observed, as a rare unfavorable evolution, in children with self-limited focal epilepsies (7).

Genetic factors are difficult to define. A recent review has provided an overview of all genetic etiologies which have been reported to be associated with ESES spectrum. The conclusion was that SCN2A, KCNQ2, KCNB1, KCNA2 and GRIN2A contributed to the etiology of many patients with ESES (84).

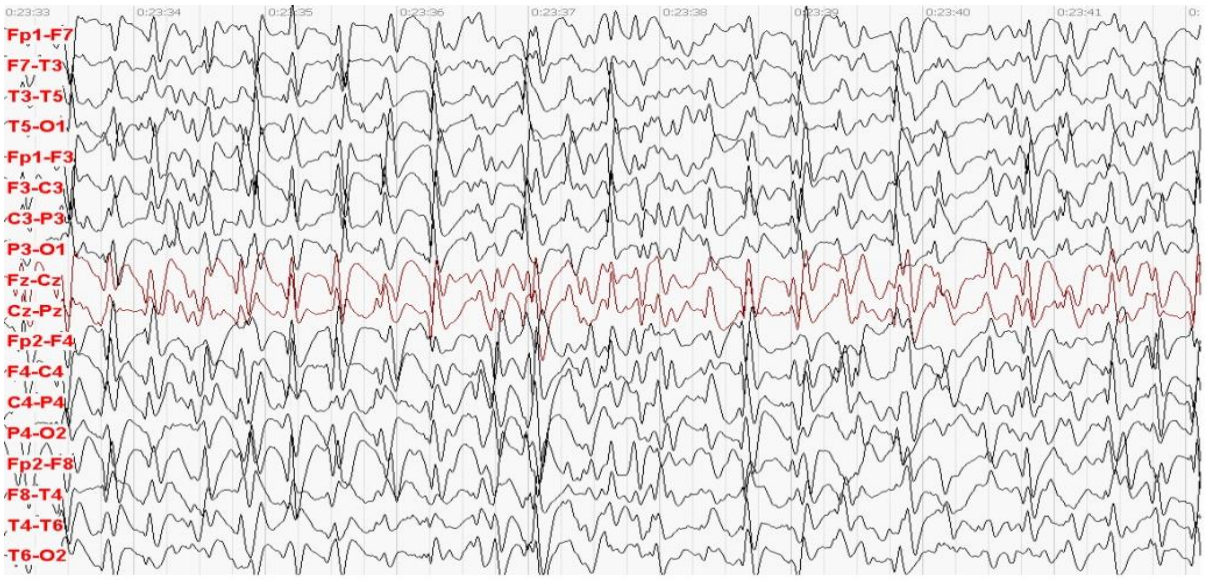

Fig. 21: ***Encephalopathy related to status epilepticus during slow sleep:*** *Continuous diffuse spike and waves activities during NREM sleep in a 5-year-old boy with ESES syndrome.*

Treatment: Therapeutic options must intend not only to reduce epileptic seizures but above all to "treat" the ESES responsible for the encephalopathy. BDZ, VPA, ESM, CBZ, PHT are the drugs most commonly used to treat the seizures. Taking into account the relationship between the occurence of ESES and the neuropsychological deterioration, a rapid aggressive therapy of ESES is mandatory. Treatment options include variety of antiseizure medications, immunosupressant treatments or surgical approach. Chronic oral treatment with CLB, CLZ associated with VPA or ESM seems to be effective. In drug-resistant cases, steroid treatment has been proposed (85). Intravenous immunoglobulins were also reported as succesful in some

cases (86). Limited evidence is available in favour of ketogenic diet, however there are some succesfully treated patients reported (87).

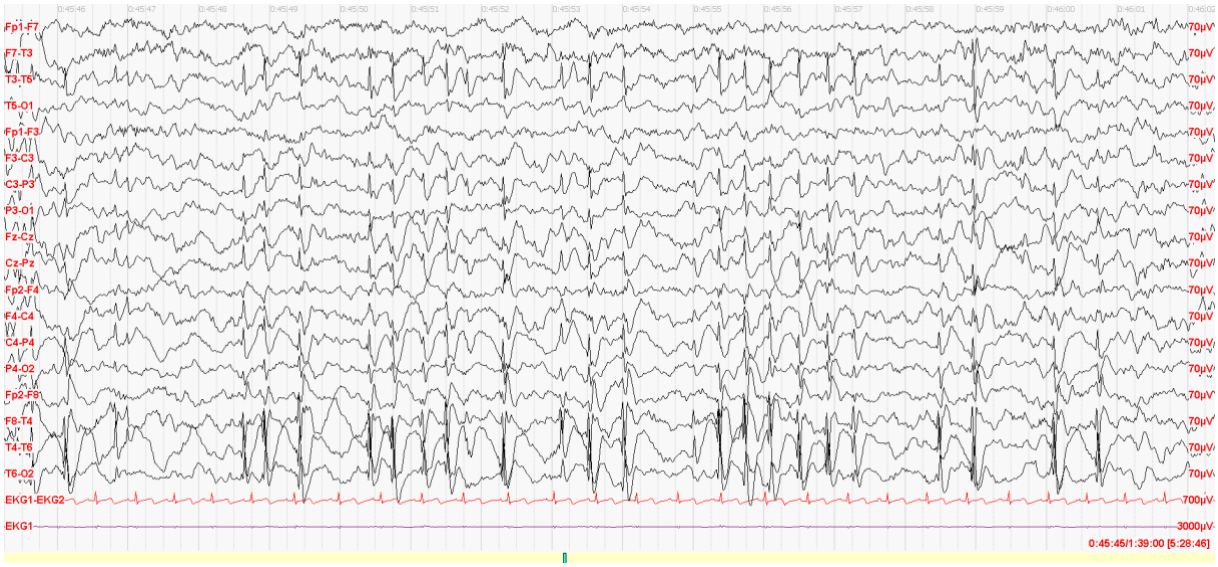

Fig. 22: ***Landau-Kleffner syndrome:*** *Continuous diffuse spike and waves activities during NREM sleep with right temporal dominance.*

1.4.2.3 Childhood absence epilepsy (CAE)

CAE is a genetic generalized epilepsy or idiopathic generlized epilepsy defined as follows: occurs in children of school age (age at onset between 4-10 years, peak manifestation age 6-7 years), with a strong genetic predisposition in otherwise normal children. It is characterized by very frequent typical absences with abrupt and severe impairment of consciousness. Automatism are frequent but have no significance in the diagnosis.

EEG: ictal discharges of generalized high-amplitude spike and slow wave complexes. They are rhythmic at around 3 Hz. Their duration varies from 4-20 seconds. Normal background activity (Fig. 23).

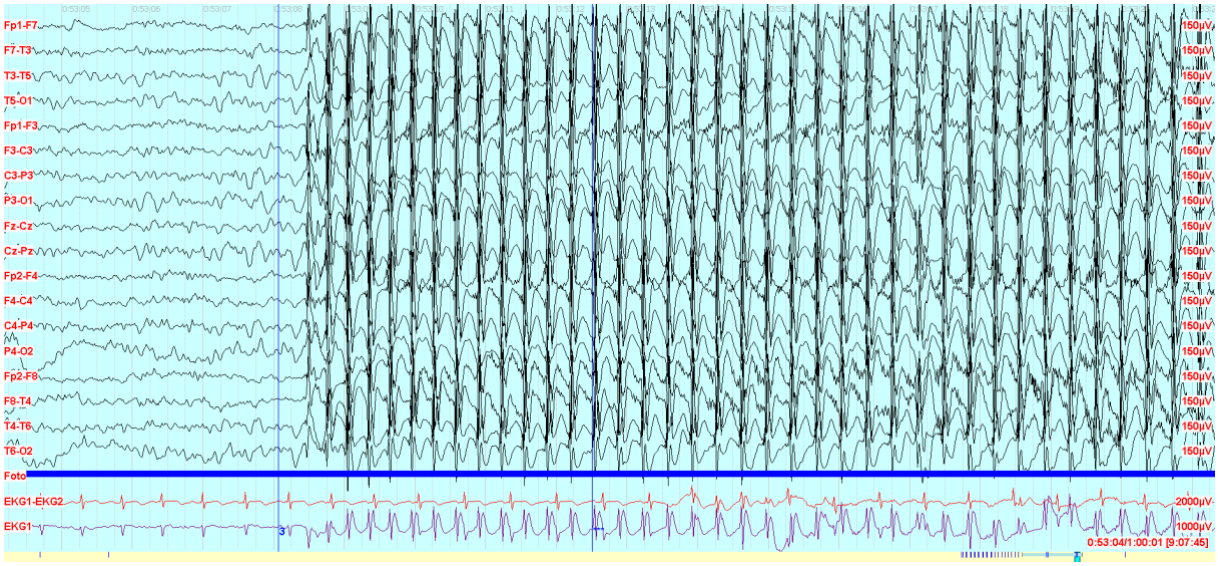

Fig.23: ***Childhood absence epilepsy:*** *Ictal EEG in a 5-year–old boy with CAE. Abrupt onset of generalized 3Hz SWC during hyperventilation.*

Treatment: ESM, VPA or LTG alone or in combination. Gradual withdrawal of medication is reccomended in patients with CAE who have been seizure-free for 1-2 years and have a normalized EEG.

1.4.3 Epilepsy syndromes of adolescence

1.4.3.1 Juvenile absence epilepsy (JAE)

JAE is an idiopathic (genetic) generalized epilepsy characterized by genetic predisposition, an average age at onset around puberty, no evidence of neurological or intellectual deficit. Seizures are typical absences, longer and less frequent than i CAE, GTCSs in 80% and sporadic myoclonic jerks in 20%.

EEG: the interictal EEG shows a normal background and ictal EEG shows generalized symmetric spike-waves or polyspike-waves with frontal accentuation. The frequency is usually faster than 3 Hz (3.5-4Hz) (Fig. 24).

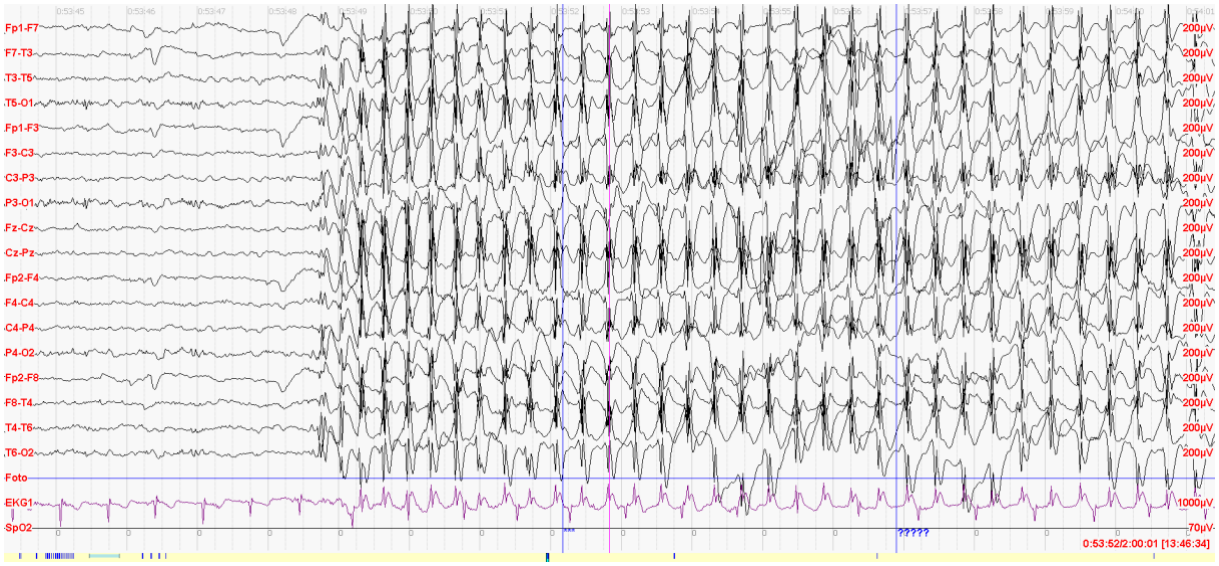

Fig. 24: ***Juvenile absence epilepsy:*** *Ictal EEG in a 9-year-old boy with JAE. Initial generalized PSWC discharge followed by 3.5-4Hz diffuse SWC activity.*

Etiology: The etiology of JAE is a subject primarily of a genetic research. The research results have shown that genetic mutations for voltage-gated sodium channels (CACNB4 gene) (88,89) and potassium channels (CLCN2 gene) (88) are involved. Different mutations were found in genes for GABA receptors (ligand ion channels), specifically in the GABRA1 gene (90).

Treatment and prognosis: Approximately 80% of cases become seizure-free with ESM and VPA, but the rate of relapse after drug discontinuation is probably close to 100% (91). As author already mentioned above, the study with 46 patients who met criteria for the diagnosis of JAE was performed in the Center for epilepsy Brno between 2006-2011 (16).

According to the type of seizure control during the five-year observational period (OP) and at the end of the OP, following outcome groups were defined:

1. Completely seizure free

2. Only absence seizures

3. Only GTCSs with a frequency 1 seizure per year

4. Only GTCSs with a frequency >1 seizure per year

5. Both GTCS and absence seizures; GTCSs with a frequency 1 seizure per year

6. Both GTCS and absence seizures; GTCSs with frequency >1seizure per year

The average patient age at the time of the first clinical manifestation was 12.9±5.6 years (ranged from 3 to 28 years). In 30 of the 46 patients (65.2%) the first clinical manifestation of JAE were absences, in 15 patients (32.6%) GTCS, and in 1 patient (2.2%) absence status epilepticus. In 43 patients (93.5%), at least one GTCS occurred in the course of the disease. At the end of the OP, 7 of the 46 patients (15.2%) had been seizure free during the whole OP (Group 1). In the same period, 8 patients (17.4%) had only absences (Group 2). Other types of predefined outcomes are presented in Fig. 25. In total, 31 patients (67.4%) experienced at least 1 GTCS during the OP. The assessment of antiseizure medication revealed that the number of drugs used in the history varied from 1 to 10 with an average of 3.8± 2.3 antiseizure drugs (Tab. 3). The most commonly used ASM in the series was LTG (25 patients; 12 in monotherapy and 13 in combined therapy), followed by VPA (20 patients; 5 in monotherapy and 15 in combined therapy) and LEV (11 patients; all in combined therapy). Other ASM used both in monotherapy and in combinations are noted in Tab. 3.

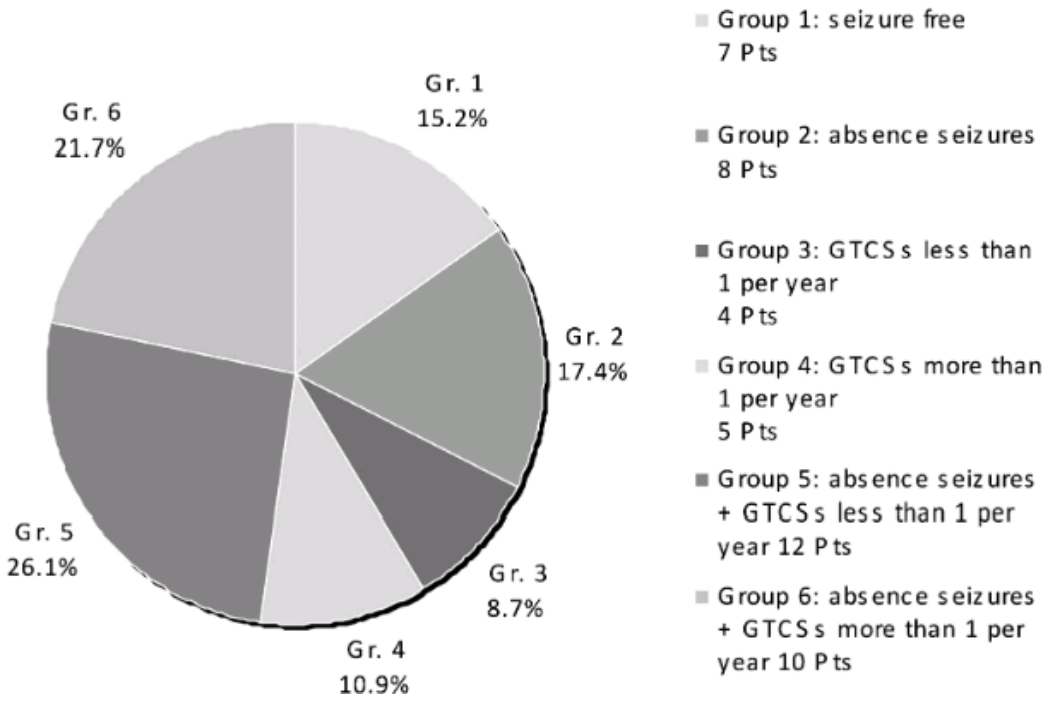

Fig. 25: Number of patients in different groups according to the rate of seizure control at the end of the OP (pts: patients)

Treatment type	AEDs	No. of pts.	Total no. of pts.
Monotherapy	LTG	12	20
	VPA	5	
	ETS	2	
	CBZ	1	
Combination of 2 AEDs	VPA + LTG	5	20
	VPA + LEV	4	
	LTG + LEV	3	
	TPM + ZNS	2	
	TPM + LTG	2	
	LTG + ZNS; LTG + ESM; CBZ + PRM; VPA + TPM	Each 1	
Combination of 3 AEDs	VPA + PRM + LEV; VPA + LEV + ZNS; LEV + LTG + ZNS	Each 1	3
Combination of 4 AEDs	VPA + LEV + CBZ + CLN; VPA + LTG + PRM + CLN; VPA + LTG + LEV + CLN	Each 1	3

No.: number; pts.: patients.

Tab. 3: AED treatment in the whole cohort of patients with JAE

There are some studies that indicate that the outcome of patients with JAE is not favorable as a rule. Wirell et al. (92) studied the prognostic factors of initial pharmacotherapy failure. According to the study results, only 3 of the 11 children with JAE (27.3%) were seizure free after the drug initiation (mostly VPA). There were 7 out of 46 patients (15.2%) seizure free (Group 1) during the OP in this study. These patients did not achieve seizure freedom after administration of 1 AED as we would expect. They tried 1–3 AEDs and only 5 of them (10.9%) stayed on 1 AED during the whole OP. Compared to the literature, Tovia et al. (93) presented nine of the 17 patients (52.9%) who were responsive for the first AED, but only 6 patients (35.3%) stayed seizure free on mono- therapy during the follow-up period. These results show that even in the group of patient who were seizure free, the seizure freedom was not achieved in the simple way and does not have to be permanent. They showed that the occurrence of GTCS predicted a worse prognosis (93). Only 37.5% of the patients in that study who experienced GTCSs were seizure free during the follow-up period, compared with 55.5% of patients without GTCSs. Similar results were observed by Trinka et al. (94) where the proportion of seizure free patients in the follow-up period who experienced GTCSs was 35% compared to 78% of the patients with only absence seizures. In this study, there was also a strong correlation between the mean follow-up duration and outcome, indicating a lower proportion of seizure-free patients with longer follow up periods. From this point of view, the occurrence of GTCSs during the course of the disease seems to be another important prognostic factor for the long-term outcome in patients with JAE. The author´s retrospective analysis of patients with JAE indicates that more than half of the patients with this epileptic syndrome show problems with seizure management and often require more AEDs to reach partial or total seizure freedom.

Annex 2

1.4.3.2 Epilepsy with myoclonic absences (EMA)

This epileptic syndrome is characterized by a specific seizure type: a myoclonic absence. Loss of contact and impairment of consciousness are of variable intensity, less pronounced than in CAE. The myoclonias are felt as a very disturbing experience. The duraton ranges from 10 to 60 seconds. In one third of patients, MA are the only seizure type observed throughout the evolution. GTCS were observed in 45% of cases.

EEG: the ictal EEG consists of rhythmic spike-wave discharges at 3 Hz that are bilateral, synchronous and symmetric. SW complexes are intermixed with polyspikes. Normal background activity.

Treamtent: Myoclonic absences can be completely controlled by VPA or ESM or in combination – in case GTCSs do not occur.

1.4.3.3 Juvenile myoclonic epilepsy (JME)

JME appears around adolescence and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall. No disturbance of consciousness is noticeable. Often, there are GTCSs and, less often, absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation.

EEG: Interictal and ictal EEGs have rapid, generalized, often irregular spike-waves and polyspike-waves, there is no close phase correlation between EEG spikes and clinical jerks. Frequently, the patients are photosensitive (Fig. 26).

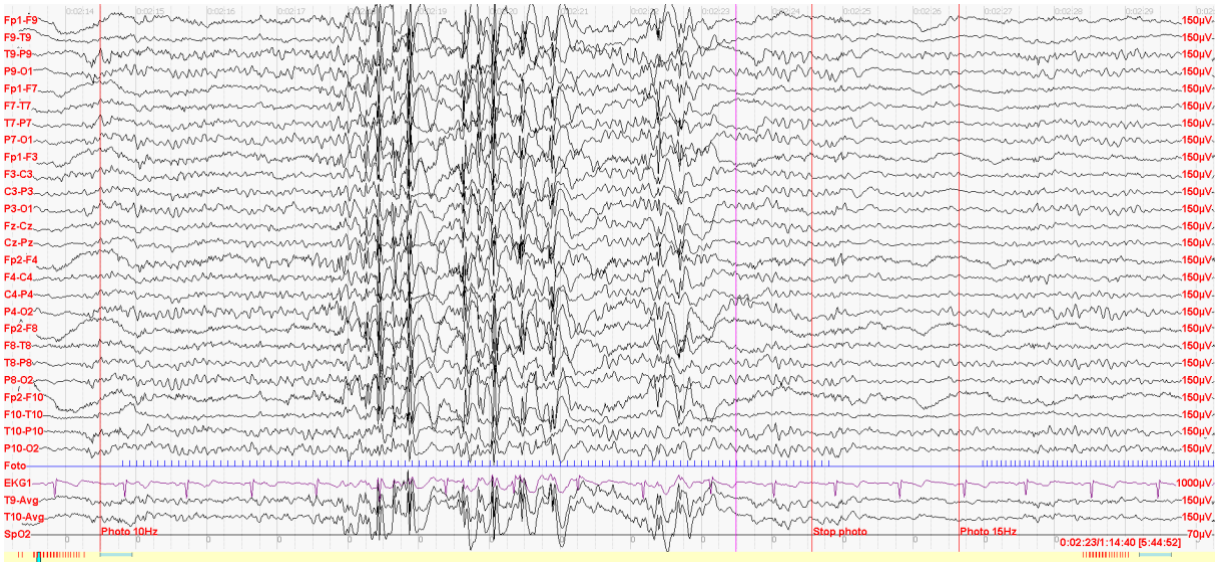

Fig. 26: ***Juvenile myoclonic epilepsy*** *in a 16-year-old girl. Generalized polyspike wave discharges during photostimulation with clinical correlate of myoclonic jerks. Normal background activity.*

Etiology: Family history is positive in one third of patients (95). Three genes have been identified in the etiology of JME: GABRA1 (96), EFHC1 (97) and ICK (98). Other susceptibility genes include: BRD2 (99) and 15q13.3 microdeletions (100). From a genetic point of wiev, JME appears highly heterogenous (21).

Treatment: Counseling of lifestyle is essential: avoiding of sleep deprivation, excessive alcohol intake and visual stimuli when patients are photosensitive.

Antiseizure medication is reccomended in almost all patients. LTG and LEV are considered as the first-line drugs, still we have to be careful with LTG for its potential to aggravate myoclonic jerks, which may occur after a long delay (21). TPM and ZNS can be considered second-line drugs, perampanel (PER) is promising. VPA was also prooved very effective, but it is no longer recommended for its side effects in the first-line therapy.

Prognosis: JME cannot be considered a truly benign conditon, although it may remit, at least partially, with age. Some patients are pharmacoresistant. A logical therapeutic attitude is to maintain treatment in most patients beyond early adulthood.

1.5 The new ILAE proposal for the classification of epileptic syndromes

In 2021, ILAE members presented four papers dealing with definitions of age-related epileptic syndromes. The ILAE acceptance process requires feedback and comments from individual members. These comments will be reviewed by the working group before the document is finalized and published. So far, the draft of this document can be viewed at: https://www.ilae.org/guidelines/definition-and-classification/proposed-classification-and-definition-of-epilepsy-syndromes.

The works are divided into 4 groups - the first deals with epileptic syndromes of neonatal and infant age, the second deals with epileptic syndromes in childhood, the third deals with epileptic syndromes of variable age at onset and the fourth with idiopathic generalized epilepsy.

1.5.1 ILAE Classification & Definition of epilepsy syndromes in the neonate and infant: Position statement by the ILAE Task Force on nosology and definitions

Syndromes are broadly divided into Self-limited epilepsies (where there is likely to be spontaneous remission) and Developmental and epileptic encephalopathies (disorders where there is developmental impairment related to both the underlying etiology independent of epileptiform activity and the epileptic encephalopathy). Etiology-specific epilepsy syndromes are due to specific genetic, structural, metabolic, immune or infectious etiologies, and have consistent electroclinical features, management and prognostic implications. Most etiology specific syndromes that begin in the neonatal or infantile period are DEEs. See Fig. 27.

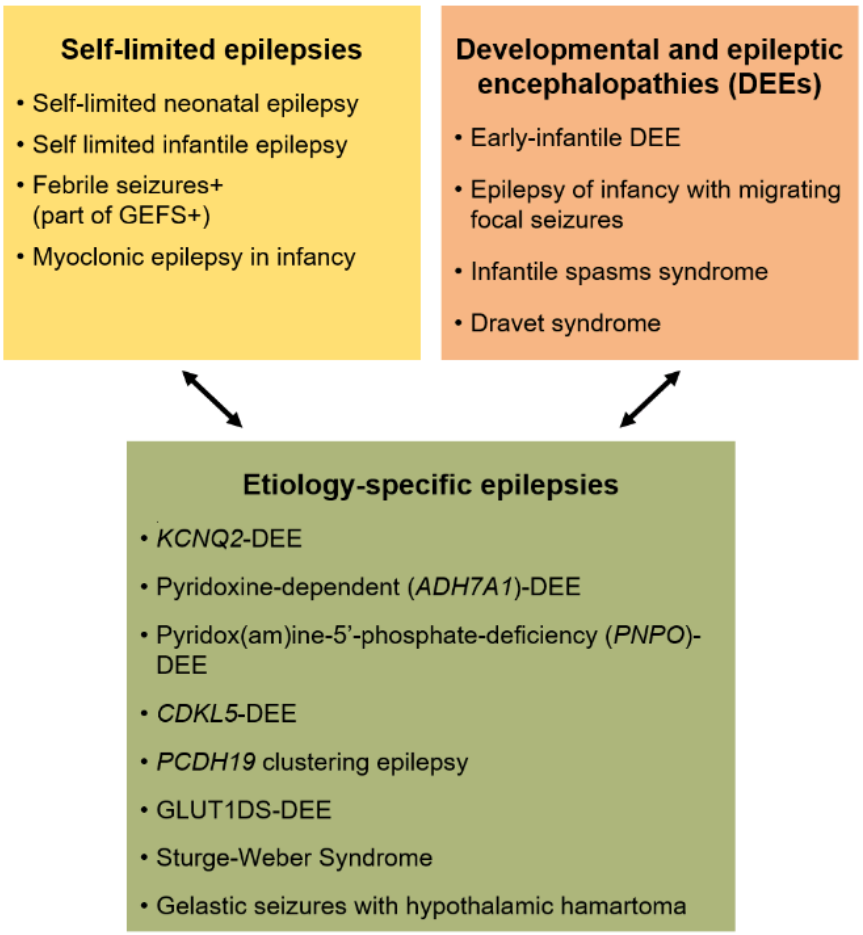

Fig. 27: ILAE Classification & Definition of Epilepsy Syndromes in the Neonate and Infant: Position Statement by the ILAE Task Force on Nosology and Definitions

https://www.ilae.org/guidelines/definition-and-classification/proposed-classification-and-definition-of-epilepsy-syndromes/proposed-classification-syndromes-in-neonates-and-infants

1.5.2 ILAE Classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on nosology and definitions

Here, too, based on the ILAE 2017 Classification of the epilepsies, the names of some syndromes were updated using terms directly describing the semiology of seizures. Epileptic syndromes beginning in childhood were divided into three groups:

1. Self-limited focal epilepsy, comprising four syndromes: Self-limited epilepsy with centrotemporal spikes, Self-limited epilepsy with autonomic seizures, Childhood occipital visual epilepsy and Photosensitive occipital lobe epilepsy;

2. Generalized epilepsy involving four syndromes: Myoclonic-atonic epilepsy, Childhood absence epilepsy, Epilepsy with myoclonic absences and Epilepsy with eyelid myoclonia;

3. Developmental and epileptic encephalopathies comprising four syndromes: Lennox-Gastaut syndrome, developmental and/or epileptic encephalopathy with spike-wave activation in sleep, Hemiconvulsion-hemiplegia epilepsy and FIRES (Febrile infection related epilepsy syndrome). For each syndrome, typical seizures, EEG findings, phenotypic specifics, and findings of other key examinations are defined. These syndromes are summarized in Tab. 4.

Epilepsy syndromes with focal seizures	Formerly known as	Epilepsy syndromes with generalized seizures	Formerly known as	Developmental and epileptic encephalopathies	Formerly known as
Self-limited Focal Epilepsies (SeLFE)		***Genetic Generalized epilepsies (GGE)***		***Developmental and epileptic encephalopathies (DEE)***	
SeLECTS *Self-Limited Epilepsy with Centrotemporal Spikes*	Childhood Epilepsy with Centrotemporal Spikes, (Benign) Rolandic Epilepsy, (Benign) Epilepsy with Centrotemporal Spikes	***MAE*** *Myoclonic-Atonic Epilepsy*	Epilepsy with Myoclonic-Atonic Seizures (Doose syndrome)	***LGS*** *Lennox-Gastaut syndrome*	No changes
SeLEAS *Self-Limited Epilepsy with Autonomic Seizures*	Panayiotopoulos syndrome, Early Onset (Benign) Occipital Epilepsy	***CAE*** *Childhood absence epilepsy**	Pyknolepsy, Petit mal	***D/EE-SWAS*** *Developmental and Epileptic Encephalopathy with spike-wave activation in sleep*	Landau-Kleffner syndrome, Epileptic Encephalopathy with Continuous Spike-Wave in Sleep, Atypical (Benign) Partial Epilepsy (pseudo-Lennox syndrome)
COVE *Childhood Occipital Visual Epilepsy*	Late-onset (Benign) Occipital Epilepsy or Idiopathic childhood Occipital Epilepsy – Gastaut type	***E-EM*** *Epilepsy with Eyelid Myoclonia*	Jeavons Syndrome	***FIRES*** *Febrile Infection-Related Epilepsy Syndrome*	Acute encephalitis with refractory, repetitive partial seizures (AERRPS), devastating epileptic encephalopathy in school-aged children (DESC)
POLE *Photosensitive Occipital Lobe Epilepsy*	Idiopathic Photosensitive Occipital Lobe Epilepsy	***E-MA*** *Epilepsy with Myoclonic Absences*	Bureau and Tassinari syndrome	***HHE*** *Hemiconvulsion-Hemiplegia-Epilepsy*	No changes

Tab. 4: ILAE Classification and Definition of Epilepsy Syndromes with Onset in Childhood: Position Paper by the ILAE Task Force on Nosology and Definitions

https://www.ilae.org/guidelines/definition-and-classification/proposed-classification-and-definition-of-epilepsy-syndromes/proposed-classification-syndromes-in-children/proposed-classification-syndromes-in-children

1.5.3 ILAE Classification and definition of epilepsy syndromes with onset at a variable age: Position statement by the ILAE Task Force on nosology and definitions – Fig. 28.

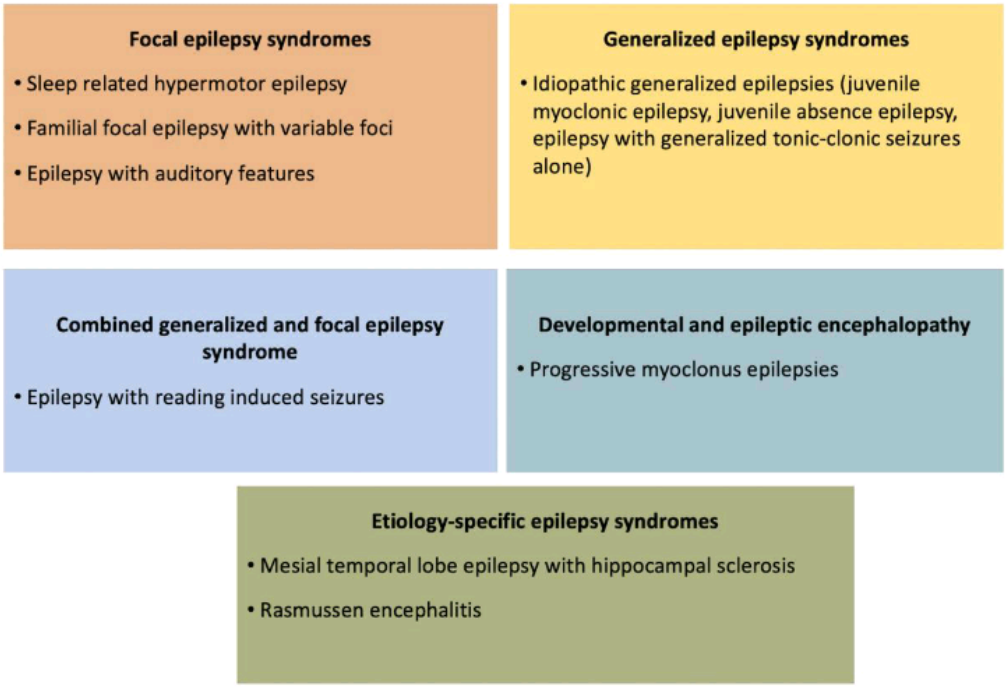

Fig. 28: The epilepsy syndromes that begin in adolescents, adults and at a variable age

https://www.ilae.org/guidelines/definition-and-classification/proposed-classification-and-definition-of-epilepsy-syndromes/proposed-classification-syndromes-with-onset-at-variable-ages

1.5.4 ILAE Definition of the Idiopathic generalized epilepsy syndromes: Position statement by the ILAE Task Force on nosology and definitions

The IGEs are a specific subgroup of Genetic Generalized Epilepsies, comprised solely of CAE, JAE, JME and GTCA. In addition to the IGEs, Genetic Generalized Epilepsies include:

1. individuals with generalized seizure types and generalized 2.5-5.5 spike-wave discharge on EEG who do not meet criteria for a specific syndrome

2. syndromes which have genetic overlap with the IGE syndromes but may also, at times, be associated with DEEs, such as Myoclonic-atonic epilepsy, Epilepsy with myoclonic absences

and Epilepsy with eyelid myoclonia; other syndromes such as Myoclonic epilepsy in infancy are more consistent with a generalized epilepsy which may have a developmental encephalopathy (ie. intellectual disability). Additionally, certain cases of GEFS+, with only generalized seizure types could be classified as GGEs, but individuals with GEFS+ and focal seizures would not be included. The triangles denote individuals with generalized epilepsies and developmental delay/intellectual disability (dark blue) and those with DEEs (light blue). The distinction between these two groups is that patients with DEEs have developmental slowing or regression with frequent epileptiform activity on EEG and/or frequent seizures. See Fig. 29.

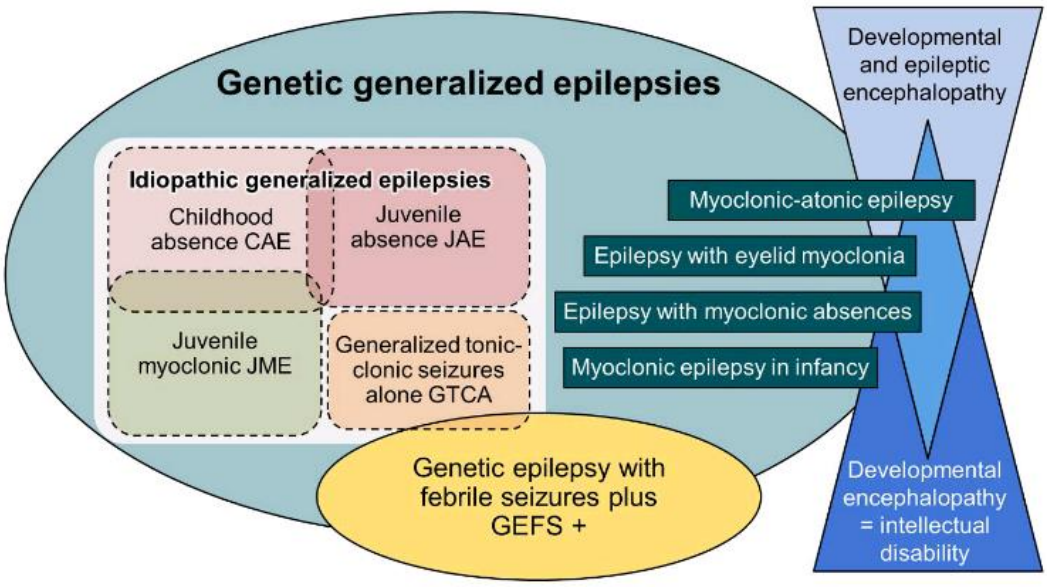

Fig. 29: ILAE Definition of the Idiopathic generalized epilepsy syndromes: Position statement by the ILAE Task Force on nosology and definitions

https://www.ilae.org/guidelines/definition-and-classification/proposed-classification-and-definition-of-epilepsy-syndromes/proposed-classification-idiopathic-generalized-epilepsies

1.6 Etiology

The creation of a new classification of the epilepsies has been more than desirable for a long time, especially in terms of fast scientific development (not only) in the field of epileptology. New possibilities for neuroimaging, the revolutionary development of genetics with the domestication of new genetic methods such as next-generation sequencing (NGS panels, whole-exome sequencing (WES), etc.), discoveries in molecular biology and a number of other factors have shown that the ILAE 1989 Classification of the epilepsies is not sufficient.

In the ILAE 2017 Classification of the epilepsies, there is a parallel division of epilepsy according to etiology into six groups: structural, genetic, infectious, metabolic, immune and of unknown etiology (Fig. 3). There is no hierarchy in this division and the classification of a patient into a given group depends on different circumstances. For example, a patient with tuberous sclerosis may be included in the structural group if epileptosurgery is crucial for further treatment of this patient, or in the genetic group, which in turn is important in terms of genetic counseling and/or new therapeutic options such as in the case of mTOR inhibitors (14).

1.6.1 Structural etiology

The concept behind a structural etiology is that a structural abnormality has a substantially increased risk of being associated with epilepsy based on appropriately designed studies (14). Structural etiologies may be acquired such as stroke, trauma, infection, or genetic such as many malformations of cortical development. Identification of a subtle structural lesion requires appropriate MRI studies using specific epilepsy protocols (101). There are well recognised associations within the epilepsies with a structural etiology (eg. temporal lobe seizures with hippocampal sclerosis, gelastic seizures with hypothalamic hamartoma, Rasmussen syndrome and hemiconvulsion-hemiplegia epilepsy) (14).

Another interesting point is that the underlying basis for a structural abnormality may be genetic or acquired or both. For example, polymicrogyria may be secondary to mutations in genes such as GPR56, or acquired secondary to intrauterine cytomegalovirus infection (102).

1.6.2 Genetic etiology

The concept of a genetic epilepsy is that it directly results from a known or presumed genetic mutation in which seizures are a core symptom of the disorder.

Firstly, the genetic etiology of epilepsy can be presumed on the basis of positive family history of an autosomal dominant disorder. For example, in Benign familial neonatal seizures, most families have mutations of one of the pottasium channel genes, KCNQ2 or KCNQ3 (103). Genetic etiology can also be suggested by clinical research in populations with the same syndrome, such as JME (14).

If the epilepsy syndrome is accompanied by dysmorphic features, cognitive regression and autism-like features, one can start looking for structural variants like copy number variants (CNVs), deletion/duplication by array comparative genomic hybridisation (CGH-array). In single gene epileptic disorders, a specific gene may be targeted (eg. tuberous sclerosis complex TSC1, TSC2) or a panel of multiple genes associated with a specific phenotype in a so-called panel that can target hundreds of genes (21).

Next generation sequencing (NGS) is currently experiencing a great boom in the diagnosis of epilepsy; NGS is revolutionary especially in terms of the possibility of simultaneously examining many genes. Combining NGS with CNV analysis (exon-level deletion/duplication analysis) makes it possible to detect most disease-causing variants in epilepsy genes in a single test. NGS testing includes not only specific gene panels, but a methodology that can encompass the entire exome (whole exome sequencing, WES) or genome (whole genome sequencing, WGS), methods that have the potential to further increase the yield of genetic testing in patients with epilepsy. Geneticists interpret and report detected sequence variants on the basis of currently valid recommendations according to the American College of Medical Genetics and Genomics (ACMG) (104). Thus, each sequence variant is included in the group of pathogenic (P), likely pathogenic (LP), benign (B), likely benign (LB), or with uncertain significance (VUS). The thorough genotypic-phenotypic correlation and interpretation of genetic results from the neurological-epileptological point of view, taking into account other anamnestic data, is an integral and crucial part of the process of interpreting the result of NGS; it importantly increases the diagnostic yield of NGS examination. Knowing the genetic cause of epilepsy in a patient opens new horizons in terms of understanding the pathophysiology of the epileptological process, and it also creates a space for the study of pharmacological models of antiepileptic drugs. The definition of precision medicine thus takes on real proportions in some patients with epilepsy.

NGS of multiple disease-related genes is an effective tool for diagnosing the cause of epilepsy (105–108). This finding is particularly true for early onset epileptic encephalopathy, which has been reported to have a higher proportion of monogenic causes than other epilepsies (109).

The author performed a single-centre retrospective study with total of 175 patients (95 males and 80 females) aged 0-19 years. They were examined between 2015 and 2020 using an NGS epilepsy gene panel (255 genes). The results show a 26.28% yield of NGS epilepsy gene panel with 255 genes associated with epilepsy (110). The yield of different multigene panels varies from 18% to 48%, depending on the results of various studies (111). The individual panels differ in the number and proportion of individual genes; after careful examination, it is clear that there is no direct relationship between the number of genes in the NGS epilepsy gene panel and its yield. It is evident that only a few genes are still repeated in the results, and the SCN1A, KCNQ2, CDKL5, SCN2A, and STXBP1 genes are most often represented in positive cases (111). Thus, the diagnostic yield of the NGS panel appears to be determined by the number of commonly mutated genes included in the panel rather than the total number of genes in the panel (112). It is worth mentioning the comparison of the yield of the NGS epilepsy gene panel and examinations using WES or WGS technique. The largest meta-analysis from 2021 shows that the yield of the NGS panel was on average 24%; WES was 27.2%, i.e. slightly higher. A smaller meta-analysis showed the yield of WES analysis was 31% (113). The truth is that accurate quantification of the positive results of WES analysis is very difficult given that WES is very often tested in patients with negative results using the NGS epilepsy gene panel technique. If WES is performed independently of the NGS multiple gene panel, its yield may be significantly higher (19% vs. 37%) (106).

Consistent with the world literature (112,114) is the fact that the age at epilepsy manifestation in positive patients is lower. The mean age of epilepsy manifestation in the author´s group was around 2.5 years; in the children who tested positive it was 1.5 years and in the children with a negative result it was almost 3.5 years. It is also worth noting that cohorts with patients with early onset epilepsy encephalopathies, i.e. children at neonatal age (0-3 months), show a higher yield of NGS panel. Costain et al. even showed a panel yield in children under 12 months of 72% (106), higher yields in newborns (37.1%) were also shown in the study by Ko et al. (114). These results are in line with the author´s observation, in which the yield in the group of children under 3 months was 38.46%. These observations are logical and are based on the fact that severe developmental and epileptic encephalopathies manifest in the neonatal period and a serious clinical picture often requires prompt diagnosis leading to the detection of the cause and the

introduction of possible specific therapy in indicated cases. Therefore, these children receive a genetic diagnosis much earlier. For these reasons, genetic diagnosis using new multi-gene sequencing techniques is recommended as a standard diagnostic tool for children with neonatal DEE (108,115). Making an early molecular diagnosis can also end the genetic odyssey, enable recurrence risk counselling, guide participation in gene-specific clinical trials, and provide families with the opportunity to interact with support groups or advocate for research (105). Oates et al. showed that early genetic diagnosis in children with DEE can reduce costs up to 70% compared to its failure (116). The argument based on the high cost of genetic testing therefore seems unfounded.

Few studies have emphasized the precise systematic and standardized procedure in interpreting the results of the NGS panel (107,114). Accurate interpretation of NGS panel results includes several key areas:

1. population data and database review
2. computational data, allelic data, and literature review
3. clinical review and family study
4. consensus multidisciplinary discussions (107).

The results of this work show that the multidisciplinary approach led to a definitive diagnosis in some patients with novel not previously described variants and increased the diagnostic yield of NGS analysis from 30 to 46 patients, which is by 53.33%. This is very important from a clinical point of view.

Annex 4

The author has dealt with the genetics and clinical spectrum of Dravet syndrome since the introduction of its diagnostics at the Department of Pediatric Neurology, Faculty of Medicine, Masaryk University and University Hospital Brno in 2011 into clinical practice. Diagnostics is performed in the Center of Molecular Biology and Gene Therapy, Faculty of Medicine, Masaryk University and University Hospital Brno. Its implementation into practice has brought new insights into the genetics of epilepsy. In up to 80% of cases, patients with Dravet syndrome have a pathogenic variant in the SCN1A gene (37). Interestingly, this pathogenic variant can

lead to very variable clinical expression, from genetic epilepsy with febrile seizures plus (GEFS +) to Dravet syndrome with a very severe clinical course. In her works, the author studied case series of patients with DS (117,118), wrote a review concerning the clinical course of Dravet syndrome in childhood (119) and adulthood (120).

The author and her team studied the structure of the SCN1A channel in relation to individual pathogenic sequence variants and phenotypic expression (121). This study included 6 patients with pathogenic sequence variant in SCN1A gene, 3 males and 3 females. Clinical characteristics of all patients are summarized in Tab. 5. In 3 patients (50%), a milder clinical phenotype was observed, which was mainly associated with the occurrence of recurrent febrile convulsions or GTCSs. Neurological examination was normal. In 2/3 of patients, the genetic analysis showed a positive family history for an identical pathogenic sequence variant. In both patients, the carrier was the father. The parents also had a very mild course of the disease. However, the DS phenotype was observed in 50% of patients. Status epilepticus was reported in 66% of these patients. All of them suffered from various seizure types (myoclonic, GTCS, absence, focal motor seizures). In 2/3 of patients with this severe phenotype, there was an alteration of the neurological status and pathogenic sequence variants were all *de novo.* Based on the knowledge of the particular sequence variant, these were localized into a particular region of the alpha one subunit of the sodium channel (Fig. 30). The authors report the correlation of the clinical course of the disease and the localization of the pathogenic sequence variant in the SCN1A gene. Missense mutations located in the pore region or in the region of the voltage sensor predict so-called „loss of function“, or „partial loss of function“, ie severe functional impairment (LOF, p-LOF). Mutations located in the terminal region or in the region of the D-linkers, which are remote from the pore region, cause rather milder phenotype (121). Missense mutations in other regions cause heterogeneous manifestations. However, for a more accurate analysis of a specific degree of functional damage, it is necessary to perform a functional analysis.

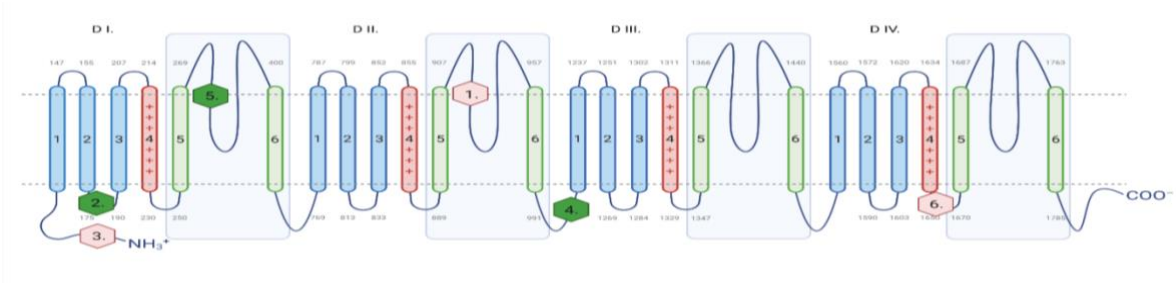

Fig. 30: Localisation of pathogenic sequence variants in the α-1-subunit of the SCN1A channel. Patients´ pathogenic sequence variants marked 1-6 (121).

	Sex	Year of birth	Age at epilepsy onset (months)	Seizure provocation	Seizure type	Status epilepticus	Neurological status	Family history of epilepsy	Type of mutation	Fenotype
1.	F	1999	16	+	Febrile seizure, focal myoclonus, GTCS	0	Attention deficit, learning disability, memory deficit	0	missense	SMEI
2.	M	2015	16	+	Febrile seizure	0	normal	+ (father)	missense	GEFS+
3.	M	2017	4	+	Febrile seizure	+	normal	0	missense	SMEI
4.	M	1986	36	+	Febrile seizure GTCS	0	normal	0	missense	GEFS+
5.	F	2018	15	+	Febrile seizure	0	normal	+ (father)	missense	GEFS+
6.	M	2020	4	+	Myoclonus, GTCS	+	hypotonie centr. typu, mikroccefalie, invertované bradavky	0	missense	SMEI

Tab. 5: Clinical characteristics of patient with DS included in the study, patients 1-6 (121).

Annex 5, 6, 7, 8

The phenotypic expression of a given pathogenic sequence variant is dependent on many factors in its expression. As noted above, localization of the product of the mutation near a significant portion of the channel leads to a more severe phenotype than localization at sites less important

for channel function, and this is certainly logical. The next point of view is whether the product of the mutated gene has a so-called "gain of function" or "loss of function". An illustrative case is in the GNAO1 gene. Mutations in GNAO1 were first reported in patients with Ohtahara syndrome and early infantile epileptic encephalopathy 17 (EIEE17) (122,123). But the clinical course can be very different and patients with GNAO1 patogenic variant can present with movement disorder. GNAO1 (guanine nucleotide-binding protein 1) encodes the α-subunit of a heterotrimeric guanine nucleotide-binding protein (Gαo) which is the most abundant membrane protein in the mammalian central nervous system (124). The author reported a case of a 12-year-old boy with GNAO1 mutation who presented with severe biballistic symptomatology with dystonic features (DSAP 3) and required emergency deep brain stimulation (DBS) to avoid life-threatening symptoms (125). The boy was first examined at the Department of Pediatric Neurology at the age of 2 years. At the age of 12 years, the patient deteriorated after respiratory infection and worsening of extrapyramidal symptomatology with dominating biballism and dystonic features developed with the threat of status dystonicus. He experienced almost continuous generalized ballistic movements combined with dystonic postures, which were very painful and limited his normal activity, feeding, or sleep (DSAP 3). The patient was hospitalized in the ICU with the necessity of muscle relaxation. Taking into consideration the seriousness of this condition, DBS of bilateral globus pallidus internus (DBS-GPi) was performed. The sedative medication was gradually tapered off over the next 14 days and his condition rapidly improved to DSAP 1. Half a year after DBS, motor functions returned to the condition before the brittle biballism-dystonia developed. Whole exome sequencing (WES) identified a heterozygous missense variant in GNAO1 gene c.625 C>T; p. (Arg209Cys) previously described in the study by Koy et al. (2018) (126) and considered as pathogenic. The mutation was absent in the patient's parents and considered as *de novo*.

When pre-status dystonicus persists despite orally active anti-dystonia drugs and unsuccessful weaning from sedative or anesthetic agents, intrathecal baclofen or deep brain stimulation should be considered (124). Several case reports and one small series have been published in which DBS was effective in patients with a GNAO1 mutation (123,126) . DBS may be effective due to its general effects in modulating aberrant synchronization in the basal ganglia-thalamo-cortical loops. The effect of DBS in our patient was very fast, with the improvement to DSAP 1 in 14 days. The patient tolerated the stimulation very well; however, only 3 months after initiation he developed generalized epileptic seizure. It is uncertain whether this occurred as a result of DBS (potentially triggered by tapering off the medication during the switching on and

adjusting the DBS parameters) or was merely a coincidence in a patient with a history of epilepsy. In any case, stimulation should be increased cautiously and mildly in patients with epilepsy. After the introduction of LEV, no further seizures occurred. In patients with GNAO1 mutation and severe dystonia, GPi-DBS could be a treatment option with life-saving potential.

Annex 9

1.6.3 Infectious etiology

The concept of an infectious etiology is that it directly results from a known infection in which seizures are a core symptom of the disorder. It is the most common etiology of epilepsy and accoridng to specific regions can be caused by neurocysticercosis, tuberculosis, HIV, malaria, toxoplasmosis and congenital infections such as Zika virus or cytomegalovirus (14).

1.6.4 Metabolic etiology

Metabolic causes refer to a well delineated metabolic defect with manifestations or biochemical changes throughout the body such as porfyria, uremia, amino-acidopathies or pyridoxine dependent seizures. In many cases, metabolic disorders will have a genetic defect. The identification of specific metabolic causes of epilepsy is extremely important due to the imlications for specific therapies and potential prevention of intellectual impairement.

1.6.5 Immune etiology

A range of immune epilepsies has been recently recognised with characteristic presentations in both adults and children (127). Diagnosis of these autoimmune encephalopathides is rapidly increasing, particularly with greater access to antibody testing. The most common are anti-NMDA receptor encephalitis and anti-LG1 encephalitis.

1.2.1 Unknown etiology

There remain many patients with epilepsy for whom the cause is not known.

1.7 Developmental and epileptic encephalopathies

This section is dedicated to a relatively new entity that is of immense importance from the point of view of pediatric epileptology.

The term "epileptic encephalopathy" was redefined in the Berg et al. 2010 report (6) as where the epileptic acitvity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone. In an epileptic encephalopathy, the abundant epileptiform activity interferes with development resulting in cognitive slowing and often regression, and sometimes associated with psychiatric and behavioral consequences. A key component of the concept is that amelioration of the epileptiform activity may have the potential to improve the developmental consequences of the disorder.

The influence of epileptiform discharges on development and cognitive functions is evident not only in severe epileptic encephalopathies, but also in the so-called "benign" syndromes, as the author explains in the previous part of the work dealing with Rolandic epilepsy.

Many of the genetic epileptic encephalopathies also have developmental consequences arising directly from the effect of the genetic mutation, in addition to the effect of the frequent epileptic activity on development. A well-known example is Dravet syndrome, in which developmental slowing occurs between one and two years of age, at a time when epileptiform activity on EEG is typically not yet frequent. This suggests a developmental component in addition to an epileptic component with both occuring secondary to the underlying sodium channel subunit gene (SCN1A) mutation. Another example is in KCNQ2 encephalopathy or STXBP1 encephalopathy where the epilepsy settle down relatively early in the child´s history but the developmental consequences may remain profound. These reasons lead to the concept of "developmental and epileptic encephalopathy" where both aspects are involved (14).

Common epileptic syndromes such as Ohtahara syndrome, West syndrome, Lennox-Gastaut syndrome, etc. are wll known and described. They are clearly defined, clinically and electrographically, and we can see these patients in everyday practice. In the light of the development of novel genetic techniques, we went much further, to the level of individual genes and gene sequence variants, so we clarified the etiology in number of patients with these epileptic syndromes and began to notice gentle nuances in the clinical and EEG manifestation. Then, we can find that Ohtahara syndrome may have slightly different specifics in patients with KCNQ2 mutation than in patients with SCN2A mutation, and we arrive at the concept of SCN2A-related or KCNQ2-related developmental and epileptic encephalopathies. We can specify the disease at the genetic level and thus differentiate subtle phenotypic variations in the spectrum of clinical manifestation. In cases, where a genetic variant of mayor effect is identified, the term "developmental and epileptic encephalopathy" may be subsumed by using the name of the underlying condition (for example STXBP1-related DEE) (14).

An example can be a group of 6 patients with a pathogenic sequence variant in the SCN2A gene, who have been diagnosed and treated at the Department of Pediatric Neurology, Faculty of Medicine, Masaryk University, University Hospital Brno. A detailed description is shown in Tab. 6. This case serie was presented by the author at the 54th Czech-Slovak Pediatric Neurology Conference in 2021 (128).

	pathogenic variant	origin	protein domain	age at seizure onset (months)	time to genetic diagnosis (months)	epilepsy syndrome	neurological examination	MRI	anti-seizure medication
1	SCN2A (NM_001040143.1): c.2642T>C p.(Leu881Pro)	de novo	Transmembrane helical domain	4	9	**WS→F**	mikrocephaly, quadruparetic cerebral palsy with central hypotonia and extrapyramidal symptomatology, severe impairment of psychomotor development	negative	VGB, ACTH, CLB, LEV, **PHT**, ZNS, RFN
2	SCN2A (NM_001040143) c.4633A>G p.Met1545Val	de novo	Transmembrane helical domain	neonatal	23	**EME→near-WS**	mikrocephaly, quadruparetic cerebral palsy with central hypotonia and extrapyramidal symptomatology, severe impairment of psychomotor development	negative	B6,VPA, PB, LEV, BRV
3	**SCN2A (NM_001040143) c.416T>C p.Ile139Thr - nová**	de novo	Transmembrane helical domain	neonatal	8	**EIEE→WS**	mikrocephaly, quadruparetic cerebral palsy with central hypotonia and extrapyramidal symptomatology, severe impairment of psychomotor development	negative	B6, PB, LEV, CLZ, PHT, TPM, CLZ
4	SCN2A (NM_001040143) c.788C>T p.Ala263Val	de novo	Transmembrane helical domain	neonatal	120	**EME→F**	mikrocephaly, quadruparetic cerebral palsy with central hypotonia and extrapyramidal symptomatology, severe impairment of psychomotor development	cerebellar atrophy	PHT, VGB, CLZ, PB, CLB
5	**SCN2A NM_001040143.1 c.5626C>T p.(Arg1876*) - nová**	de novo	Variant causing premature translation termination	8	7	**EME→near-WS**	mikrocephaly, quadruparetic cerebral palsy with central hypotonia and extrapyramidal symptomatology, severe impairment of psychomotor development	negative	PB, LEV, VPA, CLB
6	SCN2A NM_001040143.1 c.3973G>A p.(Val1325Ile)	maternal	**Cytoplasmic domain**	4	9	**F**	developmental dysphasia, ASD	negat.	LEV, VPA

Tab. 6: Clinical characteristics of a case serie of patients with SCN2A-related DEE (128).

Results show that common features of SCN2A-related DEE in this group are:

1) early manifestation of seizures - most often during the first year of life (maximum in the neonatal period)
2) combination of seizures and electroclinical correlation leading to the classification of the epileptic syndrome as EME / EIEE / WS, but with certain atypia
3) severe neurological deficit with a predominant central hypotonia with quadruparetic syndrome and extrapyramidal symptoms, severe psychomotor retardation
4) the effect of PHT in patients with neonatal seizures
5) a sequence variant located in the cytoplasmic domain may cause a milder phenotype than a variant located in the transmembrane domain

For SCN2A-related DEE, two groups can be distinguished (49):

1) DEE with onset before 3 months of age, mutations with "gain-of-function" effect, with very good PHT (HD) effect, another possibly effective antiseizure drugs are CBZ, OXC, LCM, ZNS.
2) DEE with onset after 3 months of age, mutations with "loss-of-function" effect, where PHT is not effective or even worsens seizures, possible effect of LEV, BDZ, VPA.

And other examples of DEEs could follow and undoubtedly will with knowledge and identification of other pathogenic sequence variants in various genes.

1.8 Precision medicine strategy:

Genetic diagnosis of monogenic epilepsies presents great challenges. Knowledge of the pathophysiological mechanisms of the epileptic process could make it possible to use the principles of precision medicine and optimize the patient's therapeutic regime. For example, some drugs are more effective than others in some genetic epilepsy syndromes, i.e. sodium channel blockers (SCBs) in KCNQ2- and PRRT2-related seizures (129,130). Some antiseizure medication can worsen the seizure activity, as observed in SCBs in SCN1A-related epilepsies (131). Some antiseizure drugs can lead to fatal liver failure, as observed in patients with POLG-associated epilepsy receiving VPA (132). In the author´s study with 175 patients who underwent genetic testing with NGS panel of 155 genes, 46 patients had pathogenic sequence

variant causing the epilepsy (110). In 13 of these 46 patients (28.26%) the therapeutic regimen was modified. This was effective in reducing seizures by at least 50% in 9 of them (69.23%). Due to the size of the cohort, these are only case observations, and will be discussed in details below. Eighteen of these patients underwent targeted therapies. Eight of the patients carried a SCN1A variant, which was the most frequent sequence variant detected in our cohort. In most patients, the phenotype of Dravet's syndrome was presumed before targeted molecular genetic diagnosis, so a combination of VPA, CLB, and STP was used. None of these patients were treated with SCBs at the time of diagnosis. Several studies proved that there is an improvement not only in seizure frequency after SCBs are tapered off but also in cognitive performance, language skills, and general well-being.(133). One of the SCN1A positive patients importantly improved on TPM and another on STP.

In one patient, a ketogenic diet led to a 70% seizure reduction. Six patients with SCN2A-related DEE were diagnosed. PHT was administered in four of them: in one patient with a clinical manifestation of DEE at 4 months of age, PHT was ineffective; in three patients with a clinical manifestation in neonatal age, SCB therapy had a very good effect, with more than 50% seizure reduction which is in accordance with the principles of "gain of function" and "loss of function" model as published by Wolff et al. (49).

Two patients carried a SLC2A1 variant (GLUT1-deficiency) and were administered ketogenic diet. One of them improved promptly and became seizure-free. In the second patient, ketogenic diet was without significant effect. The sequence variant identified in this patient was located in exon 9 of the SLC2A1 gene, a site where causal mutations in patients with GLUT1-deficiency syndrome are often found, as has been well documented (134). Thus, the sequence variant was marked as pathogenic, and a biochemical correlate of the disease with a pathological absolute concentration of glucose in cerebrospinal fluid (CSF) and ratio of glucose concentration in CSF and serum was also confirmed. The patient's phenotype was not in conflict with the diagnosis of GLUT1-deficiency syndrome. Molecular diagnosis of the disease was made with a latency of almost 6 years from the manifestation of epilepsy, so ketogenic diet was introduced late, which may be related to its lower effectiveness (135). The ketogenic diet in patient was also less tolerant and it was not possible to increase the energy intake to provide sufficient energy for the CNS cells due to the fact that he did not tolerate the higher fat intake and he vomited. The poorer response to diet was relatively accented by the fact that the patient was also diagnosed with bilateral MTS on brain MRI, which, the authors assume, developed

secondarily after prolonged seizure activity and could continue to maintain the epileptogenic process regardless of the primary cause of epilepsy. One patient was diagnosed with pyridoxin-dependent epilepsy and carried an ALDH7A1 variant; he became seizure-free after vitamin B6 was administered. One was diagnosed with CACNA1A variant, severely aggravated after ethosuximide (ESM) administration. The worsening of seizures after a calcium blocker can be explained by the fact that the given variant is either of a loss-of-function or gain-of-function nature, which we were not able to determine for the given patient. It is documented that gain-of-function and loss-of-function CACNA1A mutations are associated with similarly severe DEEs and that functional validation is required to clarify the underlying molecular mechanisms and to guide therapies (136). Here we can only state that such a negative response to ESM is evidence that the patient's sequence variant is pathogenic.

1.9 Conclusion:

We are currently able to diagnose some epilepsies down to the level of individual pathogenic sequence variants. We have therefore come to understand the genetic cause of epilepsy in some cases. The possibilities of development of new molecules dedicated to treatment of epilepsy and future perspectives of gene therapy emerge and open up new research and treatment horizons.

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2 Annexes - Collection of author´s published scholarly works with commentary

2.1 Annex 1:

Danhofer P, Tomečková M, Černá D, Zapletalová D, Horák O, Aulická Š, Juříková L, Doamnský J, Kovalčíková P, Pavlík T, Štěrba J, Ošlejšková H. **Prognostic factors and seizure outcome in posterior reversible encephalopathy syndrome (PRES) in children with hematological malignancies and bone marrow failure: A retrospective monocentric study.** Seizure. 2019 Nov;72:1–10. doi: 10.1016/j.seizure.2019.08.007.

Summary:

Purpose: The aim of this study was to evaluate seizure outcome in children with hematological malignancies and PRES and to identify prognostic factors that could help manage the syndrome.

Method: We retrospectively reviewed the report data of 21 patients diagnosed with hematological malignancy or aplastic anemia and PRES between 2008 and 2018. Basic demographic data, oncology treatment, presymptomatic hypertension before PRES manifestation, neurological status, seizure type, and EEG and MRI findings at PRES onset and at the one-year follow-up visit were studied. Patients who developed remote symptomatic seizures or epilepsy were identified.

Results: We included 21 children (11 females and 10 males) in the study. Sixteen patients (76.2%) were diagnosed with ALL and the rest individually with AML, CML, T-lymphoma, Burkitt lymphoma, and severe aplastic anemia. Presymptomatic hypertension (PSH) was evaluated in 19 patients and was present in 18 (94.7%). The duration was 9 h and more in 16 patients (88.8%); the severity was grade II in 12 patients (66.7%). Seizures as the initial symptom of PRES were present in 17 patients (80.9%). Four patients (19.0%) were assessed with remote symptomatic seizures. Two of them (9.5%) had ongoing seizures at the one-year follow-up visit and were diagnosed with epilepsy. The presence of gliosis on follow-up MRI indicated worse outcome with development of epilepsy (without statistical significance).

Conclusions: PRES syndrome has an overall good prognosis and the evolution to epilepsy is rare. The severity and duration of PSH or seizure severity and EEG findings at PRES onsetwere not associated with worse neurological outcomes in this study.

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Prognostic factors and seizure outcome in posterior reversible encephalopathy syndrome (PRES) in children with hematological malignancies and bone marrow failure: A retrospective monocentric study

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ABSTRACT

Purpose: The aim of this study was to evaluate seizure outcome in children with hematological malignancies and PRES and to identify prognostic factors that could help manage the syndrome.
Method: We retrospectively reviewed the report data of 21 patients diagnosed with hematological malignancy or aplastic anemia and PRES between 2008 and 2018. Basic demographic data, oncology treatment, presymptomatic hypertension before PRES manifestation, neurological status, seizure type, and EEG and MRI findings at PRES onset and at the one-year follow-up visit were studied. Patients who developed remote symptomatic seizures or epilepsy were identified.
Results: We included 21 children (11 females and 10 males) in the study. Sixteen patients (76.2%) were diagnosed with ALL and the rest individually with AML, CML, T-lymphoma, Burkitt lymphoma, and severe aplastic anemia. Presymptomatic hypertension (PSH) was evaluated in 19 patients and was present in 18 (94.7%). The duration was 9 h and more in 16 patients (88.8%); the severity was grade II in 12 patients (66.7%). Seizures as the initial symptom of PRES were present in 17 patients (80.9%). Four patients (19.0%) were assessed with remote symptomatic seizures. Two of them (9.5%) had ongoing seizures at the one-year follow-up visit and were diagnosed with epilepsy. The presence of gliosis on follow-up MRI indicated worse outcome with development of epilepsy (without statistical significance).
Conclusions: PRES syndrome has an overall good prognosis and the evolution to epilepsy is rare. The severity and duration of PSH or seizure severity and EEG findings at PRES onsetwere not associated with worse neurological outcomes in this study.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES), as defined by Hinchey et al., is a phenomenon of transient cerebral vasogenic edema occurring preferentially in posterior circulation [1]. Clinically, PRES is characterized by headaches, seizures, reduced consciousness, and visual and other focal neurological symptoms [2,3]. PRES is a clinicoradiological syndrome; a characteristic radiologic finding is vasogenic edema in the bilateral parietal-occipital lobes, which might be related to the lower concentrations of sympathetic innervation of the posterior intracranial arteries in comparison with other cerebral regions, resulting in lower autoregulatory capacity in these vessels [4]. However, other cerebral areas can be involved, and focal areas of PRES vasogenic edema may also be seen in the basal ganglia, brainstem, and deep white matter [5]. Systemic lupus erythematosus, sickle cell disease, sepsis, use of cytotoxic medications (for malignancy or immune suppression), renal failure, and organ transplantation are some of the conditions that have been associated with PRES [6,7]. There is still controversy concerning the pathophysiologic mechanisms of the syndrome; however, the mechanism that produces vasogenic edema (arterial hypertension and endothelial dysfunction) seems to be associated with loss of integrity of the blood-brain barrier [8]. Moderate-to-severe

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hypertension is seen in approximately 75% of patients with PRES [9].

There are many detailed studies regarding the clinical and radiologic aspects of PRES in adults or children. However, the data regarding electroencephalographic changes and seizure outcome are very limited. Furthermore, few studies have yet focused on the very specific group of high-risk pediatric patients: children with hematopoietic or lymphoid tissue tumors or bone marrow failure.

The aim of this study was to retrospectively evaluate neurological status and EEG and MRI findings in children with hematological malignancies or bone marrow failure and PRES. The neurological outcome beyond the acute phase and the development of remote symptomatic seizures (RSS) in these patients was evaluated.

The secondary aim was to correlate these data with the severity and duration of presymptomatic hypertension (PSH) in this group of patients. Arterial hypertension is considered to be an important pathophysiological mechanism of PRES and can be influenced in order to achieve more favorable outcomes in these patients.

2. Material and methods

We retrospectively analyzed 24 patients diagnosed with PRES from 2008 to 2018 at the University Hospital Brno, Czech Republic, from the hospital database. All patients were diagnosed with malignancy or bone marrow failure and treated at the Pediatric Oncology Department, University Hospital Brno, according to appropriate protocols.

The inclusion criteria were: 1) acute clinical symptoms of PRES – alteration of consciousness, encephalopathy, seizures, headache, and visual disturbances and/or other focal neurological deficit; 2) PRES on MRI as diagnosed by a neuroradiologist; and 3) clinical agreement by treating physicians whose reports also were relied upon to determine the etiology.

We collected and analyzed clinical, radiographic, and encephalographic data from the institutional database.

Demographic data were analyzed: sex, age at the manifestation of malignancy, and PRES.

Each patient's clinical manifestation and causal factors were identified: oncological diagnosis, protocol treatment, and phase of treatment with medication in the last 4 weeks. We retrospectively evaluated PSH. Every patient admitted for hospitalization was measured by BP cuff in 3 -h intervals; if hypertension was present, the measurements were taken in 1-h intervals. We evaluated the severity and duration of the PSH prior to PRES clinical manifestation. The blood pressure was classified as normal, prehypertension, hypertension grade I, and hypertension grade II according to the age- and height-related standardized percentile graphs for pediatric populations. All patients were hospitalized at the time of PRES manifestation for various reasons (protocol treatment, febrile neutropenia, infection, *etc.*) so the collection of arterial pressure measurements were complete from the beginning of the PSH. Patients for whom the data were incomplete, *e.g.* PSH onset after admission with hypertension, were excluded from the analysis.

Neurological examination was established by the institutional neurologist at PRES manifestation – up to 3 h from the manifestation and then every 3 months, or more often if needed. We evaluated the neurological status at PRES manifestation and after one year of follow-up care.

Neurological status was classified as follows: 1 – normal; 2 – focal deficit without loss of consciousness; 3 – qualitative disturbance of consciousness (hypoactive or hyperactive delirium: confusion, disorientation, memory disturbance, illusions, or hallucinations); 4 – quantitative disturbance of consciousness – somnolence; 5 – quantitative disturbance of consciousness – sopor; 6 – quantitative disturbance of consciousness – coma.

The interpretation of EEGs was established by epileptologists from the Department of Child Neurology, University Hospital Brno. EEG were recorded digitally using a standard 10–20 system with standard 20-minute recordings with or without activations. All patients had EEG at PRES manifestation or in the first 12 h and then follow-up EEG every 3 months, or more often if needed. We evaluated the EEG at PRES manifestation and after one year of follow-up care.

EEGs were classified as follows: 1 – normal; 2 – focal slowing; 3 – diffuse slowing; 4 – focal epileptiform discharges; 5 – generalized epileptiform activity; 6 – LPDs.

Epileptic seizures were classified as follows according to the 2017 ILAE classification: 1 – no seizures; 2 – focal – aware; 3 – focal – impaired awareness; 4 – focal to bilateral tonic-clonic seizure (FBTCS); 5 – generalized tonic clonic seizure (GTCS); 6 – non-convulsive status epilepticus (NCSE); 7 – convulsive status epilepticus (CSE).

Acute symptomatic seizures were defined as seizures occurring in direct association with the PRES syndrome and/or within 6 weeks of its termination. Seizures that occurred later in the course of the oncological disease but still in possible association with PRES syndrome and with no other identified cause were defined as *remote symptomatic seizures (RSS)*. We arbitrarily determined *one year from the manifestation of PRES* as the borderline for another assessment: the one-year follow-up visit.

2.1. Statistics

Categorical variables were summarized using absolute and relative frequencies. To summarize the continuous characteristics, mean, standard deviation (SD), median, minimum and maximum were used.

Testing was carried out using Fisher's exact test. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Basic data

We identified 24 patients out of 1627 (1.4%) diagnosed with PRES and treated at the Pediatric Oncology Department at the University Hospital Brno between 2008 and 2018. Three patients were lost to follow-up care; they died due to the complications of treatment of malignancy. Therefore, 21 patients (11 females and 10 males) with PRES syndrome were included in the study. All patients had been diagnosed with malignancies; one patient was diagnosed with bone marrow failure. The average patient age at presentation was 6.6 ± 4.0 years (ranged from 2 to 16 years). Sixteen out of 21 patients (76.2%) were diagnosed with acute lymphoblastic leukemia (ALL), one patient (4.8%) had a diagnosis of acute myeloid leukemia (AML), one patient (4.8%) was diagnosed with chronic myeloid leukemia (CML), two patients (9.4%) were diagnosed with non-Hodgkin lymphoma (NHL - T-lymphoma and Burkitt lymphoma), and one patient (4.8%) was treated for severe aplastic anemia (Table 1). The incidence of PRES for each diagnosis for 10 years (2008–2018) can be expressed as follows: 16 out of 174 patients with ALL (9.2%), one out of 33 patients with AML (3.0%), one out of 15 patients with CML (6.6%), two out of 74 patients with NHL (2.7%), and one out of 9 patients with severe aplastic anemia (11.0%).

The time from the diagnosis of malignancy to the manifestation of PRES was 4.4 ± 4.9 months (ranged from 0.1 to 19.7 months). All patients received some form of chemotherapy according to the appropriate treatment protocol. The most common drugs used at the onset of PRES were intrathecal methotrexate (N = 18; 85.7%), corticosteroids (N = 16; 76.2%), L-asparaginase (N = 15; 71.4%), vincristine (N = 14; 66.7%), doxorubicin (N = 13; 61.9%), and cytarabine (N = 9; 42.9%); fewer than five patients used other drugs. In accordance with the treatment protocol, all patients were using polytherapy; see Table 1 and Table 3. Intrathecal methotrexate is used at the child oncology clinic in the treatment of hematological malignancies, and it is known for possible neurotoxicity. PRES syndrome developed in 18 patients out of 248 (7.2%) treated with intrathecal methotrexate between 2008 and 2018.

Table 1
Factors involved in the pathogenesis of PRES.

Factors involved in the pathogenesis of PRES			
oncological diagnosis: 21 patients			
ALL	16	76.2%	
AML	1	4.8%	
CML	1	4.8%	
T-lymfoma	1	9.4%	
Burkitt lymfoma	1		
severe aplastic anemia	1	4.8%	
blood pressure: 19 patients			
normotension	1	5.3%	not included in the evaluation of PSH
presymptomatic hypertension: 18 patients			
hypertension grade I	6	33.3%	
hypertension grade II	12	66.7%	
duration (hours)			
6	2	11.2%	
9	8	44.4%	
12	6	33.4%	
15	1	5.5%	
18	1	5.5%	
protocol treatment at the PRES onset and /or 4 weeks before			
methotrexat	18	85.7%	
corticosteroids	16	76.2%	
L-asparaginase	15	71.4%	
vincristine	14	66.7%	
doxorubicine	13	61.9%	
cytarabine	9	42.9%	
puri-nethol	6	28.6%	

PSH was assessed in 19 patients; data from 2 patients were incomplete. Only 1 patient out of 19 (5.3%) had normal blood pressure in the presymptomatic period and prehypertension at PRES manifestation; this patient was not included in the statistical evaluation. Two patients out of 18 (11.2%) had 6 -h long PSH, 8 patients out of 18 (44.4%) had 9 -h long PSH, and another 8 patients out of 18 (44.4%) had more than 9 -h long PSH with 18 h as maximum.

The PSH severity was as follows: 1 patient out of 19 (5.3%) had normal pressure, 6 patients out of 18 (33.3%) had hypertension grade I, and 12 patients out of 18 (66.7%) had hypertension grade II. Factors involved in the pathogenesis of PRES (oncological diagnosis and treatment and PSH) are summarized in Table 1.

We compared the number of antihypertensives used to achieve normotension and the duration of antihypertensive therapy in *non-RSS patients* and *RSS patients*. In the first group, 236 ± 1.33 antihypertensive drugs (ranged from 1 to 5 drugs) were used for 2.14 ± 2.88 months (ranged from 0 to 12 months). In the second group, 3.75 ± 0.83 antihypertensive drugs (ranged from 3 to 5 drugs) were used for 4.25 ± 4.49 months (ranged from 1 to 12 months). Although higher values in the second group are obvious, results in such a small sample size are not statistically significant.

3.2. Clinical-radiological diagnosis of PRES

The PRES clinical manifestations were as follows: seizures with or without disturbance in consciousness, in 17 patients out of 21 (80.9%); quantitative or qualitative disturbance of consciousness without seizures, in 4 patients out of 21 (19.0%); headache, in 4 patients out of 21 (19.0%); and visual disturbances, in 3 patients out of 21 (14.3%). Headache and visual disturbances were not the first symptoms of PRES reported by the patient but they were often immediately described after seizure or restoration of consciousness. Patients who reported headache as one of the first symptoms of PRES were 8.50 ± 4.50 years of age (ranged from 5 to 16 years). Visual disturbances at PRES onset were reported at 8.33 ± 1.36 years of age (ranged from 7 to 10 years). This is in accordance with the fact that small children often have difficulty describing their symptoms, so these symptoms could have been overlooked.

The neurological examination at PRES onset was normal in 4 patients out of 21 (19.0%); 1 patient out of 21 (4.8%) had only focal deficit without disturbance of consciousness; 8 patients out of 21 (38.1%) had qualitative disturbance of consciousness; 1 patient out of 21 (4.8%) had somnolence; 4 patients out of 21 (19.0%) were in sopor; and 3 patients out of 21 (14.3%) were in coma state; see Table 2.

In the *non-RSS* group, the neurological status normalized in 4.75 ± 8.82 days (ranged from 1 to 28 days). In the RSS group of patients, the neurological status normalised in 69.25 ± 105.81 days (ranged from 1 to 252 days); see Table 2.

All patients underwent a structural examination of the brain, either CT or MRI. Two patients out of 21 patients had only a CT scan, with hypodense lesions in the posterior regions correlating with the image of vasogenic edema; 19 patients out of 21 had MRI scans in correlation with the radiologic diagnosis of PRES; 15 patients out of 21 (71.4%) had lesions typically in the parieto-occipital region; 2 patients out of 21 (9.5%) had pathology in the parieto-occipital region, but also with frontal involvement; 4 patients out of 21 (19.1%) had severe diffuse involvement in bilateral fronto-temporo-parieto-occipital regions, including the cerebellum or brainstem in 2 of them; see Table 2. Follow-up MRI was performed in all patients after 43.1 ± 29.6 days (ranged from 12 to 90 days): 19 patients out of 21 (90.5%) had normal follow-up MRI; 2 patients out of 21 (9.5%) had persisting gliosis in the parieto-occipital region on MRI at the one-year follow-up visit (Table 2, Figs. 1–4).

3.3. Seizures at PRES manifestation and RSS

Seventeen patients out of 21 (80.9%) had seizures as the clinical manifestation of PRES (Table 2). Focal seizures were described in one patient out of 17 (5.9%); focal seizures with impaired awareness in 5 patients out of 17 (29.4%); focal seizures with evolution to tonic-clonic seizure in 1 patient out of 17 (5.9%); generalized tonic-clonic seizures were described in 4 patients out of 17 (23.6%); nonconvulsive status epilepticus in 3 patients out of 17 (17.6%); and convulsive status epilepticus also in 3 patients out of 17 (17.6%).

Four patients out of 21 (19%) were assessed as having *RSS*; 2 of them (9.5%) had ongoing seizures at the one-year follow-up visit.

Antiepileptic drugs (AEDs) used in the management of acute symptomatic seizures at PRES onset and chronic AEDs are presented in Table 3. All patients with RSS took levetiracetam (LEV) at the one-year follow-up visit. Three patients out of 17 (17.6%) from the *non-RSS* group were also on AEDs at the one-year follow-up visit (see Table 3). GBP was used in the treatment of neuropatic pain. All AEDs in these patients were tapered off in the course of the second year after PRES onset. We have to take into consideration that this fact could possibly mask the development of RSS in these patients during the one-year follow-up period. However, these patients arbitrarily met the study inclusion criteria, so they were included in the non-RSS group of patients.

3.4. EEG findings (*Table 2*)

All patients had EEG recorded directly at PRES manifestation or within no more than 12 h (24/7 EEG availability is provided). Follow-up EEG were performed every 3 months in all patients, or often if needed.

Normal EEG at PRES manifestation was described in 4 patients out of 21 (19.0%); focal or regional slowing was present 9 patients out of 21 (42.8%); and diffuse slowing was present in 2 patients out of 21 (9.6%). Three patients out of 21 (14.3%) had focal epileptiform discharges on EEG, and 3 patients out of 21 (14.3%) had LPDs on EEG.

Localization of focal slow waves or epileptiform discharges on EEG was predominantly in the parieto-occipital region (for details, see Table 2).

Table 2
Clinical characteristics and EEG and MRI findings of patients with PRES.

Patient No.	oncological diagnosis	treatment protocol	age at oncological diagnosis (years)	PRES onset - from oncological diagnosis (months)	acute PRES onset					
					neurological examination	seizure type	EEG	localisation on EEG	MRI	duration of PSH (hours)
1	T-ALL	ALL-IC 2002	17	10	3	1	1	normal	PO bilat.	0
2	praeB-ALL	ALL-IC BFM 2002	8	1	6	5	2	slowing PO bilat.	PO bilat.	9
3	cALL	ALL-IC BFM 2002	6	2	1	5	2	slowing O bilat.	PO bilat. (CT)	9
4	praeB-ALL	ALL-IC BFM 2002	7	1	1	3	1	normal	F right, O left	6
5	ALL	ALL-IC BFM 2002	4	10	5	3	2	slowing O bilat.	PO bilat.(CT)	NA
6	cALL	AIEOP-BFM ALL 2009	2	11	3	3	2	slowing TPO right	PO bilat.	NA
7	cALL	AIEOP-BFM ALL 2009	4	2	3	6	6	LPDs PT right	FTPO bilat., cerebellum	15
8	praeB-ALL	ALL-IC BFM 2002	3	0	5	1	1	normal	PO bilat.	9
9	T-ALL	AEIOP- BFM ALL 2009	6	1	6	5	2	slowing O bilat.	O bilat.	12
10	cALL	ALL-IC BFM 2002	16	1	3	1	2	slowing O bilat.	O bilat.	9
11	AML	AML BFM 2012	5	2	3	1	3	diffuse slowing	FTPO bilat., brain stem	9
12	preB-ALL	ALL-IC BFM 2002	7	2	4	7	6	LPDs PO right	PO bilat.	12
13	cALL	AIEOP-BFM ALL 2009	4	7	3	6	4	SWC TPO left	PO bilat.	6
14	cALL	AIEOP BFM ALL 2009	3	7	5	4	1	normal	FP bilat.	9
15	NHL	AIEOP-BFM ALL 2009	7	5	5	3	2	slowing TO left	PO bilat.	18
16	AA	EWOG SAA 2010	5	1	3	6	4	SWC FTPO right, max F	PO bilat.	12
17	BL	INT BNHL 2010	8	1	1	7	2	slowing right P	P right	12
patients with remote symptomatic seizures										
1	praeB-ALL	AIEOP-BFM ALL 2009	13	8	1	2	2	slowing PO bilat.	FTPO bilat.	12
2	CML	CML paed 2006	10	19	3	5	3	diffuse slowing	FPO bilat.	9
3	cALL	AIEOP-BFM ALL 2009	7	1	2	3	6	LPDs TO right	O bilat.	12
4	praeB-ALL	AIEOP BFM ALL 2009	3	1	6	6	4	SWC TO right	FTPO bilat. cerebellum	9

Patient No.	acute PRES onset	restoration after acute state			one-year follow-up visit				
	severity of PSH (grade)	neurological examination (days)	EEG (days)	duration of anti-HT therapy (months)	neurological examination	EEG	AEDs	MRI	time to follow-up MRI (days)
1	normal	1	NA	NA	1	1	0	normal	12
2	2	1	1	0	1	1	0	normal	12
3	2	1	1	0	1	1	0	normal	60
4	2	1	NA	3	1	1	0	normal	60
5	NA	1	3	NA	1	1	0	normal	14
6	NA	1	28	NA	1	1	0	normal	60
7	2	28	NA	12	1	3	LEV	normal	60
8	2	NA	NA	1	1	1	0	normal	14
9	2	3	3	2	1	1	0	normal	14
10	1	1	1	1	1	1	GBP + VPA	normal	14
11	2	3	28	3	1	1	0	normal	90
12	2	1	90	1	1	1	GBP	normal	14
13	1	1	90	1	1	1	0	normal	21
14	1	1	NA	3	1	1	0	normal	60
15	2	3	90	1	1	1	0	normal	28
16	2	28	NA	1	1	2	0	normal	14
17	1	1	90	1	1	1	0	normal	90
patients with remote symptomatic seizures									
1	2	1	3	1	1	1	LEV	normal	28

(*continued on next page*)

Table 2 (*continued*)

	acute PRES onset	restoration after acute state			one-year follow-up visit				
Patient No.	severity of PSH (grade)	neurological examination (days)	EEG (days)	duration of anti-HT therapy (months)	neurological examination	EEG	AEDs	MRI	time to follow-up MRI (days)
2	1	3	3	12	1	1	LEV	normal	60
3	1	21	NA	2	1	2	LEV	O bilat. gliosis	90
4	2	252	90	2	1	1	LEV	PO bilat. gliosis	90

Neurological examination: 1 – normal; 2 – focal deficit without loss of consciousness; 3 – qualitative disturbance of consciousness (hypoactive or hyperactive delirium: confusion, disorientation, memory disturbance, illusions or hallucinations); 4 – quantitative disturbance of consciousness – somnolence; 5 – quantitative disturbance of consciousness – sopor; 6 – quantitative disturbance of consciousness – coma. **Seizure type:** 1 – no seizures; 2 – focal – aware; 3 – focal – impaired awareness; 4 – focal to bilateral tonic-clonic seizure (FBTCS); 5 – generalized tonic clonic seizure (GTCS); 6 – non-convulsive status epilepticus (NCSE); 7 – convulsive status epilepticus (CSE). **EEG:** 1 – normal; 2 – focal slowing; 3 – diffuse slowing; 4 – focal epileptiform discharges; 5 – generalized epileptiform activity; 6 – LPDs.
Oncological diagnosis: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, NHL-Non-Hodgkin lymphoma, AA – aplastic anemia, BL – Burkitt lymphoma, CML – chronic myeloid leukemia; **localization on EEG and MRI:** F- frontal, P-parietal, T-temporal, O-occipital; **anti-HT** - antihyperensive, **AEDs** – antiepileptic drugs: LEV – levetiracetam; GBP – gabapentine; VPA – valproate.

In the non-RSS group, EEG was normalized in 38.64 ± 39.96 days (ranged from 1 to 90 days), in the RSS group, EEG was normalised in 32.67 ± 40.55 days (ranged from 3 to 90 days); see Table 2.

At the one-year follow-up visit, 18 patients out of 21 (85.7%) had normal EEG; 2 patients out of 21 (9.5%) had focal slowing; and 1 patient out of 21 (4.8%) had diffuse slowing on EEG. No epileptiform discharges were recorded.

3.5. Findings in patients with RSS

Four patients out of 21 (19%) were assessed as having with *RSS*. The small sample size prevents a statistically significant analysis, but it is possible to describe these patients' important characteristics. There were 3 girls and 1 boy in this group, ages 13, 10, 7, and 3 years respectively at the PRES onset. Three of them were diagnosed with ALL and one had CML. PSH took 9 h in 2 patients and 12 h in 2 patients; PSH was grade I in 2 patients and grade II in two patients. The seizure type at PRES onset was different in each patient: focal aware, GTCS, focal with impaired awareness, or NCSE. Acute EEG findings were different in each patient as well: focal slowing, diffuse slowing, LPDs, or focal epileptiform discharges. All patients started treatment with levetiracetam at a dose of 40–50 mg/kg/day after acute symptomatic seizures.

The first patient had two focal aware RSS 3 months after PRES onset, leading to an increase in the dose of levetiracetam to 60 mg/kg/day. Acute MRI showed diffuse lesions in the fronto-temporo-parieto-occipital region correlating with edema. Control MRI was normal after one month. The patient was seizure free at the one-year follow-up visit with normal neurological examination and EEG, still taking levetiracetam.

The second patient had one RSS with headache and visual illusion + ns 9 months after PRES onset, while tapering off levetiracetam. Acute MRI correlated with PRES syndrome with fronto-parieto-occipital lesions. A follow-up MRI 3 months later was normal. The patient was seizure-free at the one-year follow-up visit with normal neurological examination and EEG; the patient was still taking levetiracetam.

The third patient had repeated seizures, continuing at one-year follow-up visit. The patient described positive visual symptoms and headache while fully aware. The dose of levetiracetam was increased to 60 mg/kg/day and the seizures reduced in frequency (1/month). The patient and his parents preferred not to change medications; the seizures did not disturb him. The patient had occipital lesions on acute MRI with right-sided predominance; gliosis in the same region persisted on MRI at the one-year follow-up visit (Figs. 1 and 2). Neurological examination was normal after one year, with focal slowing on EEG (occipital right).

The fourth patient had focal aware repeated seizures, continuing at the one-year follow-up visit. The dose of levetiracetam was increased with partial effect, eslicarbazepine was added at the one-year follow-up visit with effect and the patient became seizure-free. Acute MRI was with diffuse cortico-subcortical fronto-temporo-parieto-occipital findings and with cerebellum involvment; these lesions persisted with occipital predominance as gliosis on MRI at the one-year follow-up visit (Figs. 3 and 4). Neurological examination and EEG was normal after one year.

3.6. Statistics

Statistical analysis did not reveal a statistically significant difference between sex or age at PRES onset (patients younger than 6 years *vs*. 6 years and older) in terms of duration and severity of PSH, clinical manifestation, seizure type, or EEG findings at PRES onset and at the one-year follow-up visit and the occurrence of RSS.

Statistical analysis also did not reveal a statistically significant difference between the group of patients with PSH grade I and those with grade II in terms of neurological status, seizure type, or EEG findings at PRES onset and at the one-year follow-up visit and the occurrence of

Table 3
Characteristics of oncological, antihypertensive and antiepileptic treatment.

Patient No.	oncological diagnosis	treatment protocol	oncological treatment 6 weeks before and/or at PRES manifestation	antihypertensive treatment	No. of anti-HT drugs	acute AEDs i.v.	chronic AEDs
1	T-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, asparaginase	NA	NA	0	0
2	praeB-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	furosemide	1	DZP	0
3	cALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, cyclophosphamide	enalapril	1	DZP	0
4	praeB-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	captopril, isradipine	2	0	0
5	ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, asparaginase	NA	NA	DZP	0
6	cALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, asparaginase	NA	NA	DZP	0
7	cALL	AIEOP-BFM ALL 2009	i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine	enalapril	1	DZP,LEV	LEV
8	praeB-ALL	ALL-IC BFM 2002	corticosteroids	furosemide	1	0	0
9	T-ALL	AEIOP-BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	enalapril, furosemide, propranolol, esmolol	4	DZP,LEV	0
10	cALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, asparaginase	captopril, furosemide	2	DZP,VPA	GBP, VPA
11	AML	AML BFM 2012	i.th. MTX, i.th. cytarabin, i.th. prednisone, cytarabin, etoposid	dihydralazine, furosemide, clonidine, enalapril, amlodipine	5	0	0
12	preB-ALL	ALL-IC BFM 2002	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	captopril, isradipine	2	DZP,CLZ	GBP
13	cALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	dihydralazine, furosemide, enalapril	3	DZP,PB,LEV	0
14	cALL	AIEOP BFM ALL 2009	i.th. MTX, cytarabine, thioguanine, cyklophosphamide, asparaginase	enalapril	1	DZP,LEV	0
15	NHL	AIEOP-BFM ALL 2009	i.th. MTX, vincristine, asparaginase	dihydralazine, clonidine, enalapril, metoprolol	4	LEV, VPA	0
16	AA	EWOG SAA 2010	Atgam, cyclosporine A, corticosteroids	dihydralazine, furosemide, clonidine, enalapril, amlodipine	5	LEV	0
17	BL	INT BNHL 2010	corticosteroids, i.th. and i.v. MTX, i.th. cytarabin, cyclophosphamide, vincritsine, doxorubicin, rituximab	enalapril	1	LEV	0
patients with remote symptomatic seizures							
1	praeB-ALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, cytarabin, cyclophosphamide, mercaptopurine, vincritsine, doxorubicin, erwinase	clonidine, metipranolol, enalapril	3	CLZ,LEV	LEV
2	CML	CML paed 2006	Atgam, melphalan, cyclophosphamide, thiotepa, fludarabine	dihydralazine, lercanidipine, perindopril, metoprolol, captopril	5	CLZ,LEV	LEV
3	cALL	AIEOP-BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	dihydralazine, enalapril, furosemide	3	CLZ, LEV	LEV
4	praeB-ALL	AIEOP BFM ALL 2009	corticosteroids, i.th. MTX, vincritsine, doxorubicin, asparaginase	dihydralazine, clonidine, enalapril, propranolol	4	DZP, LEV	LEV

Oncological diagnosis: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, NHL-Non-Hodgkin lymphoma, AA – aplastic anemia, BL – Burkitt lymphoma, CML – chronic myeloid leukemia.
MTX – methotrexate, i.th. – intrathecal, AEDs – antiepileptioc drugs, anti-HT – antihypertensive, DZP- diazepame, CLZ – clonazepame, PB- phenobarbital, GBP – gabapentine, VPA – valproate, LEV – levetiracetame.

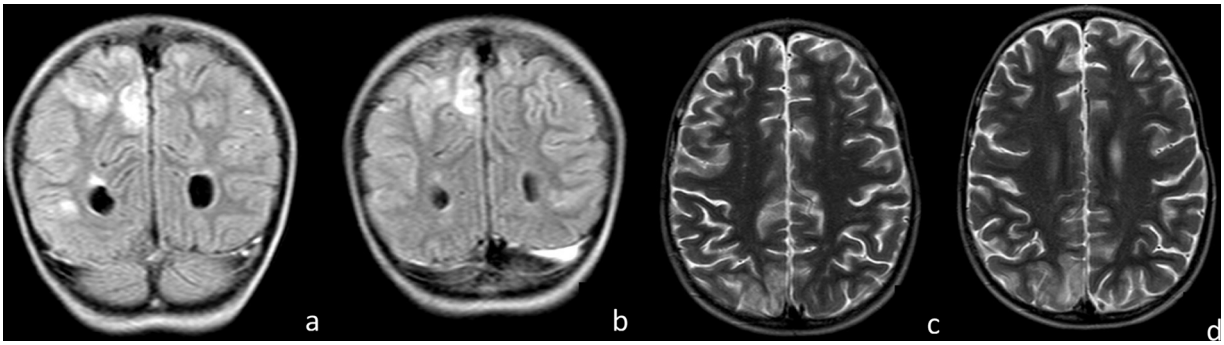

Fig. 1. Patient No. 3 from RSS group: MRI at PRES onset showing FLAIR (a,b) and T2-weighted (c,d) subcortical hyperintensities in occipital regions with right predominance.

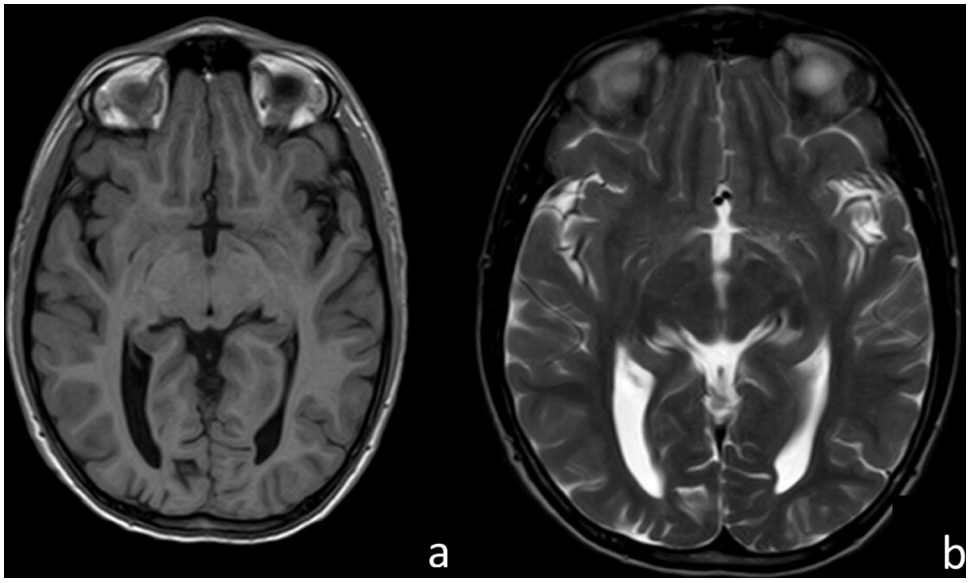

Fig. 2. Patient No. 3 from RSS group: follow-up MRI showing T1-weighted (a) hypointensities and T2- weighted hyperintensities in occipital regions with right predominance correlating to gliosis.

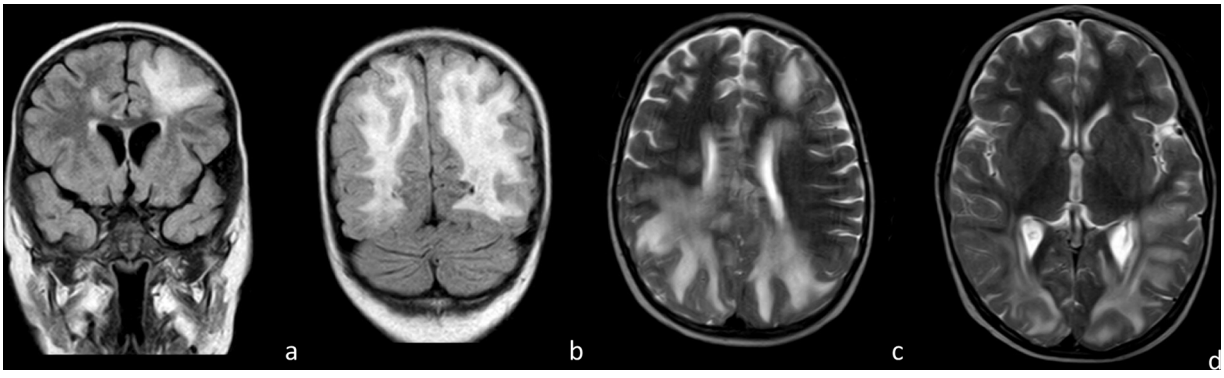

Fig. 3. Patient No. 4 from RSS group: MRI at PRES onset showing FLAIR (a,b) and T2-weighted (c,d) diffuse supratentorial cortical-subcortical hyperintensities with occipital predominance.

RSS. Neither were there statistically significant differences between the group of patients with PSH of duration ≤ 9 h and > 9 h in terms of neurological status, seizure type, or EEG findings at PRES onset and at the one-year follow-up visit and the occurrence of RSS.

We tested the relationship between the seizure type and EEG or MRI findings at PRES onset and the occurrence of RSS. There was not a statistically significant difference between these variables.

4. Discussion

4.1. Pathophysiology of PRES in children with malignancy or bone marrow failure

PRES is a possible complication in children undergoing chemotherapy [6,10]. The overall incidence of PRES in child malignancies

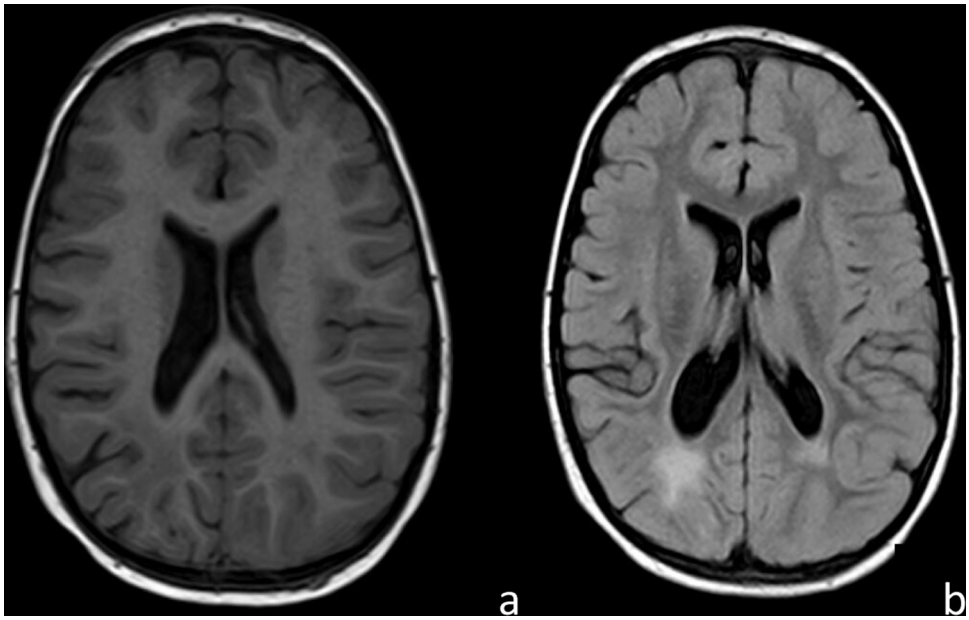

Fig. 4. Patient No. 4 from RSS group: follow-up MRI showing T1-weighted (a) hypointensities and T2- weighted hyperintensities in parietooccipital regions with right predominance correlating to postischemic lesions and gliosis.

in our series is 1.4%, which makes this diagnosis very rare. According to the literature, it affects mainly patients with ALL (55%), and less frequently patients with AML (9%), which is also due to the different incidence of these diagnoses [11]. There are also reports of PRES associated with Langerhans histiocytosis, Hodgkin's lymphoma, non-Hodgkin's lymphoma [12], and aplastic anemia [13]. In our series, the majority of patients in the study had ALL (76.2%) individual patients were also diagnosed with AML, CML, lymphoma, or severe aplastic anemia.

Corticosteroid treatment, L-asparaginase, cyclosporin A, and intrathecal methotrexate are suggested to have an important role in the development of PRES [6,14]. In total, 85.7% of patients were treated with intrathecal methotrexate, 76.2% of patients with corticosteroids, and 71.4% of patients with L-asparaginase. Intrathecal methotrexate is known for its neurotoxicity, and case reports with acute polyradiculoneuropathy [15], acute myelopathy [16] or MTX-induced stroke-like neurotoxicity [17] after intrathecal methotrexate administration have been published. Recent studies with animal models indicate possible late cognitive deficits induced by methotrexate [18,19]. In our study, PRES syndrome developed in 7.2% of patients with malignancy treated with intrathecal methotrexate over a 10-year period. It has been hypothesized that endotheliotoxic effects of both immunosuppressive as well as cytostatic drugs may lead to blood-brain barrier disturbances as well as to the impairment of cerebral vascular autoregulation [20] with the development of brain vasogenic edema. In addition, corticosteroids may play an indirect role in the development of PRES due to the higher risk of steroid-related hypertension [11].

Hypertension is considered to be another key risk factor of PRES. Severe hypertension leads to failed autoregulation and subsequent hyperperfusion, again with the development of vasogenic edema [21]. Hypertension is often seen in children with PRES (100% according to Morris [12]; 68% according to Kim [6]. We observed hypertension in all patients except one (94.7%) and the hypertension was severe: grade II in the majority of patients. The duration of PSH was 9 h or longer in almost all patients. The clinical manifestation of PRES was observed most often between 9 and 12 h of the PSH.

The effect of PSH on PRES severity was studied in 65 patients with PRES by Lee et al. [22]. The brain lesion distribution degree, or lesion scoring point (LSP) on MRI was numerically calculated and compared with presymptomatic blood pressure. The LSP was significantly correlated with pre-MAP (mean arterial pressure before the clinical manifestation of PRES). The authors concluded that patients with PRES who have relatively higher blood pressure in the presymptomatic period could have worse degrees of impaired cerebral autoregulation and are more likely to have wider lesion distributions than patients with lower blood pressure. A possible limitation is that only the distribution of edematous lesions was studied (number of brain regions affected), which does not necessarily correlate with their severity. In our study, we examined the relationship between PSH and neurological outcomes in children with PRES: neurological status, type of seizures, and EEG at PRES onset and at the one-year follow-up visit. We did not find any statistically significant relationship.

We can conclude that hypertension is not the only causative factor in the pathogenesis of PRES, especially in this specific group of patients with hematological malignancies, in whom it is necessary to consider the endothelial dysfunction caused by the cytotoxic and immunosuppressive drugs used. It is also necessary to highlight the hypertensive effect of corticosteroids used in most patients. However, targeted and prompt blood pressure control can be crucial in the management of PRES and should not be underestimated in the context of the multifactorial etiology of this syndrome.

4.2. Seizure outcome in patients with PRES

Many studies describe the clinical and radiological features of PRES in adults and in children. However, studies concerning the electroencephalographic findings and seizure occurrence and prognosis are rare and are mostly designed for the adult population.

Seizures are significantly more frequent in pediatric PRES patients as an initial PRES-related symptom than in adults [11,20]. Experimental data suggest that exposure to calcineurin inhibitors causes more severe neurotoxicity at a young age due to an increased permeability of the immature blood-brain barrier, allowing PRES-mediating circulating substances to act on the brain [5,23]. These factors might contribute to the high incidence of seizures observed in pediatric PRES, possibly sharing pathophysiological similarities with pediatric febrile seizures, a common pediatric condition that might also be partially triggered by fever-associated circulating proinflammatory cytokines [24].

Seizure occurrence in patients with PRES suggests that this syndrome is not just a subcortical pathology. Cortical irritation resulting from the adjacent vasogenic edema that follows disruption of the blood brain barrier is the most probable implicating factor [9].

Seventeen patients out of 21 (80.9%) had seizures as the clinical manifestation of PRES. Almost half of the patients had severe seizure manifestation at PRES onset: GTCS was observed in 4 patients out of 17 (23.6%), NCSE was observed in 3 patients out of 17 (17.6%), as was convulsive SE. Only one patient of this group – the patient with NCSE – developed RSS.

EEG patterns are not well described, but common patterns are reported and include diffuse and focal (mostly posterior) slowing with or without epileptiform discharges [9,10,25] as we found in our series. Lateralized periodic discharges (LPDs) are not commonly associated with PRES [11,13,26] but when they occur, they are associated with a worse prognosis and the development of ongoing seizures or epilepsy [26]. In our study, 3 patients out of 21 (14.3%) had LPDs on acute EEG; only one of them developed RSS.

The results from our study showed that neither the severity of seizure type at PRES onset nor the severity of acute EEG findings are associated with worse neurological prognosis in patients with PRES syndrome. But we have to take into consideration relatively small number of patients in the study.

RSS or the development of epilepsy after PRES syndrome is rare. Recurrent seizures were observed in 4 adult patients out of 46 (8.7%); 3 of those patients had atypical PRES pattern on MRI (involvement of the basal ganglia, thalamus, corpus callosum, and periventricular white matter, in addition to typical lesions) [27]. Sha et al. published a series of 75 adult patients with PRES: 4 of them (5.3%) developed RSS, 2 patients (2.6%) developed epilepsy with seizures occurring more than one year after the PRES [25]. An interesting Swedish study of 52 children with ALL and PRES syndrome was recently published. According to this study, 7 patients out of 52 (13.4%) had epilepsy after PRES and the same number of patients had neurocognitive difficulties as a consequence of ALL diagnosis and treatment [28]. In our study, almost one fifth of patients (19%) had RSS beyond the acute phase of PRES syndrome. Statistical analysis in such a small cohort is not strong enough to trace common factors provoking RSS after PRES syndrome. If this group of patients is studied more closely, it emerges that patients with persisting gliosis on MRI had ongoing seizures at the one-year follow-up visit. According to the definition of epilepsy (ILAE 2017), these 2 patients can be classified as having epilepsy (9.5%). It seems that a persisting structural lesion on MRI is important prognostically. In a study by Sha et al. in which 4 patients out of 75 developed RSS, two patients had post-ischemic lesions on MRI, one patient had focal atrophy, and one patient had normal MRI at the follow-up visit [25]. To date, the correlations between imaging findings and seizure outcome have been poorly described [25,29]. Yamamoto et al. (2015) studied a group of 40 children with PRES; 10% developed focal epilepsy [30]. The same study examined cytotoxic edema on MRI, represented by ADC reduction, which can lead to irreversible cerebral damage; vasogenic edema is likely to be reversible. Almost half of the studied patients had focal gliosis or atrophy on follow-up MRI; this finding was associated with ADC reduction during the acute period. Three of four patients with focal epilepsy had gliosis or atrophy on follow-up MRI. The study concluded that cytotoxic edema with ADC reduction during the acute period and subsequent focal lesions could lead to epileptogenic focus. Recently, atypical neuroimaging findings such as cytotoxic edema, infarction, hemorrhage, contrast enhancement, and a non-reversible clinical course including subsequent epilepsy, have been highlighted [29,31,32]. The pathogenesis of cytotoxic edema in PRES syndrome is not clear. A comparative study of 19 pediatric versus 100 adult patients with PRES proved ADC reduction was statistically significant in children as compared to adults [33]. Further studies are needed to clarify the cause of persistent lesions on MRI and their relationship to PRES syndrome, its neurological outcome, and possible epileptogenesis.

4.3. Study limitations

The results of this study have to be assessed in the context of the following facts. The study is retrospective and the cohort is not large; we included 21 patients in the study. Comparing the data with the literature, this is one of few studies assessing EEG and MRI findings and seizure outcome in children with PRES. Other studies are designed for the adult population. Literature concerning clinico-radiologic findings in children with PRES often describe small series: 7 patients [11], 5 patients [14], 19 patients [15], and 8 patients [16]. Nevertheless, the number of patients in this study limits the statistical analysis. MRI data are inconsistent. We have CT scans in the acute phase of only two patients and MRI was performed on various machines with different protocols between 2008 and 2018 (0.2 T, 1 T, and 1.5 T). For these reasons, the MRI data cannot be studied more precisely (the extent of lesions, ADC maps, *etc*.).

5. Conclusion

PRES is a rare complication in the treatment of children with hematological malignancies and bone marrow failure. It is considered to be a reversible condition, but RSS or epilepsy can develop. Persisting structural lesions on follow-up MRI can be associated with a worse prognosis, but further studies are needed to explain the pathophysiology of these MRI changes and their epileptogenesis. The severity and duration of PSH does not correlate with the neurological and seizure outcomes, but the study nevertheless encourages the prompt and targeted treatment of hypertension in patients with PRES.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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2.2 Annex 2:

Danhofer P, Brázdil M, Ošlejšková H, Kuba R. **Long-term seizure outcome in patients with juvenile absence epilepsy; a retrospective study in a tertiary referral center.** Seizure. 2014 Jun;23(6):443–7. doi: 10.1016/j.seizure.2014.03.002.

Summary:

Purpose: The study aim was to evaluate pharmacotherapy effects and long-term seizure outcomes in patients with juvenile absence epilepsy (JAE) during a five-year follow-up period. The secondary aim was to identify factors from patient history and determine their influence on seizure control.

Method: We retrospectively studied 46 patients with JAE in the period between 2006 and 2011. The age at seizure onset, onset seizure type, family history of epilepsy, status epilepticus in history, medication history, and the rate of seizure control were studied.

Results: There were 30 females (65.2%) and 16 males (34.8%) in the study. The mean age at seizure onset was 12.9±5.6 years (ranged from 3 to 28 years). In 30 patients (65.2%), seizure onset was with absences, in 15 patients (32.6%) with generalized tonic-clonic seizure (GTCS), and in 1 patient (2.2%) with absence status. In 43 patients (93.5%), GTCS occurred in the course of the disease. Family history for epilepsy was positive in 10 patients (21.7%). In the five-year follow-up period, seizure freedom (Group 1) was achieved in 7 patients (15.2%). In total, 22 patients (47.8%) were classified into the groups involving very poor seizure control and antiepileptic drug resistance (Groups 5 and 6). The mean number of antiepileptic drugs (AEDs) used in the course of the disease in appropriate therapeutic doses was 3.8±2.3 (1-10 AEDs).

Conclusion: The study results show that almost half of JAE patients have poor seizure control with a high rate of pharmacoresistance. The outcome of JAE can be very uncertain.

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Long-term seizure outcome in patients with juvenile absence epilepsy; a retrospective study in a tertiary referral center

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ABSTRACT

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Conclusion: The study results show that almost half of JAE patients have poor seizure control with a high rate of pharmacoresistance. The outcome of JAE can be very uncertain.

1. Introduction

According to ILAE Epilepsy Classification (1989),[1] juvenile absence epilepsy (JAE) is classified among the age-related idiopathic generalized epilepsies in adolescence. The proposed ILAE Epilepsy Classification revision[2] gives preference to the terms "genetic" or "unknown" instead of "idiopathic". The presumably genetic cause and specific mutation in most patients with JAE is still unknown. JAE is characterized by typical absence seizures, a long-life prevalence of GTCS for 80–83% of patients,[3,4] and sporadic myoclonic jerks are observed in 20% of patients. The seizure onset is typically between 9 and 13 years of age. GTCS and myoclonic seizures often occur 1–10 years after the absence seizure onset.[4] No sex predominance has been observed among the patients with JAE.[4] The incidence of JAE is not precisely known. JAE patients account for approximately 2–3% of patients with adult epilepsy in general, and about 8–10% of patients with idiopathic generalized epilepsy (IGE).[4] The etiology of JAE is a subject primarily of genetic research. The research results have shown that genetic mutations for voltage-gated sodium channels (CACNB4 gene)[5,6] and potassium channels (CLCN2 gene)[5] are involved. Different mutations were found in genes for GABA receptors (ligand ion channels), specifically in the GABRA1 gene.[7]

The aim of this retrospective study is to evaluate the effects of pharmacotherapy and the long-term seizure outcome in patients with JAE in a tertiary referral center. To our knowledge, there is insufficient information concerning the long-term outcome of

Abbreviations: ESM, ethosuximide; GTCS, generalized tonic-clonic seizure; IGE, idiopathic generalized epilepsy; ILAE, International League Against Epilepsy; JAE, juvenile absence epilepsy; LEV, levetiracetam; LTG, lamotrigine; MRI, magnetic resonance imaging; PRM, primidone; PSWC, polyspike-wave complex; SE, status epilepticus; SWC, spike-wave complex; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

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patients with JAE. Another aim of this study is to identify selected case history data (age at seizure onset, type of seizure at onset, family history) and determine their influence on the rate of seizure control.

2. Methods

We retrospectively evaluated the long-term seizure outcome in patients with JAE who had been referred to the Epilepsy Center Brno. We included only patients who had been observed and clinically managed in the center for at least five years (specifically in the period between 2006 and 2011). This period was described as the observational period (OP).

All patients met the criteria of JAE according to the ILAE 1989 Classification[1] i.e. clinical (age at seizure onset, normal psychomotor development, presence of absence seizures, GTCS or non-dominant myoclonic jerks) and electroencephalographic (normal background activity, ictal pattern of bilateral, symmetric, and synchronous discharge of regular 3–4 Hz spike wave discharges). All patients underwent a 1.5 T MRI scan, which excluded patients with potentially epileptogenic lesions.

We retrospectively evaluated the patient age at seizure onset, seizure type, family history of epilepsy, status epilepticus in the patient history, and history of medication, including the number of AEDs and AED treatment during the OP. The rate of seizure control was evaluated at the end of the five-year OP. The data concerning the types of seizures and their frequency were based on interviews with the patients and their caregivers. All of the patients were regularly followed up during the whole OP for clinical purposes. Patients from whom we could not obtain complete data or who were assessed irregularly were excluded from the study.

According to the type of seizure control during the five-year OP and at the end of the OP, we defined the following outcome groups:

1. Completely seizure free
2. Only absence seizures
3. Only GTCSs with a frequency $\leq$1 seizure per year
4. Only GTCSs with a frequency >1 seizure per year
5. Both GTCS and absence seizures; GTCSs with a frequency $\leq$1 seizure per year
6. Both GTCS and absence seizures; GTCSs with frequency >1 seizure per year

Since the data regarding the absence seizures were based on interviews with patients and their caregivers, without video EEG verification, we did not precisely evaluate the frequency of this type of seizure.

2.1. Statistics

We used the Mann–Whitney *U*-Test to analyze the possible differences among patients who were or were not completely seizure free during the whole OP in terms of their age, age at epilepsy onset, and epilepsy duration. A chi-square test was used to evaluate the possible differences among patients who were or were not completely seizure free during the whole OP in terms of the positive/negative family history and type of the seizure as a first manifestation of JAE (i.e. absences or GTCS). A value of $p < 0.05$ was considered statistically significant.

3. Results

We studied a group of 46 patients (30 females and 16 males) who met the criteria for JAE according to the ILAE 1989 Classification[1] and had been observed for at least 5 years. The patient age ranged from 19 to 49 years with an average age of 31.2 ± 8 years. There were 10 out of 46 patients (21.7%) with a positive family history for epilepsy in our cohort. Because the evaluation was retrospective, we were only able to obtain exact and specific data concerning the type of epilepsy in each patients' relative from 4 of the 10 patients. IGE (not more specified) was present in 2 patients' relatives, 1 patient had a brother with febrile convulsions, and 1 patient had a child with benign neonatal convulsions. Precise data concerning the family history from other patients were not available.

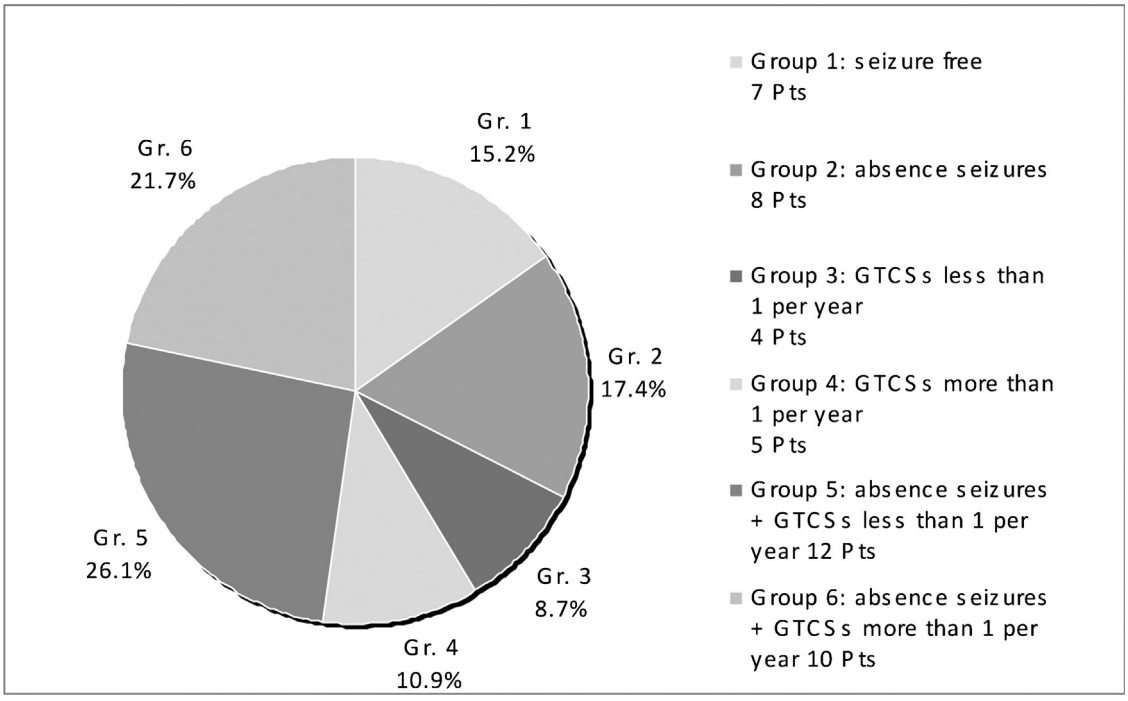

Fig. 1. Number of patients in different groups according to the rate of seizure control at the end of the OP (pts: patients).

Table 1
AED treatment in the whole cohort of patients with JAE.

Treatment type	AEDs	No. of pts.	Total no. of pts.
Monotherapy	LTG	12	20
	VPA	5	
	ETS	2	
	CBZ	1	
Combination of 2 AEDs	VPA + LTG	5	20
	VPA + LEV	4	
	LTG + LEV	3	
	TPM + ZNS	2	
	TPM + LTG	2	
	LTG + ZNS; LTG + ESM; CBZ + PRM; VPA + TPM	Each 1	
Combination of 3 AEDs	VPA + PRM + LEV; VPA + LEV + ZNS; LEV + LTG + ZNS	Each 1	3
Combination of 4 AEDs	VPA + LEV + CBZ + CLN; VPA + LTG + PRM + CLN; VPA + LTG + LEV + CLN	Each 1	3

No.: number; pts.: patients.

The average patient age at the time of the first clinical manifestation was 12.9 ± 5.6 years (ranged from 3 to 28 years). In 30 of the 46 patients (65.2%) the first clinical manifestation of JAE were absences, in 15 patients (32.6%) GTCS, and in 1 patient (2.2%) absence status epilepticus. In 43 patients (93.5%), at least one GTCS occurred in the course of the disease.

At the end of the OP, 7 of the 46 patients (15.2%) had been seizure free during the whole OP (Group 1). In the same period, 8 patients (17.4%) had only absences (Group 2). Other types of predefined outcomes are presented in Fig. 1. In total, 31 patients (67.4%) experienced at least 1 GTCS during the OP.

The assessment of AED treatment revealed that the number of AEDs used in the history varied from 1 to 10 with an average of 3.8 ± 2.3 AEDs. Only 8 of the 46 patients (17.4%) had just 1 AED, 19 patients (41.3%) had 3 or fewer AEDs, and 27 patients (58.7%) had 4 or more AEDs.

At the end of the OP, 20 of the 46 patients (43.5%) had been treated by monotherapy, 20 patients (43.5%) used a combination of 2 AEDs concurrently, 3 patients (6.5%) used a combination of 3 AEDs, and 3 patients (6.5%) used a combination of 4 AEDs.

Patients from Group 1 (i.e. seizure-free patients during the whole OP) were seizure free on 1 AED in 5 cases (71.4%) and on 2 AEDs in 2 cases (28.6%). In these patients, seizure freedom was achieved by the use of 1 to 3 AEDs: 1 patient tried 1 AED, 4 patients 2 AEDs, and 2 patients 3 AEDs. Finally, 3 patients remains seizure-free on monotherapy of LTG, 2 patients on monotherapy of VPA, 1 patient on the combination of VPA + LTG and 1 patient on the combination of LTG + ESM.

The most commonly used AED in our series was lamotrigine (25 patients; 12 in monotherapy and 13 in combined therapy), followed by valproic acid (20 patients; 5 in monotherapy and 15 in combined therapy) and levetiracetam (11 patients; all in combined therapy). Other AEDs used both in monotherapy and in combinations are noted in Table 1.

Statistical analysis did not reveal a statistically significant difference between the group of patients who were completely seizure free during the whole OP (Group 1) and the patients who were not (Groups 2–6) in terms of their age ($p = 0.736$), age at epilepsy onset ($p = 0.747$), epilepsy duration ($p = 0.666$), positive/negative family history ($p = 0.557$), or the type of seizure that was the first manifestation of JAE (0.854).

4. Discussion

Patients fulfilling the criteria for JAE according to the ILAE 1989 Classification[1] were enrolled in the study. The sub-classification of absence epilepsies in CAE and JAE is still a source of some controversy. We tried to exclude patients with CAE in terms of the seizure onset (younger than 10 years) and the dominant type of seizures (less often associated with other seizure types – GTCS and myoclonic seizures). Patients with EEG characterized by polyspike wave and wave complexes and dominant myoclonic seizures, which fit the diagnosis of JME, were also excluded from the study even if they started with absences as a dominant seizure type at the onset. Patients overlapping the boundaries between all the syndromes, and who thus could not be assigned to one or another group without effort and uncertainty, were excluded from the study.

To our knowledge, there are not many studies concerning the pharmacotherapy and long-term treatment outcome in patients with JAE. This could be due to the relatively low prevalence of this syndrome and the general opinion that JAE is classified as a syndrome with a good prognosis and therapy responsiveness.

Literature data provide inconsistent results concerning the long-term prognosis of patients with JAE. For example, Tovia et al.[8] published a study of 17 patients with JAE with an average follow-up period of 6.05 years (2–12 years). In the course of the follow-up period, 8 of the 17 patients (43.7%) were seizure free. The average disease duration was 6.93 years (1–13 years). The average patient age when the remission of absences was observed was 15.75 years. Eight of the 17 patients (47%) had GTCS in the course of the disease. Trinka et al.[9] published a study of 64 patients with JAE with an average follow-up period of 25.8 years (3–69 years). Of the 64 patients, 40 patients (62%) were seizure free during the follow-up for 2 or more years. Generally, seizure freedom can be achieved with antiepileptic medication in 62–84% of all patients with JAE.[4,9,10]

There are some studies that indicate that the outcome of patients with JAE is not favorable as a rule. Wirell et al.[11] studied the prognostic factors of initial pharmacotherapy failure. According to the study results, only 3 of the 11 children with JAE (27.3%) were seizure free after the drug initiation (mostly VPA).

There were 7 out of 46 patients (15.2%) seizure free (Group 1) during the OP in this study. These patients did not achieve seizure freedom after administration of 1 AED as we would expect. They tried 1–3 AEDs and only 5 of them (10.9%) stayed on 1 AED during the whole OP. Compared to the literature, Tovia et al.[8] presented nine of the 17 patients (52.9%) who were responsive for the first AED, but only 6 patients (35.3%) stayed seizure free on monotherapy during the follow-up period. These results show that even in the group of patient who were seizure free, the seizure freedom was not achieved in the simple way and does not have to be permanent.

Tovia et al.[8] showed that the occurrence of GTCS predicted a worse prognosis. Only 37.5% of the patients in that study who experienced GTCSs were seizure free during the follow-up period, compared with 55.5% of patients without GTCSs. Similar results were observed by Trinka et al.[9] where the proportion of seizure free patients in the follow-up period who experienced GTCSs was 35% compared to 78% of the patients with only absence seizures. In this study, there was also a strong correlation between the mean follow-up duration and outcome, indicating a lower proportion of seizure-free patients with longer follow up periods. From this point of view, the occurrence of GTCSs during the course of the disease seems to be another important prognostic factor for the long-term outcome in patients with JAE. In our study, only 8.7% of the patients did not experience GTCS during the course of the disease; therefore, we were unable to perform this type of analysis.

The AEDs of choice in the JAE therapy are VPA and LTG. VPA is the second medication choice for young women. Efficacy was also proved in ETS, LEV, TPM, and ZNS. VPA is an efficient treatment for all types of seizures in patients with JAE in 70–80% of patients, LTG in 50–60% of patients.[4,12] If VPA deals with only partial seizure control, add-on LTG (GTCS) or ETS (absence seizures) can be beneficial.[13] LEV can be efficient in GTCS and myoclonic seizures, and its efficacy in absence seizures was also recently proved.[14–16] The first AED in JAE therapy can be efficient in 60% of cases, especially in patients on VPA in monotherapy or in patients with isolated absence seizures. With monotherapy failure, the prognosis becomes less favorable and the rate of pharmacoresistance increases.[11] The results of this study concerning pharmacological treatment show that patients used an average of almost 4 AEDs during the course of the disease, and that 58.7% of patients tried more than 4 AEDs during the course of the disease from the seizure onset. At the end of the follow up period, all of the patients were on AED treatment: 43.5% were on monotherapy, 43.5% used a combination of 2 AEDs, 6.5% used a combination of 3 or 4 AEDs. LTG was studied in the paper published by Gericke et al.[13] who observed 12 patients with JAE on add-on therapy with lamotrigine. The average follow-up was 25.5 months. Ten of the 12 patients (83.3%) became seizure free on lamotrigine; in 2 of the 12 patients (16.6%) there was a seizure reduction of more than 50% during the follow-up period.

Trinka et al. published a study of patients with CAE, JAE and patients that could not be clearly defined as either CAE or JAE, and were therefore called ''the overlap group''. The follow-up period was 25.8 years (range 3–69). 61 of the 81 patients (75%) with nonpyknoleptic absences (JAE and ''overlap group'') were on AEDs at the last follow-up visit. Of the 61 patients, 42 patients (69%) were on VPA monotherapy; 11 patients (18%) were treated with VPA in combination with other AEDs (LTG, ETS, PRM, TPM).

Our retrospective analysis of patients with JAE indicates that more than half of the patients with this epileptic syndrome show problems with seizure management and often require more AEDs to reach partial or total seizure freedom. Although we did not reveal a statistically significant difference between the groups of patients who were completely seizure free during the whole OP and the patients who were not in terms of different variables, we noticed that these patients became seizure free using less number of AEDs. The number of studied patients did not allow us to evaluate this difference statistically.

The results of this study have to be assessed in the context of several facts:

- The study involves patients observed at a specialized center for epilepsy. These are patients sent from outpatient clinics due to their difficult seizure management. The prognosis of these patients is considered to be more grave.
- The study is retrospective. We were able to precisely assess the frequency of GTCS, because their clinical manifestation is noticeable. With absence seizures, patients do not often take them into consideration and it is difficult to count them exactly, so we did not assess their frequency. Thus, we did not distinguish between patients with rare absence seizures and daily absence seizures. This could be quite misleading in the context of assessing clinical manifestation.
- The assessment of patients was strictly set between 2006 and 2011. In this period of time, every patient presented in a different phase of the disease.

5. Conclusion

The prognosis of patients with JAE is often unfavorable, and the rate of pharmacoresistance can be quite important. To better understand the course of the disease and its prognosis, more studies are needed. We emphasize the need for studies with longer follow-up periods that assess the rate of seizure management and the cognitive and behavioral changes in patients with JAE.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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2.3 Annex 3:

Danhofer P, Pejčochová J, Dušek L, Rektor I, Ošlejšková H. **The influence of EEG-detected nocturnal centrotemporal discharges on the expression of core symptoms of ADHD in children with benign childhood epilepsy with centrotemporal spikes (BCECTS): A prospective study in a tertiary referral center.** Epilepsy Behav EB. 2018 Feb;79:75–81. doi: 10.1016/j.yebeh.2017.11.007.

Summary:

Benign childhood epilepsy with centrotemporal spikes (BCECTS) is the most frequent benign focal epilepsy in childhood. Although it is described as a benign epilepsy syndrome, many studies have revealed that a significant number of patients have some degree of neuropsychological impairment. Thirty-two patients with BCECTS aged 6-11years were included in the study. All patients (without any antiepileptic or psychiatric medication) underwent all-night EEG monitoring and complex neuropsychological testing to diagnose the presence of core symptoms of attention-deficit/hyperactivity disorder (ADHD). The spike index (number of spikes per minute) on awake and asleep EEG, age at seizure onset, family history of epilepsy, and perinatal risks were correlated with the results of neuropsychological testing. Of the 32 patients, 21 patients (65.6%) fulfilled the criteria for ADHD diagnosis. Children who were younger at epilepsy onset demonstrated lower IQ and higher attention deficit (P=0.004) and higher impulsivity (P=0.016). The occurence of epileptiform discharges on nocturnal EEG was positively related to higher attention deficit and higher impulsivity. The findings are discussed in terms of how interictal discharges in the centrotemporal region during sleep affect the development of cognitive functions in children during critical epochs of neuropsychological development.

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The influence of EEG-detected nocturnal centrotemporal discharges on the expression of core symptoms of ADHD in children with benign childhood epilepsy with centrotemporal spikes (BCECTS): A prospective study in a tertiary referral center

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ABSTRACT

Benign childhood epilepsy with centrotemporal spikes (BCECTS) is the most frequent benign focal epilepsy in childhood. Although it is described as a benign epilepsy syndrome, many studies have revealed that a significant number of patients have some degree of neuropsychological impairment.

Thirty-two patients with BCECTS aged 6–11 years were included in the study. All patients (without any antiepileptic or psychiatric medication) underwent all-night EEG monitoring and complex neuropsychological testing to diagnose the presence of core symptoms of attention-deficit/hyperactivity disorder (ADHD).

The spike index (number of spikes per minute) on awake and asleep EEG, age at seizure onset, family history of epilepsy, and perinatal risks were correlated with the results of neuropsychological testing.

Of the 32 patients, 21 patients (65.6%) fulfilled the criteria for ADHD diagnosis. Children who were younger at epilepsy onset demonstrated lower IQ and higher attention deficit ($P = 0.004$) and higher impulsivity ($P = 0.016$). The occurence of epileptiform discharges on nocturnal EEG was positively related to higher attention deficit and higher impulsivity.

The findings are discussed in terms of how interictal discharges in the centrotemporal region during sleep affect the development of cognitive functions in children during critical epochs of neuropsychological development.

1. Introduction

Benign childhood epilepsy with centrotemporal spikes (BCECTS) is the most frequent benign focal epilepsy in childhood and represents around 15% to 25% of epilepsy syndromes in children below 15 years of age [1,2]. The age at onset is between 4 and 10 years in 90% of the patients, and the median age at onset is around 7 years. The BCECTS is seen more frequently in males than females, with a ratio of 3:2 [2]. Seizures are clearly related to sleep in 80% to 90% of the patients, but in 10% of the patients, the seizures occur only in waking states [2]. Seizure frequency is usually low; around 10% of cases present only one seizure. The seizures are characterized by hemifacial motor signs, with speech arrest usually preceded by somatosensory signs; seizures often involve the limbs ipsilateral to the involved facial side [2]. Electroencephalogram (EEG) in BCECTS typically reveals specific epileptiform foci characterized by a wide, biphasic spike–wave complex localized in a centrotemporal region, with a normal background [3]. Epileptiform discharges amplify during nonrapid eye movement (NREM) sleep by a factor of two to five times without disturbing sleep organization [1].

Although BCECTS is described as a benign epilepsy syndrome, many studies have revealed that a significant number of patients have some degree of neuropsychological impairment. Despite a favorable seizure outcome and normal intelligence, children with BCECTS often have difficulties in various domains of neuropsychological functioning, such as behavior [4–7], language [8–11], cognition [6,12–16], attention [11,17–20], and memory [11,21], which may lead to learning difficulties [9,22,23]. A prominent comorbidity in children with BCECTS is attention-deficit/hyperactivity disorder (ADHD) [11,15,17–20,24–26]. The prevalence of ADHD in the general population is 3% to 7% [27]; it is 31% in children with BCECTS [15].

Some studies have tried to identify the factors responsible for the development of neuropsychological impairment and especially ADHD

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symptomatology in children with BCECTS. Age at seizure onset, epilepsy duration, impact of AED treatment, etc., have been evaluated, as having the impact of epileptiform discharges, their lateralization, and mainly their sleep activation [19,22,28]. The atypical evolutions of BCECTS – to 'BCECTS plus conditions' such as Landau–Kleffner syndrome, to electrical status epilepticus in slow wave sleep, or to atypical forms of BCECTS which can be present in 1% to 7% of patients [1] – prove that ongoing nocturnal interictal epileptiform activity can influence neuropsychological deficits in children and the severity can depend on the sleep activation of EEG discharges [15].

The aim of our study was to quantify the prevalence of ADHD in children with BCECTS and to analyze the effect of nocturnal epileptiform discharge activation on the development of executive functions and ADHD symptomatology in children with BCECTS. We discuss hypotheses of how sleep disruption interferes with the complexity of specific neuronal networks.

2. Methods

2.1. Participants

This prospective single center study included 52 consecutive children diagnosed with BCECTS at the Brno Epilepsy Center, Department of Pediatric Neurology of the University Hospital Brno between 2008 and 2016. All patients were admitted to the hospital directly after the first epileptic seizure. None of the patients had been diagnosed with ADHD before the manifestation of the first seizure.

Inclusion criteria were the following: a) aged 6–11 years; b) diagnosis of BCECTS made by a board-certified pediatric neurologist based on International League Against Epilepsy (ILAE) criteria [29]; and c) normal neurological examination.

The following exclusion criteria were applied: a) any neurological or psychiatric medication 6 months prior to the diagnosis or during EEG and neuropsychological testing; b) any structural brain magnetic resonance imaging abnormality that could exclude the diagnosis of BCECTS; c) any accompanying neurological disorder; and d) mental retardation (intelligence quotient (IQ) less than 70).

In total, 32 patients of the initial 52 were enrolled in the study; 20 patients were excluded because of improper age, a lack of asleep EEG needed for the evaluation, or incomplete neuropsychological testing.

2.2. EEG

Applying the international 10-20 system, awake and asleep EEG recordings were performed for all patients. Electroencephalogram recordings were obtained before the initiation of antiepileptic drug (AED) or psychiatric treatment. At least 30 min of awake EEG recording consisted of routine activation procedures including eye closing and opening, photic stimulation, and hyperventilation. Asleep EEG was performed as an all-night EEG lasting 6 to 8 h. In BCECTS, the frequency of epileptiform discharges is known to increase upon falling asleep and during the first NREM phase of sleep. To eliminate the impact of this observation resulting in a false higher activation of the epileptiform discharges, we evaluated the asleep EEG throughout the whole night.

The number of interictal epileptiform discharges in the centro-temporal region was manually counted during the whole awake EEG and in ten randomly chosen 20-minute epochs in NREM I–II and NREM III. Patients were divided into three groups according to the laterality of spikes on EEG (left, right, and bilateral).

The spike index (SI) (number of spikes per minute) was calculated during wakefulness, NREM I–II, NREM III, and total NREM sleep. The rate of occurrence of epileptiform discharges on EEG was evaluated by SI differently in the awake and asleep states. An SI lower than 10 was assessed as *low occurrence* during wakefulness; an SI higher than 10 was assessed as *high occurrence*. The border for this assessment during the different sleep phases was 30, with SI under 30 assessed as *low occurence* and SI above 30 as *high occurence*.

2.3. Neuropsychology

Czech versions of standardized neuropsychological batteries were applied to assess the core symptoms of ADHD (attention deficit, hyperactivity, and impulsivity) (Table 1). All neuropsychological testings were performed by a certified child psychologist. The assessment of patients according to the core symptoms of ADHD was established on the basis of a study by McGrew [30].

All patients were AED and psychiatric drug naive at the testing. The Wechsler Intelligence Scale for Children III (WISC III) and its subtests were used for assessing IQ in order to exclude patients with mental retardation (IQ less than 70). The WISC III subtests for Coding, Symbol Search, Letter Number Sequencing, and Labyrinths were used for assessing attention deficit; impulsivity was also evaluated using Labyrinths. A scaled score of 8 or lower (1 standard deviation below the mean) was taken as indicative of attention impairment. The Number Sequencing Test was applied for evaluating attention deficit. A sten score of 4 or less (1 standard deviation below the mean) was taken as indicative of attention deficit. The Trail Making Test was similarly applied for impulsivity. The results of these tests were not directly used to diagnose ADHD or to assess ADHD severity.

The Conners' Parent Rating Scale (CPRS) and the Test Observation Form were used to examine the core symptoms of ADHD. According to the results, subjects were divided into two groups: with ADHD and without ADHD. The T-score border was 60; higher values led to a diagnosis of ADHD.

2.4. Procedures

The patients were admitted to the department after the first seizure. Once the diagnosis of BCECTS has been established, they underwent all-night EEG recording and complete neuropsychological testing. Both examinations were performed within 2–5 days, and all patients were AED and psychiatric drug naïve at the testing.

Age at seizure onset, sex, handedness, family history of epilepsy, and perinatal risks were assessed.

2.5. Statistical analysis

Standard summary statistics were used to express primary data, absolute and relative frequencies for categorical and binary data, arithmetic mean supplied with standard deviation, and median supplied with minimum–maximum range for continuous data.

The statistical significance of the differences among the groups of patients in continuous variables was tested by the nonparametric Mann–Whitney or Kruskal–Wallis test. Robust rank methods were used because assumptions of normality could not be fulfilled in the primary distribution of values.

The degree of relationship between continuous variables was described by Spearman's rank correlation coefficient and its statistical significance.

Analysis was performed in SPSS software 24.0.0.0 (IBM Corporation, 2015).

3. Results

3.1. Baseline data (Table 2)

We studied a group of 32 patients (17 males and 15 females). All patients met the BCECTS criteria according to the 1989 ILAE Classification.

The average patient age at seizure onset was 7.5 ± 1.4 years; median: 8.0 years (6.0; 11.0).

Table 1
Neuropsychological test list according to the core symptoms of ADHD assessed.

Neuropsychological test	Subtest	Assessing	Evaluation	
Wechsler Intelligence Scale for Children III (WISC III)	Total IQ (IQt)	Intelligence	Standard scores	
	Verbal IQ (IQv)	Intelligence	Standard scores	
	Performance IQ (IQp)	Intelligence	Standard scores	
	Coding	Attention deficit	Scaled scores	
	Symbol Search	Attention deficit	Scaled scores	
	Letter Number Sequencing	Attention deficit	Scaled scores	
	Labyrinths	Attention deficit, impulsivity	Scaled scores	
Number Sequencing Test		Attention deficit	Sten	M1 — time in the first half M2 — time in the second half M — total time
Trail Making Test		Impulsivity	Sten	
Conners' Parent Rating Scale (CPRS)	Oppositional (Op)		T scores	
	Inattention/cognitive problems (In)	Attention deficit	T scores	
	Hyperactivity (Hy)	Hyperactivity	T scores	
Test Observation Form (TOF)	Inattention (In)	Attention deficit	T scores	
	Hyperactivity–impulsivity (H–I)	Hyperactivity, impulsivity	T scores	
	Summing index according to DSM (AD/HP)	Attention deficit, hyperactivity, impulsivity	T scores	

Of the 32 patients, 2 patients (6.3%) were left handed; and 30 (93.7%) were right handed. Three patients had a positive family history for epilepsy (9.4%); the type of epilepsy was not specified. Perinatal risks were present in 17 patients (53.1%): prolonged delivery with asphyxia and oxygen therapy in 8 patients, neonatal icterus with phototherapy in 5 patients, preeclampsia in 2 patients, gestation diabetes in 1 patient, and placenta abruption with preterm delivery (in the 32nd week of gestation) in 1 patient.

3.2. EEG profile (Table 2)

Electroencephalogram investigation revealed that of the 32 patients, 10 patients (31.3%) had left localized centrotemporal epileptiform activity, 6 patients (18.8%) had right localized centrotemporal epileptiform activity on EEG, and 16 patients (49.9%) had bilateral epileptiform activity. The average SI in the awake state was 11.0 ± 10.2 with a median of 7.4 (0.0; 38,7); in NREM I–II, 35.9 ± 17.2 with a median of 29.4 (7.5; 77.0); in NREM III, 28.2 ± 14.3 with a median of 23.2 (5.7; 55.8); and in total NREM sleep, the average SI was 32.4 ± 15.4 with a median of 27.2 (6.6; 66.4). Low occurrence of SI in the awake state was present in 18 patients (56.3%), and high occurrence of SI was present in 14 patients (43.7%). Low occurence of SI in NREM I–II was observed in 17 patients (53.1%), and high occurence of SI in NREM I–II was observed in 15 patients (46.9%). Low occurence of SI in NREM III was observed in 17 patients (53.1%), and high occurence of SI in NREM III was observed in 15 patients (46.9%). Low occurence in total NREM was observed in 18 patients (56.3%), and high occurence of SI in total NREM was present in 14 patients (43.7%).

Table 2
Clinical and EEG characteristics of patients.

Clinical characteristics		
Sex	Males	17 (56.2%)
	Females	15 (43.8%)
Age at seizure onset (years)	7.5 (1.4); 8.0 (6.0; 11.0)	
6–8 years, n (%)	26 (81.2%)	
9–11 years, n (%)	6 (18.8%)	
Laterality	Left	3 (9.4%)
	Right	29 (90.6%)
Family history of epilepsy	Yes	3 (9.4%)
	No	29 (90.6%)
Perinatal risks	Yes	17 (53.1%)
	No	15 (46.9%)
EEG characteristics		
Spike index		
Wakefulness		11.0 (10.2); 7.4 (0.0; 38.7)
NREM I–II		35.9 (17.2); 29.4 (7.5; 77.0)
NREM III		28.2 (14.3); 23.2 (5.7; 55.8)
Total NREM		32.4 (15.3); 27.2 (6.6; 66.4)
Laterality of EEG discharges	Left	10 (31.3%)
	Right	6 (18.8%)
	Bilateral	16 (49.9%)

3.3. ADHD profile

The criteria for the diagnosis of ADHD were fulfilled in 21 of the 32 patients (65.6%) according to Conners' Parent Rating Scale (CRPS) and Test Observation Form (TOF) results, with the highest average T-score of 72.7. Thus, all patients with ADHD had mild symptomatology.

3.4. Correlations

First, clinical characteristics and EEG findings were compared between patients with ADHD and those without ADHD according to the CRPS and TOF results (Table 3). Statistical analysis did not reveal a statistical difference between the group of patients with ADHD and those without ADHD in terms of their sex, family history of epilepsy, perinatal risks, age at seizure onset, awake and sleep SI occurrence, and laterality of centrotemporal epileptiform discharges on EEG.

Second, we correlated the results of detailed neuropsychological tests (Table 1) with similar clinical and EEG characteristics as in the first step described above (sex, family history of epilepsy, perinatal risks, age at seizure onset and SI on EEG in wakefulness, NREM I–II, NREM III, and total NREM – Table 4). Overall, children demonstrated average intellect with IQt 101.5, consistent with a normal distribution. There was a relationship between IQ (IQt, IQv, IQp) and the age at seizure onset: the lower the age at seizure onset, the lower the IQ, but this relationship was not statistically significant ($P = 0.091$ for IQp, $P = 0.106$ for IQt, and $P = 0.127$ for IQv). Children with a family history of epilepsy had lower IQs than the other group, but there was no statistical significance in this relationship. The correlation between IQ and SI in the awake state showed a negative trend in IQt ($P = 0.017$) and IQp ($P = 0.026$).

Some other associations were found in other neuropsychological testings. Girls showed higher attention deficit in TOF, with statistical significance ($P = 0.030$). The lower the age at seizure onset, the lower the scores in subtests of WISC III for attention deficit (Symbol Search $P = 0.004$) and in the Trail Making Test ($P = 0.016$), demonstrating higher attention deficit and impulsivity in these children.

Relationship between SI on EEG and results of neuropsychological testing indicated negative trends in Coding and in the Trail Making Test, which can be interpreted as higher rates of attention deficit and impulsivity in patients with higher SI in the awake state and in total NREM; however, this was without exact statistical significance (P value ranged from 0.165 to 0.186). There was also a positive trend between TOF results in all three domains and SI in NREM I–II and NREM III, again without statistical significance (P value ranged from 0.112 to 0.370). There was

Table 3
Comparison of clinical and EEG characteristics between patients with ADHD and without ADHD.

	All patients	With ADHD	Without ADHD	P
	n = 32	n = 21	n = 11	
Males, n (%)	17	13	4	0.266
Females, n (%)	15	8	7	
Family history of epilepsy, n (%)	3	3	0	0.539
Perinatal risks, n (%)	17	9	8	0.198
Age at seizure onset (years)				
6–8 years, n (%)	26	15	11	0.683
9–11 years, n (%)	6	5	1	
Spike index				
Wakefulness	SI < 10/min	12 (66.7%)	6 (33.3%)	1.000
	SI ≥ 10/min	9 (64.3%)	5 (35.7%)	
NREM I–II	SI < 30/min	10 (58.8%)	7 (41.2%)	0.472
	SI ≥ 30/min	11 (73.3%)	4 (26.7%)	
NREM III	SI < 30/min	10 (58.8%)	7 (41.2%)	0.449
	SI ≥ 30/min	9 (75.0%)	3 (25.0%)	
NREM total	SI < 30/min	11 (61.1%)	7 (38.9%)	0.712
	SI ≥ 30/min	10 (71.4%)	4 (28.6%)	
Laterality of EEG discharges (n)				
Left	10	7	3	0.999
Right	6	4	2	
Bilateral	16	11	5	

no statistical significance in the correlation between neuropsychological testing and perinatal risks.

4. Discussion

4.1. The incidence of ADHD in patients with BCECTS

In this study, 65.6% of the patients with BCECTS had ADHD. This is much higher than the prevalence of ADHD in healthy school children (5–10%) [3–5] or in children with epilepsy (30–40%) [31–34]. Similar results can be found in a study by Kim et al. who diagnosed ADHD in 64.9% of 74 children with BCECTS [26]. The diagnosis of ADHD in our study was based on the results of CRPS and TOF. Conners parent rating scale is a questionnaire based on parental observation. We found that these results were much lower than the results of TOF, which is a questionnaire completed by a psychologist. We assume that parents try to downplay the ADHD symptomatology in their children who already have a diagnosis of epilepsy; thus, the number of patients and ADHD could be even higher. This could also be a reason why all of the children with ADHD in our study had only mild symptomatology of ADHD according to these results. Still, these numbers are very high in comparison with the epilepsy population and raise questions about a common pathophysiology of ADHD and BCECTS. The pathophysiology of cognitive dysfunction in patients with BCECTS is a subject for further research. In general, two hypotheses are discussed. The first hypothesis assumes that the presence of rolandic epileptiform discharges and especially their sleep activation in patients with BCECTS are responsible for the development of cognitive dysfunction in these patients [28]. The second hypothesis supposes that the cognitive dysfunction and epileptiform discharges are a phenomenon with a common genetic basis [9,35]. We can conclude that the genetic basis affects the brain maturation and this leads to the development of epilepsy. Electroencephalogram discharges can then worsen this cognitive deficit [36].

4.2. The role of family history of epilepsy

Of the 32 patients, 3 had a family history of epilepsy. All of them were diagnosed with ADHD, and they had lower IQs, but without statistical significance. The type of epilepsy syndrome in these families was not identified. Recent studies have attempted to determine the candidate genes in the pathogenesis of BCECTS—chromosome 15q14,

Table 4
Correlation between values of SI (wakefulness, NREM I–II, NREM III, total NREM) and results of neuropsychological testing. [1]Spearman's correlation coefficient and its statistical significance.

Correlation[1]	IQt	IQv	IQp	Cod	SS	LNS	Lab	M1	M2	M	A	B	CPRS - Op	CPRS - In	CPRS - Hy	TOF - In	TOF - H–I	TOF - A–D
Wakefulness	−0.419	−0.211	−0.393	−0.355	−0.238	−0.148	−0.148	−0.153	−0.284	−0.26	0.129	−0.337	0.150	−0.152	−0.218	0.064	0.004	0.082
	P′ = 0.017	P′ = 0.246	**P′ = 0.026**	**P′ = 0.046**	P′ = 0.190	P′ = 0.420	P′ = 0.418	P′ = 0.486	P′ = 0.190	P′ = 0.231	P′ = 0.611	P′ = 0.172	P′ = 0.414	P′ = 0.407	P′ = 0.230	P′ = 0.726	P′ = 0.983	P′ = 0.657
NREM I–II	−0.219	−0.152	−0.113	−0.196	−0.158	0.026	−0.038	−0.033	−0.024	−0.073	−0.066	−0.182	0.035	0.091	0.081	0.189	0.283	0.287
	P′ = 0.228	P′ = 0.407	P′ = 0.537	P′ = 0.282	P′ = 0.387	P′ = 0.887	P′ = 0.836	P′ = 0.881	P′ = 0.914	P′ = 0.741	P′ = 0.794	P′ = 0.470	P′ = 0.851	P′ = 0.620	P′ = 0.661	P′ = 0.299	P′ = 0.117	P′ = 0.112
NREM III	−0.126	−0.04	−0.029	−0.252	−0.085	−0.08	−0.022	0.038	0.066	0.016	−0.21	−0.173	0.194	0.13	0.056	0.283	0.186	0.173
	P′ = 0.516	P′ = 0.836	P′ = 0.883	P′ = 0.186	P′ = 0.660	P′ = 0.679	P′ = 0.908	P′ = 0.869	P′ = 0.775	P′ = 0.946	P′ = 0.436	P′ = 0.523	P′ = 0.313	P′ = 0.501	P′ = 0.774	P′ = 0.168	P′ = 0.334	P′ = 0.370
Total NREM	−0.184	−0.114	−0.094	−0.252	−0.168	−0.033	−0.020	−0.028	−0.007	−0.058	−0.144	−0.169	0.045	0.049	0.022	0.139	0.207	0.202
	P′ = 0.313	P′ = 0.534	P′ = 0.609	P′ = 0.165	P′ = 0.359	P′ = 0.859	P′ = 0.913	P′ = 0.901	P′ = 0.976	P′ = 0.793	P′ = 0.568	P′ = 0.503	P′ = 0.805	P′ = 0.789	P′ = 0.904	P′ = 0.450	P′ = 0.255	P′ = 0.267

IQt – IQ total; IQv – IQ verbal; IQp – IQ performance; Cod – Coding; SS – Symbol Search; LNS – Letter Number Sequencing; Lab – Labyrinths; M1 – Number Sequencing Test M1; M2 – Number Sequencing Test M2; M – Number Sequencing Test M; A – Trail Making Test A; B – Trail Making Test B; CPRS Op – CPRS Oppositional; CPRS In – CPRS Inattention; CPRS Hy – CPRS Hyperactivity; TOF In – TOF Inattention; TOF H–I – TOF Hyperactivity Impulsivity; TOF A–D – TOF Attention Deficit.
Bold data indicates statistical significance.

where the gene for acetylcholine receptor subunit is located [37]; chromosome 11p13; and several polymorphic markers in the gene for Elongator Protein Complex 4 (ELP4) [38]. Elongator protein regulates the growth of cortical projection neurons. A noncoding mutation in the ELP4 gene interferes with brain development and maturation and increases seizure susceptibility. Another factor is Brain-Derived Neurotrophic Factor (BDNF), for which the gene is also located on chromosome 11p13, close to ELP4 [39]. This factor is very important in synaptic plasticity and neurotransmission. Its location, so close to ELP4, indicates a possible role of this gene in the etiology of BCECTS.

4.3. The role of perinatal risks

The number of patients with perinatal risks was relatively high in this study. All perinatal risks were included in the study, even those with moderate expression, which may not have a clear effect on the development of cognitive dysfunction in the study subjects. It is difficult to determine to what extent the proportion of cognitive dysfunction is the result of perinatal insult.The possible genetic basis for the development of ADHD should also be considered.

4.4. The role of age at seizure onset

Despite studies demonstrating the genetic basis of BCECTS, the development of symptoms of this epilepsy syndrome and typical EEG discharges are age-related and time-limited. The prerequisite is thus the existence of a developmental window during which permissive factors appear that cause changes in the processes of the aging of affected brain areas. This developmental window is associated with cortical functional activity that can be defined on the basis of regional cerebral blood flow [40,41] and local metabolic changes [42,43]. At birth, the regional cortical cerebral blood flow is lower than in adults. After birth, it increases up to 5–6 years of age to values which are about 50–85% higher than in adults. It then decreases again and reaches adult values between 5 and 19 years [2]. The time required to reach adult values varies depending on the area of the cortex. The shortest is in the primary cortex and the longest in associate cortical areas. The metabolic profile measured by glucose utilization is almost identical: low at birth, rising to 4 years of age when the child's brain consumes up to twice as much glucose as an adult, and then decreasing and reaching adult values at the age of 16–18 years. These changes correlate with an initial overproduction and subsequent elimination of excessive neurons, synapses, and dendrites, which can be seen in the developing brain [2]. Early development of epilepsy can have long-term effects on the developing brain. The vulnerability of the developing brain emerges from impaired developmental processes such as synaptogenesis, dendritic branching, neural migration, and differentiation, rather than from neuronal death, which dominates in the case of development of seizures in adults when the brain is already matured [44]. For this reason, it is possible to see more global autistic regression with more severe speech deficits in children with early development of Continual Spike and Waves in Sleep Syndrome (CSWS) than in children with Landau-Kleffner Syndrome (LKS) with relatively later development where isolated speech regression is observed [45]. Very different impacts of epilepsy can therefore be expected depending on the degree of the brain maturity when epilepsy becomes active. In our study, we demonstrated that children with earlier seizure onset had lower Intelligence Quotient (IQs). In other neuropsychological testings, we found statistically significantly higher attention deficit and impulsivity in children with earlier onset of seizures. Our results are supported by another study of 25 children with rolandic epilepsy that proved that the early onset of seizures leads to worse results in neuropsychological testing of cognitive functions [28]. Another study of 33 children with BCECTS spectrum demonstrated that the patients with an average epilepsy onset at around 8 years were at higher risk of neuropsychological problems [22].

4.5. The role of lateralization in EEG epileptiform discharges

The impairment of cognitive functions in children with BCECTS may be caused by interictal paroxysmal EEG activity, which can lead to transient cognitive deficit, or it can be a consequence of the chronic effect of epileptiform discharges, resulting in cortical inhibition of the area and leading to delayed or incomplete maturation [18]. Cognitive functions are most vulnerable when the hemispheric lateralization of its neural correlates is affected by the epileptic focus. Therefore, in children with left lateralization of the epileptiform activity, speech difficulties are observed [46,47]; right lateralization of the EEG focus can be associated with spatial orientation deficit [48].

The influence of the side of epileptiform activity on EEG in children with BCECTS is very controversial. It is known that the shift of the centrotemporal spikes from one side to another can be observed in patients with BCECTS during the disease. In 86 children with epilepsy with somatosensory-evoked potentials (a kind of functional correlate of rolandic discharges), the localization was parietal in 42% of cases, centrotemporal in 32% of cases, and both parietal and centrotemporal in 26% of cases [49]. Parietal localization was dominant in younger ages (around 3–8 years), centrotemporal localization was dominant in children at the ages of 6–11 years, and the simultaneous occurrence in both areas was observed in a transitional age group of 6–8 years and probably represents the transition between these localization patterns [49].

In our study, we did not find any association between the lateralization of EEG epileptiform discharges and ADHD diagnosis and the results of detailed neuropsychological testing.

Taking into account the age-dependent focus localization, the shift of the focus from one side to another, and its bilateralization in sleep, it is very difficult to determine an influence of the lateralization of the focal epileptiform activity on cognitive functions in patients with BCECTS.

4.6. The role of nocturnal epileptiform discharges and SI

In benign focal epilepsies, BCECTS included, sleep increases the frequency of epileptiform discharges, and the discharges remain high during the first phase of NREM sleep. During REM sleep, the frequency decreases; this decrease can also be observed in other NREM sleep cycles [22]. The atypical development of BCECTS to 'BCECTS plus' conditions shows that ongoing nocturnal epileptiform activity causes neuropsychological deficit and the level of severity depends on the rate of awake and sleep pathology [50]. Night epileptiform discharges intervening during brain development may lead to the impaired development of neural networks involved in various neurocognitive functions. If these sleep discharges last for a certain time, they can lead to extensive synaptogenesis with excess growth of the axons that ensure contact with the target cells. This interferes with the process of branching of neuronal processes, thus maintaining connections that should be eliminated. The affected neural network replaces the normal functional neuronal network at the cortical level and frequent epileptiform discharges encourage it to further growth so that it cannot be recovered [51].

Slow wave activity (SWA) is the fundamental characteristic of NREM sleep on scalp EEG. Its neural correlate is the slow oscillation of membrane potentials of cortical neurons between depolarization and hyperpolarization. If these oscillations are synchronized and the majority of cortical neurons in a certain area are affected, they are detectable as slow waves on scalp EEG. The local increase in SWA during NREM sleep and the decrease in other phases of sleep are important for the plasticity of learning processes and synaptic homeostasis [52,53].

The normal reduction of SWA during sleep is absent in patients with electrical status epilepticus during slow wave sleep. The interference of epileptiform discharges with normal sleep SWA may explain the cognitive deterioration in these patients [53].

In our study, we performed an extensive battery of neuropsychological testing in order to identify the rate of ADHD core symptoms in

children with BCECTS during nocturnal EEG testing. We performed all-night EEG recordings to eliminate the impact of the high activation of discharges during drowsiness and the first sleep cycle; we also studied the discharges during the slow stages of NREM sleep (NREM III) in which the interference of epileptiform discharges with SWA in relation to cognitive dysfunction is important. We did not find any relation between the diagnosis of ADHD and SI occurence in any sleep stages. This could be explained by the fact that the division of patients into the two groups with ADHD and without ADHD was very approximate, and even the ADHD patients had mild symptomatology of the disorder. The results of detailed neuropsychological testing show that the occurrence of discharges in total NREM sleep leads to higher attention deficit and impulsivity in patients, but without proven statistical significance. Sleep SI is also positively related to the TOF results, which is a test that affects all core symptoms of ADHD, again without exact statistical significance.

The influence of temporal epileptiform discharges in children with centrotemporal EEG pathology was examined in several studies. Filippini et al. [50] conducted an extensive study of 33 children with BCECTS in which they prospectively evaluated an overnight sleep EEG recording with a two-year follow-up period. Patients were divided into 3 groups according to the frequency of nocturnal epileptiform discharges: Group 1A—less than 50% of sleep; Group 1B—50–85% of sleep; and Group 2—more than 85% of sleep. Half of the patients in Group 1A had a neuropsychological deficit by the end of the follow-up period, especially in short-term verbal memory, visuo-spatial orientation, and learning difficulties such as dyslexia and dysorthography. This deficit was more pronounced in patients with early-onset epilepsy (under the age of 5 years). All of the patients in Group 2 had persistent neuropsychological deficits, especially in the verbal area, and all patients had specific learning disabilities.

Kim et al. [26] published a study in 2014 that evaluated asleep EEG in 71 patients with BCECTS. They found that patients with a high SI (more than 40/min) had deficits in visual selective attention.

Baglietto et al. [28] studied nine children with centrotemporal discharges on EEG, who were seizure free for at least 2 months. All the children were on valproate monotherapy, and they had SI higher than 10/min confirmed on two EEG spaced 6 months apart. Electroencephalogram controls were performed every 3 months until the SI dropped to 5/min. Neuropsychological tests were performed at baseline (T0) and after a decrease of SI on sleep EEG (T1). At T0, patients showed normal IQs, but lower than the control group, and they had neuropsychological deficits in short-term memory, attention, and cognitive flexibility. At the end of the follow-up period (T1), there was a significant improvement in IQ scores and in other neuropsychological tests, and patient performance did not differ from that of controls.

All of these studies found a significant negative impact of epileptiform discharge activation in patients with BCECTS on their neuropsychological profiles.

The limitation of this study is the number of patients. It was a very limited group of closely selected patients. All of the patients were examined without any neurological or psychiatric medication, and they all completed all-night video-EEG monitoring and fairly extensive neuropsychological examinations. The patients were selected for a long period of time, 6 years, in a tertiary referral epilepsy center. In the global literature, other studies have investigated 9 [28] or 33 [50] patients; a larger study group was published with 74 patients [26]. Given the sizes of previous studies, this study group is not that small.

Conflict of interest

The authors indicated no potential conflict of interest.

Ethics in publishing report

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. We confirm that the research was approved by the Ethical Committee of the Institution and informed consent was obtained from the patients' guardians.

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2.4 Annex 4

Horák O*, Burešová M*, Kolář S*, Španělová K, Jeřábková B, Kolář S, Česká K, Réblová K, Zídková J, Fajkusová L, Ošlejšková H, Danofer P. **Next-generation sequencing in children with epilepsy: The importance of precise genotype-phenotype correlation.** Epilepsy Behav 2022; 19; 128:108564. doi: 10.1016/j.yebeh.2022.108564.

Summary:

Aim: New methods in molecular genetics, including next-generation sequencing (NGS), are powerful tools in diagnosing the cause of epilepsy. The primary goal of this study was to use a multidisciplinary approach to determine the yield of NGS epilepsy gene panels and the importance of genotype-phenotype correlations. The secondary goal was to evaluate the application of precision medicine in selected patients.

Methods: This single-centre retrospective study included a total of 175 patients (95 males and 80 females) aged 0-19 years. They were examined between 2015 and 2020 using an NGS epilepsy gene panel (255 genes). A bioinformatic analysis was performed including copy number variation identification.

Results: Out of 175 patients, 89 (50.86%) experienced developmental and epileptic encephalopathy (DEE), 45 (25.71%) were classified with generalized epilepsy (GE), and 41 (23.43%) had focal epilepsy (FE). Described pathogenic variants or novel variants with clear pathogenic impact were identified in 30 out of 175 patients (17.14%). Genotype-phenotype correlations and parental DNA analysis were performed, and genetic diagnosis was confirmed on the basis of the results in another 16 out of 175 patients (9.14%). The diagnostic yield of our study was 46 out of 175 patients (26.28%).

Interpretation: We emphasize a complex genotype-phenotype correlation and a multidisciplinary approach in evaluating the results of the NGS epilepsy gene panel, which enables the most accurate genetic diagnosis and correct interpretation of results

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Next-generation sequencing in children with epilepsy: The importance of precise genotype–phenotype correlation

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ABSTRACT

Aim: The primary goal was to determine the yield of next-generation sequencing (NGS) epilepsy gene panels used for epilepsy etiology diagnosing using a multidisciplinary approach and to demonstrate the importance of genotype–phenotype correlations. The secondary goal was to evaluate the application of precision medicine in selected patients.
Methods: This single-center retrospective study included a total of 175 patients (95 males and 80 females) aged 0–19 years. They were examined between 2015 and 2020 using an NGS epilepsy gene panel (270 genes). A bioinformatic analysis was performed including copy number variation identification. Thorough genotype–phenotype correlation was performed.
Results: Out of 175 patients, described pathogenic variants or novel variants with clear pathogenic impact were identified in 30 patients (17.14%). Genotype–phenotype correlations and parental DNA analysis were performed, and genetic diagnosis was confirmed on the basis of the results in another 16 out of 175 patients (9.14%). The diagnostic yield of our study increased from 30 to 46 patients (by 53.33%) by the precise genotype–phenotype correlation.
Interpretation: We emphasize a complex genotype–phenotype correlation and a multidisciplinary approach in evaluating the results of the NGS epilepsy gene panel, which enables the most accurate genetic diagnosis and correct interpretation of results.

1. Introduction

Epilepsy affects 0.5% to 1% of children and is the most frequent chronic neurologic condition in childhood [1]. The underlying etiology is unknown in 40–50% of cases of epilepsy, although it has been estimated that approximately 30% of epilepsy is genetic [2].

Clinical genetic diagnosis methods have become popular in recent years and include various technologies and strategies. Next generation sequencing (NGS) is revolutionary especially in terms of the possibility of simultaneously examining many genes. NGS testing includes not only specific gene panels, but a methodology that can encompass the entire exome (whole exome sequencing, WES) or genome (whole genome sequencing, WGS), methods that have the potential to further increase the yield of genetic testing in patients with epilepsy. The yield of NGS epilepsy gene panels ranges from 20 to 40% depending on the sample investigated [3–5]. Geneticists interpret and report detected sequence variants on the basis of currently valid recommendations according to the American College of Medical Genetics and Genomics (ACMG) [6]. Thus, each sequence variant is included in the group of pathogenic (P), likely pathogenic (LP), benign (B), likely benign (LB), or with uncertain significance (VUS). The thorough genotypic–phenotypic correlation and interpretation of genetic results from the neurological-epileptological point of view, taking into account other anamnestic data, are an integral and crucial part of the pro-

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cess of interpreting the result of NGS; it importantly increases the diagnostic yield of NGS examination.

Knowing the genetic cause of epilepsy in a patient opens new horizons in terms of understanding the pathophysiology of the epileptological process, and it also creates a space for the study of pharmacological models of antiepileptic drugs. The definition of precision medicine thus takes on real proportions in some patients with epilepsy.

We present our single-center experience of using targeted gene-panel sequencing to diagnose the genetic etiology of epilepsy in children and we focus on the precise multidisciplinary genotype–phenotype correlation of each patient in order to maximize the yield of this examination method.

2. Methods

This retrospective study included 175 unrelated patients aged 0 to 19 at the time of genetic testing. All patients were examined using an NGS epilepsy gene panel including 270 genes. A detailed list is attached to the work as supplementary data, table 2. All patients were examined between 2015 and 2020 at the Department of Pediatric Neurology of the Faculty of Medicine, Masaryk University and University Hospital Brno, Czech Republic, and were diagnosed with epilepsy. Informed consent for genetic testing was obtained from all the patients/parents undergoing testing. The study was approved by the Ethics Board of the Faculty of Medicine of Masaryk University and University Hospital Brno.

Medical records were retrospectively studied in all patients and the following characteristics were monitored: sex, age at epilepsy onset, time to genetic testing, family history of epilepsy, perinatal risks, and type of epilepsy: epileptic encephalopathy (EE), generalized epilepsy (GE), or focal epilepsy (FE). If possible, epilepsy was further specified according to the ILAE classification of epilepsies [7]. We also studied the neurological status in patients, associated psychiatric comorbidities, findings on brain magnetic resonance imaging (MRI, 1.5T), and changes in clinical management in relation to the sequence variant in the group of genetically positive patients. With regard to the efficacy of the therapeutic regimens, we considered the changes in clinical management as effective if they contributed to a more than 50% decrease in the seizure frequency from the baseline.

Detection of single nucleotide variants (SNV) and copy number variants by the targeted gene sequencing were performed at the Center of Molecular Biology and Genetics, Masaryk University and University Hospital Brno, Czech Republic.

2.1. Targeted gene sequencing

A custom-designed solution-based capture method (Roche NimbleGen) was used to capture exons with adjacent intron regions of the 270 genes known to be associated with epilepsy and epileptic syndromes. Sequencing of the captured regions was performed using next-generation sequencing on the NextSeq 550 System (Illumina). The individual DNA sequence reads were aligned to the published human genome reference (HG19/GRCh37) and variants were called using the software Sequence Pilot (JSI Medical Systems) or the CLC Genomics Workbench (QIAGEN). Large gene deletions/duplications were identified by CNV analysis by the software CLC Genomics Workbench. In case of large gene deletion/duplication identification, this was verified by Multiple Ligation-dependent Probe Amplification (SALSA MLPA Probemix P348 ATP1A2-CACNA1A-PRRT2, SALSA MLPA Probemix P395 MEF2C-FOXG1, SALSA MLPA Probemix P137 SCN1A; MRC Holland). Identified sequence variants were interpreted using the standards and guidelines from the joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathology (AMP) published in 2015 [6]. Using these criteria, genetic variants were divided into five categories: pathogenic (P), likely pathogenic (LP), benign (B), likely benign (LB), and variants of uncertain significance (VUS). The segregation of P/LP variants and VUS in a patient's family was assessed by Sanger sequencing. The last step in variant interpretation involved the analysis of all possible P/LP variants and VUS by the patient's pediatric neurologist or epileptologist. If the variant was evaluated as VUS, but the patient's phenotype was highly suspected of its pathogenicity, parental analysis was performed, and the variant could have been reclassified. This was a complex process where several factors, often overlapping, had to be evaluated to complete the diagnosis and reclassification of the variant to P/LP. The clinicians performed an in-depth review of each patient's phenotype and gave an opinion from their point of view. Each case was further reviewed and discussed in a consensus meeting that included the participation of the molecular and medical geneticists and clinicians. Genotype–phenotype correlation and parental DNA analysis were an integral part of the NGS diagnostic process in accordance with currently valid recommendations [6].

2.2. Statistics

Categorical variables were summarized using absolute and relative frequencies. To summarize the continuous characteristics, mean, standard deviation (SD), median, minimum, and maximum were used, see Table 1.

Testing was carried out using the Mann–Whitney U test and Fisher's exact test. A value of $p < 0.05$ was considered statistically significant.

3. Results

A total of 175 patients (95 males and 80 females) aged 0 to 19 years were included in the study. All patients had been diagnosed with epilepsy and underwent genetic testing with the NGS epilepsy gene panel between 2015 and 2020.

Dividing patients into categories by type of epilepsy, 89 out of 175 patients (50.86%) experienced developmental and epileptic encephalopathy (DEE), 45 (25.71%) were classified with generalized epilepsy (GE), and 41 (23.43%) had focal epilepsy (FE). We further classified the cohort of patients in more detail into specific epileptic syndromes according to the ILAE classification of epileptic syndromes, where possible [7].

The mean patient age at epilepsy onset was 33.05 ± 40.07 months (ranged from 0 to 215 months). Time from the epilepsy manifestation to genetic testing was 46.7 ± 52.5 months (ranged from 0 to 215 months). In 61 out of 175 patients (35.88%), a positive family history of epilepsy was identified; in 81 patients (46.29%), important perinatal risks were recorded in the medical history; and 71 out of the 166 patients tested (42.77%) had pathology on brain MRI (9 patients did not have an MRI examination). See Table 1 for more details concerning the basic characteristics.

3.1. NGS testing

The described pathogenic variants were identified in 25 patients; other 5 patients carried novel variants, but can be classified as pathogenic because the creation of a premature termination codon in genes where variants of this type occur is a known disease mechanism. Genotype–phenotype correlations and parental DNA analysis confirmed the association of the identified variants and patient diseases. Sixteen patients (marked in Table 2) carried novel

Table 1
Basic statistical data of cohort. DEE = developmental epileptic encephalopathy, GE = generalised epilepsy, FE = focal epilepsy.

Category	Subcategory	Mean/Abs. value (relative)	Min – max	SD	Median
Sex	Male	*n* = 95 (54.29%)	–	–	–
	Female	*n* = 80 (45.71%)	–	–	–
Type of epilepsy	DEE	*n* = 89 (50.86%)	–	–	–
	GE	*n* = 45 (25.71%)	–	–	–
	FE	*n* = 41 (23.43%)	–	–	–
Age at epilepsy onset (months)		33.05	0 – 215	40.07	18.00
Time from epilepsy onset to genetic diagnosis (months)		47.14	0 – 264	53.83	29.00
Contributing factors	MRI pathology	*n* = 71 (42.77%)	–	–	–
	Family history	*n* = 61 (35.88%)	–	–	–
	Perinatal risks	*n* = 81 (46.29%)	–	–	–

Table 2
Detailed characteristics of patients with newly described genetic abnormalities. These patients carry novel missense variants, which were classified as P/LP after genotype–phenotype correlations and parental DNA analysis. Variant status was determined according to the occurrence in Human Gene Mutation Database. The reference sequences can be found in supplementary information. M = male, F = female, AD = autosomal dominant, AR = autosomal recessive, XD = x-linked dominant, NA = not available/applicable, Y = yes, N = no, DEE = developmental epileptic encephalopathy, GE = generalised epilepsy, FE = focal epilepsy, DS = Dravet syndrome, GEFS+ = genetic epilepsy with febrile seizures plus, EOEE = early-onset epileptic encephalopathy, WS = West syndrome, , FIRES = Febrile Infection-Related Epilepsy Syndrome, NORSE = New-Onset Refractory Status Epilepticus, LGS = Lennox–Gastaut syndrome.

Patient No.	Sex	Pathogenic/Likely pathogenic variant	Variant status	Inheritance	Origin	Age at onset (months)	Time to diagnosis (months)	Family history	Type of epilepsy	Epileptic syndrome
1	M	*SCN1A*: c.251A > C p.(Tyr84Ser)	new	AD	de novo	4	10	N	DEE	DS
3	F	*SCN1A*: c.383 + 3A > G p.?	new	AD	de novo	6	1	N	DEE	DS
8	F	*SCN2A*: c.416 T > C p.(Ile139Thr)	new	AD	de novo	0	1	N	DEE	EOEE
11	M	*SCN2A*: c.3973G > A p.(Val1325Ile)	new	AD	maternal	4	3	mother	DEE	EOEE
17	M	*KCNT1*: c.2815 T > C p.(Ser939Pro)	new	AD	de novo	31	2	N	EE	FIRES/ NORSE
19	M	*SLC2A1*: c.1199G > C p.(Arg400Pro)	new	AD	de novo	62	71	father	FE	FE
24	M	*GABRA1*: c.911 T > G p.(Leu304Arg)	new	AD	de novo	8	179	N	DEE	LGS
26	M	*GNAO1*: c.133G > A p.(Gly45Arg)	new	AD	de novo	0	0	N	DEE	EOEE/WS
27	F	*HCN1*: c.838C > G p.(Gln280Glu)	new	AD	maternal	24	37	mother	GE	GEFS+
30	F	*PCDH19*: c.787A > C p.(Ser263Arg)	new	XD	NA	42	57	N	DEE	NA
31	F	*POLG*: c.1399G > A p.(Ala467Thr); *POLG*: c.3604A > T p.(Asn1202Tyr)	described; new	AR	maternal, paternal	54	1	brother	DEE	NA
33	F	*SCN5A*: c.5153 T > G p.(Leu1718Arg)	new	AD	de novo	7	0	N	DEE	WS
34	F	*SCN8A*: c.1243G > A, p.(Glu415Lys)	new	AD	de novo	11	168	mother	DEE	LGS
35	F	*SLC6A1*: c.739C > A p.(Pro247Thr)	new	AD	NA	36	122	N	DEE	LGS
38	M	*SZT2*: c.1769 + 1G > C p.?; *SZT2*: c.8435C > T p.(Ser2812Phe)	new; new	AR	paternal/maternal	97	74	grandfather	FE	FE
39	F	*WWOX*: c.321C > G p.(Tyr107*); *WWOX*: c.845C > A p.(Pro282Gln)	new; new	AR	maternal/ paternal	0	7	N	DEE	EOEE/WS

missense variants, which were classified as P/LP after genotype–phenotype correlations and parental DNA analysis. The diagnostic yield of our study was 46 out of 175 patients (26.28%).

P/LP sequence variants were detected in 27 genes; 17 genes are associated with autosomal dominant inheritance - *SCN1A* (8 patients), *SCN2A* (6 patients), *PRRT2* (4 patients), *CACNA1A* (2 patients), *KCNT1* (2 patients), *SLC2A1* (2 patients), *TSC2* (2 patients), and *ASXL3, GABRA1, GABRG2, GNAO1, HCN, KCNQ2, MEF2C, SCN5A, SCN8A, SLC6A1, STXBP1* (each 1 patient); 4 genes with autosomal recessive inheritance – *ALDH7A1, POLG, SZT2,* and *WWOX* (each 1 patient); and 5 genes had X-linked inheritance – *MECP2, NEXMIF, PCDH19, SMC1A,* and *WDR45* (each 1 patient). In total, 48 different types of P/LP sequencing variants were identified (44 small-scale variants and 4 large gene deletions); 23 of these variants were novel and not previously described in the literature, 18 of these are missense variants; detailed characteristics of patients with newly described missense genetic abnormalities are shown in Table 2.

Detailed characteristics of patients with newly described genetic abnormalities are clearly shown in Table 2.

3.2. Comparison of genetically positive and negative cases

When the 46 patients with positive genetic findings were compared to the 129 patients who showed negative findings in the NGS epilepsy gene panel, the age at seizure onset was significantly earlier ($p = 0.0004$) in positive cases, and the proportion of patients with DEE was significantly larger ($p = 0.0001$) and with FE was significantly smaller ($p = 0.1571$). Other characteristics were not statistically significant (Table 3). The diagnostic yield was higher in patients with seizure onset during the neonatal period (0–3 months of age), with 38.46% (10 out of 26) of patients proven

Table 3
Statistical comparison of genetically positive and negative cases. S = statistically significant ($p < 0.05$), NS = not statistically significant.

Category	Group	Mean/Abs. value (relative)	SD	Median	*p*-value	S/NS
Number of patients	Pos.	*n* = 46 (26.29%)	–	–	–	–
	Neg.	*n* = 129 (73.71%)	–	–	–	–
Age of epilepsy manifestation (months)	Pos.	17.96	22.28	8.00	–	–
	Neg.	38.43	43.35	24.00	–	–
	Pos. vs. Neg.	–	–	–	$p = 0.0004$	**S**
Time to diagnosis (months)	Pos.	51.02	66.82	11.50	–	–
	Neg.	45.75	48.05	30.00	–	–
	Pos. vs. Neg.	–	–	–	$p = 0.3742$	NS
Type of epilepsy – DEE	Pos.	*n* = 35 (76.09%)	–	–	–	–
	Neg.	*n* = 54 (41.86%)	–	–	–	–
	Pos. vs. Neg.	–	–	–	$p = 0.0001$	**S**
Type of epilepsy – GE	Pos.	*n* = 4 (8.7%)	–	–	–	–
	Neg.	*n* = 41 (31.78%)	–	–	–	–
	Pos. vs. Neg.	–	–	–	$p = 0.0016$	**S**
Type of epilepsy – FE	Pos.	*n* = 7 (15.21%)	–	–	–	–
	Neg.	*n* = 34 (26.36%)	–	–	–	–
	Pos. vs. Neg.	–	–	–	$p = 0.1571$	NS
MRI pathology	Pos.	*n* = 17 (39.53%)	–	–	–	–
	Neg.	*n* = 54 (43.90%)	–	–	–	–
	Pos. vs. Neg.	–	–	–	$p = 0.7209$	NS
Family history	Pos.	*n* = 11 (23.91%)	–	–	–	–
	Neg.	*n* = 51 (39.53%)	–	–	–	–
	Pos. vs. Neg.	–	–	–	$p = 0.0725$	NS
Perinatal risks	Pos.	*n* = 22 (47.82%)	–	–	–	–
	Neg.	*n* = 60 (46.51%)	–	–	–	–
	Pos. vs. Neg.	–	–	–	$p = 1.0000$	NS
Diagnostic yield (0–3 months vs. 4 months and older)	0–3 M	*n* = 10 (38.46%)	–	–	–	–
	4 M +	*n* = 36 (24.16%)	–	–	–	–
	0–3 M vs. 4+	–	–	–	$p = 0.1487$	NS

to have a causative mutation. Nevertheless, this was not statistically significant when compared to the patients whose seizures began after 3 months of age; they show a diagnostic yield of 24.16% ($p = 0.1487$).

3.3. Precision medicine implications

In 13 of 46 patients (28.26%) the therapeutic regimen was modified (Table 4). This was effective in reducing seizures by at least 50% in 9 of them (69.23%). Due to the size of the cohort, these are only case observations, and will be discussed in detail in the discussion section. Table 4 summarizes precision medicine applications in these 13 patients.

4. Discussion

4.1. Diagnostic yield of NGS epilepsy gene panel

Previous studies have shown that NGS of multiple disease-related genes is an effective tool for diagnosing the cause of epilepsy [8–11]. This finding is particularly true for early-onset epileptic encephalopathy, which has been reported to have a higher proportion of monogenic causes than other epilepsies [3].

The results of our retrospective study show a 26.28% yield of NGS epilepsy gene panel with 270 genes associated with epilepsy. The yield of different multigene panels varies from 20% to 40%, depending on the results of various studies [12]. The individual panels differ in the number and proportion of individual genes; after careful examination, it is clear that there is no direct relationship between the number of genes in the NGS epilepsy gene panel and its yield. It is evident that only a few genes are still repeated in the results, and the *SCN1A*, *KCNQ2, SCN2A*, and *STXBP1* genes are most often represented in positive cases [12]. Thus, the diagnostic yield of the NGS panel appears to be determined by the number of commonly mutated genes included in the panel rather than the total number of genes in the panel [13].

Consistent with the world literature is the fact that the age at epilepsy manifestation in positive patients is lower [9,11]. The mean age of epilepsy manifestation in our group was around 2.5 years; in the children who tested positive it was 1.5 years and in the children with a negative result it was almost 3.5 years. It is also worth noting that cohorts with patients with early-onset epilepsy encephalopathies, i.e. children at neonatal age (0–3 months), show a higher yield of NGS panel. Costain et al. [9] even showed a panel yield in children under 12 months of 72%, higher yields in newborns (37.1%) were also shown in the study by Ko et al. [14]. These results are in line with our observation, in which the yield in the group of children under 3 months was 38.46%. These observations are logical and are based on the fact that severe developmental and epileptic encephalopathies manifest in the neonatal period and a serious clinical picture often requires prompt diagnosis leading to the detection of the cause and the introduction of possible specific therapy in indicated cases. Therefore, these children receive a genetic diagnosis much earlier. For these reasons, genetic diagnosis using multi-gene sequencing techniques is recommended as a standard diagnostic tool for children with neonatal DEE [11,15]. Making an early molecular diagnosis can also end the genetic odyssey, enable recurrence risk counseling, guide participation in gene-specific clinical trials, and provide families with the opportunity to interact with support groups or advocate for research [8]. Oates et al. showed that early genetic diagnosis in children with DEE can reduce costs up to 70% compared to its failure or even over 85% in case of diagnosis of Dravet syndrome [16,17]. The argument based on the high cost of genetic testing therefore seems unfounded.

Few studies have emphasized the precise systematic and standardized procedure in interpreting the results of the NGS panel [10,14]. Accurate interpretation of NGS panel results includes several key areas: (1) population data and database review; (2) computational data, allelic data, and literature review; (3) clinical

Table 4
Precision medicine applications in 13 patients with P/LP variants. M = male, F = female, AD = autosomal dominant, NA = not available/applicable, Y = yes, N = no, DEE = developmental epileptic encephalopathy, FE = focal epilepsy, DS = Dravet syndrome, EOEE = early-onset epileptic encephalopathy, TPM = topiramate, KD = ketogenic diet, STP = stiripentol, PHT = phenytoin, ESM = ethosuximide, B6 = vitamin B_6.

Patient No.	Sex	Pathogenic/Likely pathogenic gene variant	Variant status	Inheritance	Origin	Type of epilepsy	Epileptic syndrome	Precision medicine (reduction of seizures more than 50%)
1	M	SCN1A	new	AD	de novo	DEE	DS	N (TPM)
2	F	SCN1A	new	AD	NA	DEE	DS	Y (KD)
3	F	SCN1A	new	AD	de novo	DEE	DS	Y (STP)
8	F	SCN2A	new	AD	de novo	DEE	EOEE	Y (PHT)
9	M	SCN2A	described	AD	de novo	DEE	EOEE	NA (PHT with very good effect before the genetic diagnosis; administered at 2 months of age)
12	F	SCN2A	described	AD	de novo	DEE	EOEE	Y (PHT)
14	M	CACNA1A	described	AD	de novo	DEE	EOEE	N (ESM with important aggravation of seizures)
16	F	KCNT1	described	AD	de novo	DEE	EOEE	Y (KD)
18	F	SLC2A1	described	AD	de novo	DEE	NA	Y (KD)
19	M	SLC2A1	new	AD	de novo	FE	FE	N (KD)
23	M	ALDH7A1, ALDH7A1	described; described	AR	maternal/paternal	DEE	DS	Y (B6)
25	F	GABRG2	described	AD	de novo	DEE	MAE	Y (KD)
43	F	SCN1A; deletion of the entire gene /CNV analysis/	NA	AD	de novo	DEE	DS	Y (STP)

review and family study; and (4) consensus multidisciplinary discussions [10]. At our workplace, we work closely with a team of molecular and medical geneticists and consult the interim results during the NGS gene panel testing. The results of this work show that the multidisciplinary approach led to a definitive diagnosis in some patients with novel not previously described variants and increased the diagnostic yield of NGS analysis from 30 to 46 patients, which is by 53.33% (yield increased from 17.14% to 26.28%). This is very important from a clinical point of view.

Unfortunately, we failed to identify causal mutations in approximately 2/3 of patients. This result is consistent with the results of many studies dealing with NGS techniques. It is clear that other genetic mechanisms come into play, such as epigenetics or somatic mutations.

It is also worth mentioning the comparison of the yield of NGS epilepsy gene panel and examination using WES or WGS technique. The largest meta-analysis from 2021 shows that the yield of the NGS panel is on average 24% compared to WES, which is 27.2%, i.e., slightly higher, as well as a smaller meta-analysis shows the yield of WES analysis 31% [18]. The truth is that accurate quantification of positive results of WES analysis is very difficult given that WES is very often tested in patients who are negative using the NGS epilepsy gene panel technique. If WES is performed independently of the NGS multiple gene panel, its yield may be significantly higher (19% vs. 37%) [9].

4.2. Precision medicine strategy

Genetic diagnosis of monogenic epilepsy presents great challenges. Knowledge of the pathophysiological mechanisms of the epileptic process could make it possible to use the principles of precision medicine and optimize the patient's therapeutic regime. For example, some AEDs are more effective than others in some genetic epilepsy syndromes, i.e., sodium channel blockers (SCBs) in *KCNQ2*- and *PRRT2*-related seizures [19,20]. Some AEDs can worsen the seizure activity, as observed in SCBs in *SCN1A*-related epilepsies [21]. Some AEDs can lead to fatal liver failure, as observed in patients with POLG-associated epilepsy receiving valproic acid (VPA) [22]. In our cohort, more than half of the patients had "actionable" genes with immediate treatment implications. Eighteen of these patients underwent targeted therapies.

Eight of the patients carried a *SCN1A* variant, which was the most frequent sequence variant detected in our cohort. In most patients, the phenotype of Dravet's syndrome was presumed before targeted molecular genetic diagnosis, so a combination of VPA, clobazam (CLB), and stiripentol (STP) was used. None of these patients were treated with SCBs at the time of diagnosis. Several studies proved that there is an improvement not only in seizure frequency after SCBs are tapered off but also in cognitive performance, language skills, and general well-being [23]. One of the *SCN1A* positive patients importantly improved on TPM and another on STP. In one patient, a ketogenic diet (KD) led to a 70% seizure reduction.

We diagnosed six patients with SCN2A-related epileptic encephalopathy. Phenytoin (PHT) was administered in four of them and led to important seizure reduction in three patients. Wolff et al. [24] reported that *SCN2A* mutations cause two distinct phenotypes: early-infantile onset (up to 3 months of age) and infantile/childhood onset (more than 3 months of age) encephalopathies. The early infantile form was associated with gain-of-function mutations, and therefore showed good response to sodium channel blockers, while the later onset form was associated with the loss-of-function variants and SCBs were rarely effective and sometimes worsened the seizures [24]. These observations are consistent with our experience: in one patient with a clinical manifestation of DEE at 4 months of age, PHT was ineffective; in three patients with a clinical manifestation in neonatal age, SCB therapy had a very good effect, with more than 50% seizure reduction.

Two patients carried a *SLC2A1* variant (Glut1-deficiency) and were administered KD. One of them improved promptly and became seizure free. In the second patient, KD was without significant effect. The sequence variant identified in this patient was located in exon 9 of the *SLC2A1* gene, a site where causal mutations in patients with Glut1-deficiency syndrome are often found, as has been well documented [25]. Thus, the sequence variant was marked as pathogenic, and a biochemical correlate of the disease with a pathological absolute concentration of glucose in cerebrospinal fluid (CSF) and ratio of glucose concentration in CSF and serum was also confirmed. The patient's phenotype was not in conflict with the diagnosis of Glut1-deficiency syndrome. Molecular diagnosis of the disease was made with a latency of almost 6 years from the manifestation of epilepsy, so KD was introduced late, which may be related to its lower effectiveness [26]. The KD patient was also less tolerant, and it was not possible to increase the energy intake to provide sufficient energy for the CNS cells

due to the fact that he did not tolerate the higher fat intake and he vomited. The poorer response to diet was relatively accented by the fact that the patient was also diagnosed with bilateral MTS on brain MRI, which, we assume, developed secondarily after prolonged seizure activity, and could continue to maintain the epileptogenic process regardless of the primary cause of epilepsy.

5. Conclusion

Our results support the introduction of the NGS epilepsy gene panel into the diagnostic algorithm, especially in children with DEE. Early diagnosis is desirable not only in terms of completing the demanding diagnostic process, but also in terms of introducing targeted therapy. In the interpretation of genetic examination results, we appeal for a very complex genotypic–phenotypic correlation and a multidisciplinary approach that will enable the most accurate genetic diagnosis and the correct interpretation of the results.

Declaration of competing interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on the issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108564.

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2.5 Annex 5

Danhofer P, Horák O, Fajkusová L, Pavloušková J, Ošlejšková H. **Syndrom Dravetové: těžká myoklonická epilepsie v časném dětství – kazuistiky**. Cesk Slov Neurol N 2014; 7/110(2): 243-6.

Summary:

Dravet syndrome (DS) is classified as a rare progressive epileptic encephalopathy. Seizure onset is in the first year of life in thus far normally developing children. Typically, prolonged generalised convulsive seizures occur. Subsequently, other types of seizures are seen, accompanied by deterioration of psychomotor development. At present, detection of a specific mutation may confirm the clinical syndrome. 70–80% of patients have mutation in SCN1A gene, 5% in PCDH19 gene. Rarely, mutations in the GABARG2 gene and SCN1B gene are detected. Early diagnosis of DS is very important from the therapeutical point of view. Two case reports of patients with typical clinical course of DS and genetically detected mutation in SCN1A gene are presented

Syndrom Dravetové: těžká myoklonická epilepsie v časném dětství – kazuistiky

Dravet Syndrome: Severe Myoclonic Epilepsy in Infancy – Case Reports

Souhrn

Syndrom Dravetové se řadí mezi vzácné progresivní epileptické encefalopatie. Klinická manifestace je v prvním roce života u dosud normálně se vyvíjejících kojenců. Typicky začíná febrilními protrahovanými konvulzivními záchvaty, později se objevují i jiné typy záchvatů a dochází k psychomotorické deterioraci. Diagnóza se dá stanovit na podkladě klinického obrazu, v současnosti je možné u převážné většiny pacientů i potvrzení genetické. U 70–80 % pacientů nalézáme mutaci v genu *SCN1A*, u 5 % je detekována mutace v *PCDH19* genu, vzácně pak v *GABARG2* a *SCN1B* genu. Časná diagnostika pacientů je velmi žádoucí vzhledem k terapeutickým specifikům nemoci. Jsou prezentovány kazuistiky dvou pacientů s typickým průběhem DS a geneticky potvrzenou mutací v *SCN1A* genu.

Abstract

Dravet syndrome (DS) is classified as a rare progressive epileptic encephalopathy. Seizure onset is in the first year of life in thus far normally developing children. Typically, prolonged generalised convulsive seizures occur. Subsequently, other types of seizures are seen, accompanied by deterioration of psychomotor development. At present, detection of a specific mutation may confirm the clinical syndrome. 70–80% of patients have mutation in *SCN1A* gene, 5% in *PCDH19* gene. Rarely, mutations in the *GABARG2* gene and *SCN1B* gene are detected. Early diagnosis of DS is very important from the therapeutical point of view. Two case reports of patients with typical clinical course of DS and genetically detected mutation in *SCN1A* gene are presented.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
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The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Klíčová slova

Dravetové syndrom – myoklonická epilepsie – epilepsie – terapie

Key words

Dravet syndrome – myoclonic epilepsy – epilepsy – therapy

Úvod

Syndrom Dravetové (DS), těžká myoklonická epilepsie v časném dětství, se řadí mezi vzácné progresivní epileptické encefalopatie [1]. Diagnostika a syndromologické zařazení se dá provést na podkladě klinického obrazu, v současné době je možné diagnózu potvrdit i geneticky. Cílem této publikace je upozornit na včasné rozpoznání pacientů s DS. Pacienti s podezřením na DS by měli být co nejdříve odesláni do specializovaných center ke genetické diagnostice a specifické terapii. Včasná diagnostika DS a jeho intenzivní léčba může vést k redukci protrahovaných epileptických záchvatů, které se nepřímo mohou spolupodílet na míře psychomotorické retardace u pacientů s DS.

Kazuistika 1

U první pacientky, aktuálně 2,5leté, se záchvaty objevily ve čtyřech měsících věku. V rodinné anamnéze bez pozoruhodností, v graviditě bez komplikací, perinatální průběh bez rizik s normální poporodní adaptací. Motorický vývoj byl lehce disharmonický s dobrým efektem rehabilitace dle Vojty. Ve čtyřech měsících věku se objevil první afebrilní protrahovaný pravostranný hemikonvulzivní záchvat. V témže měsíci pak 50minutový epileptický status s levostrannými křečemi při febrilním infektu. Provedená vyšetření (MR mozku, odběr mozkomíšního moku, EEG a odběr krve a moči k vyšetření dědičných poruch metabolizmu) byla negativní. Byla zahájena terapie fenobarbitalem v dávce 4,5 mg/kg/den. V dalším průběhu ale záchvaty trvaly s frekvencí několika paroxyzmů za měsíc. Objevovaly se konvulzivní záchvaty se střídavou lateralizací, často vázány na febrilní infekt, pacientka byla velmi citlivá i na teplé počasí, v létě se stav výrazně zhoršil, délka záchvatů byla od 5 do 40 min. Vzhledem k závažnosti a délce trvání záchvatů byla pacientka opakovaně hospitalizována na jednotce intenzivní péče, opakovaně vyžadovala i hospitalizaci na ARO s nutností intubace. Od devíti měsíců věku se začaly objevovat i protrahované záchvaty charakteru areaktivity s celkovou hypotonií a deviací hlavy a bulbů (stranově střídavě, převážně ale doprava) – záchvaty hypomotorické s verzivní složkou. Tyto záchvaty byly přítomny s frekvencí několika za měsíc. V EEG se objevilo zpomalení a dezorganizace základní aktivity do pásma delta, ojediněle i ostré vlny pod F4. V dalším průběhu byly nasazeny postupně valproát, levetiracetam a klonazepam, vždy jen s přechodným efektem a vymizením záchvatů na několik měsíců. Ve dvou letech věku byla přímou DNA analýzou potvrzena mutace c.408C>A, p.(Cys136*) v genu *SCN1A* v heterozygotní formě. Identifikovaná mutace nebyla v literatuře ani databázi HGMD (Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ac/index.php) popsána. Byla provedena detekce mutace u rodičů a dle předpokladu bylo zjištěno, že se jedná o mutaci de novo. Postupně byla zahájena redukce fenobarbitalu a levetiracetamu, pacientka poté zůstala na kombinaci valproát a klonazepam, který byl zaměněn za klobazam. Ve dvou letech věku bylo zahájeno nasazování stiripentolu v dávce 50 mg/kg/den s parciálním efektem. Došlo ke snížení frekvence záchvatů generalizovaných konvulzivních na cca jeden za měsíc, především ale byly výrazně kratší v trvání maximálně do 3 min, záchvaty hypomotorické dále rodiče nereferovali. Ve 2,5 letech věku se objevil nový typ záchvatů, atypické absence s EEG korelátem generalizovaných komplexů hrot vlna o frekvenci 3,5 Hz s počátkem temporálně vpravo. V EEG se nově objevila interiktální epileptiformní patologie vpravo temporoparietálně. Nyní pacientka zahajuje ketogenní dietu. Aktuálně ve 2,5 letech věku je v objektivním neurologickém nálezu lehká centrální hypotonie, pacientka již sama obchází kolem nábytku, jemná motorika je lehce nedokonalá. Psychický vývoj je disharmonický, odpovídá 12–15 měsícům věku. Dominuje slabší schopnost komunikace a řečového vývoje s atypiemi v sociálním chování (menší zastoupení reciprocity), vývoj však jak po motorické, tak i psychické stránce pozvolna pokračuje.

Kazuistika 2

Druhý pacient je čtyřletý chlapec. V rodinné anamnéze bez pozoruhodností, těhotenství probíhalo bez komplikací, porod byl spontánní v termínu bez perinatálních komplikací s normální poporodní adaptací. Až do klinické manifestace epileptických záchvatů byl psychomotorický vývoj normální. Záchvaty se objevily v sedmi měsících věku s konstantní vazbou na febrilní infekty. Klinicky se jednalo o konvulzivní záchvaty se střídavou lateralizací v trvání obvykle do 5 min, nejdelší záchvat byl 10minutový. Frekvence záchvatů byla jeden za měsíc. Pacient byl opakovaně hospitalizován v okresní nemocnici, kde bylo provedeno CT mozku a MR mozku s normálním nálezem, vstupní EEG negativní. Dále byl proveden odběr séra a moči na vyšetření dědičných poruch metabolizmu s negativním nálezem. V krevním obraze zjištěna lehká hypochromní anémie, na kardiologii inkompletní blok pravého Tawarova raménka. Vzhledem k četnosti záchvatů byl nasazen valproát, poté přidán klonazepam. I přes dvojkombinaci léků se záchvaty objevovaly dále s frekvencí 1–2 za měsíc, vždy s vazbou na febrilní infekt. Ke stávající dvojkombinaci léků byl přidán levetiracetam a pacient byl odeslán k vyšetření na Kliniku dětské neurologie LF MU a FN Brno, kde byla zahájena dispenzarizace. V dalším období, ve věku od 13 měsíců do dvou let byl chlapec klinicky kompenzován. Poté se objevily záchvaty opět, s četnější frekvencí a nově i bez vazby na horečku. Trvají záchvaty charakteru generalizovaných nebo stranově střídajících lateralizovaných křečí v délce do 5 min, dále se objevuje nový typ záchvatů bez křečí s areaktivitou a oroalimentárními automatizmy v trvání do 10 min. Záchvaty se objevují s frekvencí 1–2 za měsíc. V EEG zachycen opakovaně negativní nález, od tří let věku se vyskytují ojedinělé ostré vlny v bifrontální lokalizaci s pravostrannou převahou. Vzhledem k neúčinnosti stávající medikace byla zahájena redukce levetiracetamu, aktuálně je chlapec na dvojkombinaci valproátu s klobazamem, který byl nasazen výměnou za klonazepam, a nasazuje se stiripentol.

Ve 2,5 letech věku byla přímou DNA analýzou u pacienta prokázána mutace c.1989delT, p.(Phe663Phefs*9) v genu *SCN1A* v heterozygotní formě. Identifikovaná mutace nebyla v literatuře ani databázi HGMD popsána. V objektivním neurologickém nálezu lze sledovat centrální hypotonii s bederní hyperlordózou, je schopen samostatné chůze s valgózním postavením kolen a bérců. V psychologickém profilu dominuje hyperaktivita a porucha koncentrace, slabší sociální kontakt při zachovalé dovednosti jeho navázání. Intelekt celkově v pásmu normy rozkolísaný především pro slabou koncentraci.

Diskuze

Syndrom Dravetové byl poprvé popsán v roce 1978 profesorkou Charlotte Dra-

vet ve Francii [2]. Dle ILAE klasifikace epileptických syndromů z roku 1989 se řadí mezi epilepsie a epileptické syndromy nezařaditelné jako ložiskové či generalizované [3]. Dle revize této klasifikace z roku 2010 patří mezi elektroklinické syndromy časného dětství [4].

V souladu s ILAE revizí epileptických syndromů 2010 se syndrom Dravetové z etiologického hlediska řadí mezi epilepsie na genetickém podkladě. Převážná část pacientů jsou nositelé mutace v genu pro alfa1 podjednotku sodíkového kanálu (gen *SCN1A*), tato mutace se vyskytuje u 70–80 % pacientů [5]. Dochází zde ke snížení excitability GABAergních interneuronů v neokortexu a hipokampu [6], což má za následek snížení výbojů v těchto inhibičních interneuronech. Dojde tak ke zvýšení excitability v neuronální síti a rozvoji *SCN1A* epileptické encefalopatie.

Mutace v *SCN1A* genu jsou odpovědné za rozvoj velmi variabilního fenotypového vyjádření, tzv. GEFS+ spektra. Na „benigním" konci spektra se vyskytují pacienti se syndromem GEFS+ (febrilní záchvaty + afebrilní generalizované tonicko-klonické záchvaty), na druhém konci spektra se nachází DS. Mutace u pacientů s DS jsou ve 40 % tzv. truncating mutace, které způsobují předčasný vznik terminačního kodonu, čímž vedou k předčasnému ukončení translace, a nebo v dalších 40 % případů se jedná o tzv. missense mutace [7]. Za rozvoj GEFS+ je odpovědná spíše missense mutace v genu *SCN1A*, nicméně genotypová-fenotypová korelace není konzistentní. Předpokládá se, že pokud se missense mutace nachází v pór formující oblasti *SCN1A* genu, rozvine se DS, pokud je mutace mimo tuto oblast, fenotypově se rozvine spíše GEFS+ syndrom [7].

Genetika DS je ještě komplexnější. Vzácně byly identifikovány u pacientů s DS i mutace v genu *GABARG2* [8] a *SCN1B* [9].

Zhruba 5 % pacientů nese mutaci v genu *PCDH19* s X-vázanou dědičností [10]. Jedná se o gen kódující protocadherin 19, jehož funkce nebyla dosud plně objasněna, ale předpokládá se jeho zapojení v neuronálních sítích. Mutace způsobuje epilepsii limitovanou na ženy s mentální retardací (Epilepsy limited to Females with Mental Retardation, EFMR). Charakteristickým rysem je zde menší výskyt epileptických statů a jen zřídka se objevují myoklonické záchvaty.

Tab. 1. Příznaky a klinické nálezy upozorňující na diagnózu DS a další průběh onemocnění.

Příznaky a klinické nálezy upozorňující na diagnózu DS (tzv. red flags)	Další průběh DS
manifestace v kojeneckém věku	
normální objektivní neurologický nález	centrální hypotonie, ataxie
normální psychomotorický vývoj v době manifestace	rozvoj psychomotorické retardace
protrahované konvulzivní epileptické záchvaty (často SE), často lateralizované	rozvoj dalších typů záchvatů – atypické absence, myoklonické záchvaty, fokální záchvaty
febrilní záchvaty, provokace v horkém počasí	
normální iniciální EEG	dezorganizace základní aktivity, multifokální výboje hrotů a komplexů hrot/pomalá vlna, fotosenzitivita v průběhu onemocnění
normální nález na MR mozku	možný rozvoj atrofie mozku

U 45 % pacientů je mentální retardace jen mírného stupně, časté jsou autistické rysy.

U pacienta s typickým fenotypem DS dochází k rozvoji epileptických záchvatů v kojeneckém věku s vrcholem kolem 5. měsíce u dosud normálně se vyvíjejících dětí. Incidence je udávána 1 : 30 000 dětí [1], častěji jsou postiženi chlapci v poměru 2 : 1. Objevují se tyto typy záchvatů: generalizované klonicko-tonické záchvaty (resp. často lateralizované stranově střídající), myoklonické záchvaty, atypické absence a fokální záchvaty s poruchou vědomí. Velmi častý je výskyt status epilepticus, především v počátečním období, a to převážně u febrilních záchvatů. Tab. 1 ukazuje příznaky, kdy je třeba myslet na možnost DS (tzv. red flags).

V klinickém obraze pacientů s DS existuje jistá variabilita, mluvíme o DS-spektru (tab. 2) [5].

V současné době je v České republice genetické potvrzení DS možné provést v Brně a v Praze, a to na úrovni vyšetření *SCN1A* genu. V Brně vyšetření provádí Centrum molekulární biologie a genové terapie Interní hematoonkologické kliniky LF MU a FN Brno (kontakt: RNDr. Lenka Fajkusová, CSc., lfajkusova@fnbrno.cz). V Praze se lze obrátit na Ústav biologie a lékařské genetiky 2. LF UK a FN v Motole (kontakt: RNDr. Petra Hedvičáková, petra.hedvicakova@lfmotol.cuni.cz). V případě podezření na DS je vhodné provést genetickou konzultaci na výše uvedených pracovištích.

Vyšetření vzácnějších mutací DS probíhá na celoevropské úrovni pod záštitou projektu EuroEPINOMICS, a to v programu RES (genetics of Rare Epilepsy Syndromes). Pro zájemce odkazujeme na stránku http://www.euroepinomics.org/.

Terapeutické možnosti jsou poměrně bohaté, jejich efekt je však limitován vysokou farmakorezistencí pacientů. Lékem první volby jsou valproát a benzodiazepiny [11], především klobazam. Při neefektu těchto je indikován stiripentol. Stiripentol (Diacomit) je řazen mezi orphan-drug v terapii DS a je schválen jako přídatná terapie k valproátu + klobazamu. V terapii DS je v Evropě schválen od roku 2007. Dosud byly realizovány dvě randomizované placebem kontrolované studie, které sledují efekt stiripentolu jako přídatné terapie ke kombinaci VPA + CLB. Za tímto účelem byla zformována studijní skupina STICLO (STIripentol CLObazame study group) ve Francii a Itálii. Výsledky francouzské skupiny byly publikovány Catherine Chiron et al v roce 2000 [12]. Výsledky italské skupiny publikovány dosud nebyly, jsou však zahrnuty v metaanalýze [13]. Výsledky ukázaly 71 % [13], resp. 67 % [12] respondérů ve srovnání s placebem 5 % [13], resp. 9 % [12]. Další terapeutickou možností jsou topiramat [14] a levetiracetam (účinný především na myoklonické záchvaty [15]), které lze využít jako přídatné léky. Lamotrigin, karbamazepin, vigabatrin a vysoké dávky fenobarbitalu mohou záchvaty zhoršovat a je vhodné se jim v léčbě vyhnout.

Tab. 2. Klinické spektrum syndrom Dravetové – DS spektrum [5].

Název	Anglický název	Typ epileptických záchvatů	Nevyskytující se záchvaty	Psychomotorický vývoj
Těžká myoklonická epilepsie v časném dětství	Severe Myoclonic Epilepsy of Infancy (SMEI)	GTCS, absence, fokální a myoklinické záchvaty		psychomotorická deteriorace v různé míře
Hraniční těžká myoklonická epilepsie v časném dětství	Borderline Severe Myoclonic Epilepsy of infancy (SMEB)	GTCS, absence, fokální záchvaty	myoklonické záchvaty	psychomotorická deteriorace v různé míře
Rezistentní dětská epilepsie s generalizovanými tonicko-klonickými záchvaty	Intractable Childhood Epilepsy with Generalised Tonic-Clonic seizures (ICEGTC)	GTCS	myoklonické záchvaty, absence a fokální záchvaty	významná a časná psychomotorická deteriorace
Těžká multifokální epilepsie v časném dětství	Severe Infantile MultiFocal Epilepsy (SIMFE)	multifokální záchvaty	myoklonické záchvaty a nebo absence	psychomotorická deteriorace v různé míře

GTCS – generalizovaný tonicko-klonický záchvat.

V neposlední řadě je nutno uvést i ketogenní dietu, která má v terapii DS relativně vysokou účinnost ve srovnání s jinými epileptickými encefalopatiemi [16]. Příznivé výsledky ukazuje v terapii DS i implantace vagového stimulátoru [17].

Prezentované kazuistiky představují geneticky potvrzené případy DS s prokázanou mutací v genu *SCN1A*. Klinický průběh onemocnění je zde poměrně typický. Zavádějící může být fakt, že se u pacientů dosud nevyskytly myoklonické záchvaty, které má syndrom Dravetové – jako těžká myoklonická epilepsie v časném dětství – přímo v názvu. Myoklonické záchvaty se však vyskytovat vůbec nemusí [1] nebo často se objevují až po několika letech od klinické manifestace onemocnění. Název tak může být zavádějící. Již v roce 1994 Aicardi navrhoval pro DS název „těžká polymorfní epilepsie v časném dětství", který však v klasifikačním systému epileptických syndromů etablován nebyl.

U 70–80 % pacientů se syndrom geneticky potvrdit podařit nemusí. Je třeba však myslet na to, že DS lze diagnostikovat již na podkladě klinického obrazu a diagnostika genetická je pouze potvrzující. Diagnóza již na základě klinického vyjádření je zásadní, poněvadž umožní nasměrovat terapii správným směrem, vyvarovat se potenciálně zhoršujících léků a zvolit naopak ty, které by mohly mít efekt na redukci záchvatů. Zásadní je především časná diagnostika syndromu. Stiripentol se ukázal efektivní v redukci především konvulzivních záchvatů, jež mohou být v počátečním stadiu protrahované až charakteru epileptických statů. Právě ty se velkou měrou spolupodílí na rozvoji neurokognitivního deficitu pacientů a regresu v psychomotorickém vývoji [11].

Pojmenování nemoci je důležité i pro rodiče pacienta. Ukončí extenzivní a často stresující došetřování příčiny epilepsie, umožní s rodiči mluvit o prognóze, vysvětlit jim možné komplikace a soustředit se více na komplexní péči zahrnující psychologa, logopeda, ortopeda, rehabilitaci a další formy podpůrné terapie, které mohou celkový stav dítěte a jeho psychomotorický vývoj povzbudit. Důležité informace mohou rodiče i odborníci získat na stránkách http://www.dravetfoundation.org/.

Závěr

Syndrom Dravetové se řadí mezi prognosticky závažné epilepsie manifestující se v časném dětství. Časná a správná diagnostika je zásadní pro další terapii, která u DS představuje určitá specifika. V současné době je možná i diagnostika genetická, jež u většiny pacientů prokáže mutaci a pro diagnózu DS je potvrzující.

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2.6 Annex 6

Česká K, Aulická Š, Danhofer P, Horák O, Fajkusová L, Pouchlá S, Ošlejšková H. **Syndróm Dravetovej s mutáciou v SCN1A géne, genetické aspekty a klinické skúsenosti.** Cesk Slov Neurol N 2018; 81(1): 55-9.doi: 10.14735/amcsnn201855.

Summary:

Aims: We present retrospective analysis of the set of 11 patient group with SCN1A gene (sodium voltage-gated channel alpha subunit 1) positive Dravet syndrome (DS). Patients were examined with suspected DS from 2010 to February 2017. The aim of the study was to analyse epidemiological and clinical data and to assess the efficacy of drug therapy and MRI and EEG findings.

Material and methods: In the study the analysis of medical records of patients with SCN1A mutation positive DS and its statistic evaluation was used. We monitored development of disease, gender, types of epileptic seizures and their association with age of patient, findings on EEG and MRI, drug ef- fect. We also evaluated the neurological and behavioral-mental status of patients.

Results: In group of 11 patients, there were 7 women (63.6%) and 4 men (36.4%). Average age by manifestation of seizures was 6.5 months. All of the patients have mutation in SCN1A gene. The most frequent seizures were generalized tonic-clonic (81.8%). On the other hand the least occurring seizures were myoclonic seizures – only 2 from 11 (18.2%). Average time from development of symptomatology to correct diagnosis was by 116 months. In patients born before 2010 it was only 19 months.

Conclusion: DS is from prognostic point of view serious type of epilepsy. Since 2010, 52 samples of DS suspected patients were investigated. Eleven proven causal mutations represent 21% of samples. Early diagnostics of disease and correct management is crucial for further course of disease and has major impact on mental status and predicted prognosis

doi: 10.14735/amcsnn201855

Syndróm Dravetovej s mutáciou v *SCN1A* géne, genetické aspekty a klinické skúsenosti

SCN1A mutation positive Dravet syndrome, genetic aspects and clinical experiences

Súhrn

Ciele: Prezentujeme retrospektívnu analýzu súboru 11 pacientov s Dravetovej syndrómom (DS) s preukázanou mutáciou v *SCN1A* géne (sodium voltage-gated channel alpha subunit 1 – alfa1 podjednotka sodíkového kanálu). Pacienti boli vyšetrení s podozrením na DS od roku 2010 do februára 2017. Cieľom práce bola analýza epidemiologických a klinických nálezov, ako aj hodnotenie efektivity medikamentóznej terapie a nálezov na MR mozgu a EEG. *Materiál a metodika:* Zvolenou metódou bola analýza údajov a nálezov v zdravotníckej dokumentácií pacientov s DS s preukázanou mutáciou v *SCN1A* géne a jeho následné štatistické zhodnotenie. Sledovali sme rozvoj ochorenia, pohlavie, typy záchvatových prejavov a ich vekovú väzbu, nálezy na EEG a MR, efekt medikamentóznej terapie. Taktiež sme sa venovali hodnoteniu neurologického nálezu a behaviorálne-mentálneho statusu pacientov. *Výsledky:* V súbore 11 pacientov početne prevládajú ženy nad mužmi – 7 žien (63,6 %), 4 muži (36,4 %). Priemerný vek pri manifestácií záchvatov je 6,5 mesiaca. Všetci pacienti majú preukázanú mutáciu v *SCN1A* géne. Najčastejším typom záchvatov v skupine boli generalizované tonicko-klonické (81,8 %), naopak najmenej sa vyskytujú myoklonické záchvaty (2/11; tj. 18,2 %). Priemerný čas od rozvoja symptomatológie k stanoveniu správnej diagnózy bol u pacientov narodených pred rokom 2010 priemerne 116 mesiacov. U pacientov narodených po roku 2010 tento poklesol na 19 mesiacov. *Záver:* Dravetovej syndróm sa radí medzi prognosticky závažné epilepsie. Od roku 2010 sme vyšetrili celkom 52 vzoriek pacientov s podozrením na DS. Preukázaných 11 kauzálnych mutácií predstavuje 21% záchyt. Včasná diagnostika ochorenia a správny management je zásadný pre ďalší priebeh ochorenia a má veľký vplyv na mentálny status pacienta a predpokladanú prognózu.

Abstract

Aims: We present retrospective analysis of the set of 11 patient group with *SCN1A* gene (sodium voltage-gated channel alpha subunit 1) positive Dravet syndrome (DS). Patients were examined with suspected DS from 2010 to February 2017. The aim of the study was to analyse epidemiological and clinical data and to assess the efficacy of drug therapy and MRI and EEG findings. *Material and methods:* In the study the analysis of medical records of patients with *SCN1A* mutation positive DS and its statistic evaluation was used. We monitored development of disease, gender, types of epileptic seizures and their association with age of patient, findings on EEG and MRI, drug effect. We also evaluated the neurological and behavioral-mental status of patients. *Results:* In group of 11 patients, there were 7 women (63.6%) and 4 men (36.4%). Average age by manifestation of seizures was 6.5 months. All of the patients have mutation in *SCN1A* gene. The most frequent seizures were generalized tonic-clonic (81.8%). On the other hand the least occurring seizures were myoclonic seizures – only 2 from 11 (18.2%). Average time from development of symptomatology to correct diagnosis was by 116 months. In patients born before 2010 it was only 19 months. *Conclusion:* DS is from prognostic point of view serious type of epilepsy. Since 2010, 52 samples of DS suspected patients were investigated. Eleven proven causal mutations represent 21% of samples. Early diagnostics of disease and correct management is crucial for further course of disease and has major impact on mental status and predicted prognosis.

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The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Kľúčové slová

Dravetovej syndróm – *SCN1A* gén – genetická diagnostika – manifestácia – farmakorezistencia – antiepileptická medikácia

Key words

Dravet syndrome – *SCN1A* gene – genetic diagnostic – manifestation – pharmacoresistency – antiepileptic drugs

Úvod

Dravetovej syndróm sa klinicky manifestuje v priebehu 1. roku života. Podľa doporučení Medzinárodnej ligy proti epilepsii (The International League Against Epilepsy; ILAE) pre klasifikáciu epileptických záchvatov a epilepsií z roku 2017 sa z etiologického hľadiska radí DS medzi epilepsie s genetickým podkladom [1].

Klinickým prejavom sú recidivujúce febrilné protrahované záchvaty, až dĺžky status epilepticus (konvulzívne alebo hemikonvulzívne, stranovo alternujúce). Neskôr dochádza k rozvoju aj iných typov záchvatov (myoklonické záchvaty, atypické absencie, fokálne paroxyzmy). Syndróm Dravetovej vedie postupne k deteriorácií psychomotorického vývoja až k rozvoji mentálnej retardácie rôzneho stupňa [1,2]. Bližšia klinická charakteristika ochorenia, ako aj priebeh ochorenia v detstve a dospelosti je možné ďalej študovať v rôznych literárnych zdrojoch v tuzemskej aj zahraničnej literatúre [1–4].

Asi 70–80 % pacientov nesie abnormalitu v géne pre alfa1 podjednotku sodíkového kanálu – *SCN1A*. Celkom 5 % pacientov má mutáciu v géne pre *PCDH19* (gén pre proteín zvaný protokadherín 19), asociácia je preukázaná aj s *GABRG2* (gene coding gamma 2 subunit GABA receptor) a génom *SCN1B* (sodium voltage-gated channel beta subunit 1). Prvé spojenie mutácie *SCN1A* génu a DS bolo definované v roku 2001 [1].

V článku prezentujeme vlastný súbor 11 pacientov s DS.

Materiál a metodika

V našej práci sme hodnotili súbor 11 pacientov s preukázanou mutáciou v géne *SCN1A* sledovaných a diagnostikovaných na Klinice dětské neurologie FN Brno v spolupráci s Centrem molekulární biologie a genové terapie Interní hematoonkologické kliniky FN Brno. Od roku 2010, kedy bola diagnostika zavedená, sme vyšetrili celkom 52 vzoriek pacientov s podozrením na DS. Preukázaných 11 kauzálnych mutácií predstavuje 21% záchyt. Percentuálny výsledok záchytnosti ochorenia nedokážeme plausibilne vysvetliť. U dvoch pacientov s fenotypom DS nebola preukázaná kauzálna mutácia v *SCN1A* géne, a neboli preto zahrnutí do aktuálne hodnoteného súboru. Etiologické došetrovanie u týchto pacientov bolo rozšírené o ďalšie genetické vyšetrovanie (aktuálne gén, *GABRG2* a *PCDH19* u probanda ženského pohlavia), ktoré neprinieslo pozitívne výsledky. Konkrétne výsledky genetického vyšetrenia a charakteristika súboru v tab. 1.

Metódou hodnotenia bola retrospektívna analýza demografických a klinických údajov dostupných zo zdravotníckej dokumentácie Kliniky dětské neurologie FN Brno.

V súbore pacientov sme zisťovali tieto charakteristiky:

- pohlavie
- rodinná a osobná anamnéza
- vek pri vzniku ochorenia
- konkrétny typ záchvatov a vek pacientov pri ich manifestácii
- provokácia epileptických paroxysmov
- neurologický a behaviorálne-mentálny status pacienta
- elektroencefalografické charakteristiky pred rozvojom ochorenia a v jeho priebehu
- nálezy na MR mozgu
- efektivita medikamentóznej antiepileptickej terapie.

Tab. 1. Prehľad konkrétnych mutácií.

Pacient č.	Vek začiatku epilepsie (v mesiacoch)	Pohlavie	Uloženie mutácie v *SCN1A* géne
1	4	žena	c.408C>A, p.Cys136*
2	8	muž	c.1989delT/-, p.Pro663Profs*9
3	6	muž	c.3521C>G, p.Thr1174Ser
4	5	muž	c.942G>A/-, p.Trp314*
5	9	žena	c.3521C>G, p.Thr1174Ser
6	4	žena	c.1086C>T/-, p.Tyr362*
7	10	žena	c.4135G>T, p.Val1379Leu
8	8	muž	c.140delA/-
9	3	žena	c.3429+1G>A/-
10	16	žena	c.2837G>A, p.Arg946His
11	1	žena	c.4889T>G

Výsledky

Pacienti v hodnotenej skupine sú narodení od roku 1999 do roku 2015. Vyhodnocovanie klinických údajov a priebehu ochorenia prebiehalo do februára roku 2017. Ďalší klinický priebeh konkrétnych subjektov nie je zahrnutý do predkladaného prehľadu.

Rodinná anamnéza febrilných záchvatov alebo epilepsie je pozitívna u 3 pacientov (27 %). V dvoch prípadoch sa jedná o opakované epizódy febrilných kŕčov. Genetické vyšetrenie bolo u jedného z týchto rodičov negatívne na mutáciu v *SCN1A* géne a v druhom prípade nebolo v čase prípravy publikácie ošetrujúcim lekárom indikované. V poslednom prípade došlo k rozvoju záchvatových prejavov zodpovedajúcich fenotypu DS. Etiologické potvrdenie, resp. vyvrátenie diagnózy u tohto rodiča nie je možné zo sociálnych dôvodov (dieťa v starostlivosti náhradného rodiča, bez kontaktu s biologickou matkou). U 3 pacientov (27 %) boli prítomne prenatálne a perinatálne riziká – prematurita, intenzívna antiepileptická terapia matky počas gravidity.

Manifestácia klinickej symptomatológie v súbore je od veku 116 mesiacov. Priemerne vo veku 6,5 mesiaca. Najčastejším typom paroxyzmu v úvode boli febrilné hemikonvulzívne záchvaty (rozvoj priemerne vo veku 6,5 mesiaca; u 6 pacientov, tj. 54,5 %). Vo veku 3–9 mesiacov (priemer 6 mesiacov; u 8 pacientov) sa manifestujú prolongované záchvatové prejavy (trvajúce viac ako 10 minút). V priemernom veku 7,4 mesiaca sa rozvinul u našich pacientov ďalší typ záchvatov, a to generalizované tonicko-klonické, resp. klonické záchvaty. Tieto boli pozorované u 9 pacientov (81,2 %). Manifestácia status epilepticus bola priemerne v 17 mesiacoch (7; 63,6 %). U 100 % pacientov sa jednalo o konvulzívne epileptické staty. Myoklonické záchvaty sa rozvinuli u 2 pacientov (18,2 %), priemerne vo veku 32,5 mesiaca. Len u 4 pacientov sme zaznamenali výskyt atypických absencií, a to v priemernom veku 36 mesiacov. Pri 9 pacientoch (81,2 %) bola anamnesticky jasná provokácia záchvatov. U 7 (63,6 %) išlo o zvýšenú telesnú teplotu, u 1 (9,1 %) o teplú vodu (externá expozícia pri kúpeli a saune) a časovú súvislosť s očkovaním a následnými subfebríliami. U 2 pacientov (18,2 %) jasná provokácia po retrospektívnej analýze anamnézy preukázaná nebola.

V objektívnom neurologickom náleze dominujú predovšetkým poruchy tonusu v zmysle centrálnej hypotónie, a to u 5 pacientov (45,5 %), mikrocefália u 2 (18,2 %), ataxia, neistá

chôdza, motorická dyspraxia u 2 pacientov (18,2 %). Len u jednej pacientky je pozitívny ložiskový neurologický nález v zmysle hemiparézy (9,1 %). Pri hodnotení behaviorálne-mentálnych schopností sa v našom súbore vyskytujú známky Attention Deficit Hyperactivity Disorder (ADHD), a to u 4 subjektov (36,4 %), zníženie intelektu rôznej miery u 7 (63,6 %), dyslália u 5 (45,5 %). Vo väčšine prípadov rozvoj neurologickej symptomatológie a kognitívnej deteriorácie pozorujeme až v batolivom období. Známky poruchy autistického spektra sa vyvinuli v priebehu ochorenia u 2 pacientov (18,2 %) a boli zaznamenané po 3. roku života.

Pri vyhodnocované EEG sme dospeli k záverom, že len 2 pacienti (18,2 %) mali iniciálne abnormitu v EEG. V priebehu ochorenia došlo k záchytu abnormít na EEG u väčšiny pacientov – 8 (72,7 %). U 7 bola zachytená abnormita v základnej aktivite, u 5 pacientov sme zaznamenali výskyt hrotov. Komplexy hrot-vlna boli zachytené len v izolovanom prípade.

Abnormity na MR mozgu boli zaznamenané u 6 pacientov (54,5 %). Tieto boli charakteru meziotemporálnej sklerózy (záchyt vo veku 15 rokov), miernej atrofie mozgu (záchyt už v kojeneckom veku), ľahkej redukcie objemu mozočku, rozšírenia vonkajších likvorových priestorov (záchyt v predškolskom veku), cisterna magna permagna, u jednej pacientky jednostranná periventrikulárna leukomalácia (PVL). Záchyt posledných dvoch nálezov na MR bol zaznamenaný v skorom kojeneckom období.

Priemerný počet použitých antiepileptík (AEDs) (v našom súbore je 6. Ako efektívne, resp. parciálne efektívne boli vyhodnotené nasledujúce: valproát u 6 z 8 pacientov (75 %), topiramát u 6/7 (85,7 %), klobazam u 5/6 (83,3 %), clonazepam bol použitý u 5 pacientov a u 100 % mal parciálny efekt. Levetiracetam u 3/7 (42,8 %), zonisamid u 3 (100 %). Vigabatrin a primidon boli použité len izolovane a bez efektu na záchvaty. Stiripentol ako add-on terapia do kombinácie valproát + klobazam bol použitý s parciálnym efektom u 8 pacientov. Lamotrigin bol použitý u 4 pacientov a u 100 % z nich viedol k zhoršeniu početnosti záchvatov. Fenobarbital v per os forme zhoršil záchvaty čo do početnosti u 1/3 pacientov (33,3 %).

Stiripentol ako „orphan drug" (liek-sirota – liek určený pre liečbu vzácnych ochorení) bol použitý celkom u 8 pacientov. Priemerný vek pri jeho nasadení u pacientov na klinice dětské neurologie bol 3 roky a 9 mesiacov. Viditeľný efekt stiripentolu je pozorovaný predovšetkým pri redukcii počtu epileptických statov. V sledovanom súbore sa jednalo o 100% redukciu (počet epileptických statov u pacientov medikujúcich stiripentol pred jeho nasadením bol 20, po nasadení 0). Taktiež táto liečba dosahuje výrazné zníženie počtu prolongovaných záchvatov. Celkový počet prolongovaných záchvatov bol pred zavedením tejto liečby 26, po zavedení len 5, tj. došlo k poklesu ich výskytu o 80,8 %. Stiripentol vo zvolenej kombinácií AEDs však nedosiahol valné zníženie počtu kratších epileptických záchvatov. Nežiadúce účinky boli pozorované u polovice pacientov, s rôznou mierou závažnosti. U 25 % sa jednalo o agresívne správanie, v rovnakej miere pozorujeme poruchy spánku (insomnia/hypersomnia). Celkom 12,5 % pacientov trpelo únavou a známkami

Tab. 2. Charakteristika epileptických záchvatov (n = 11).

Typ záchvatu	Priemerný vek (mesiace)	Počet pacientov (%)
1. záchvat	6,5	11 (100 %)
prolongované záchvaty (> 10 min)	6	8 (72,7 %)
hemikonvulzívne záchvaty	6,5	6 (54,5 %)
generalizované tonicko-klonické/klonické záchvaty	7,4	9 (81,8 %)
status epilepticus	17	7 (63,6 %)
moklonické záchvaty	32,5	2 (18,2 %)
atypické absencie	36	4 (36,4 %)

n – počet pacientov v súbore

Tab. 3. Fenotypové charakteristiky (n = 11).

Charakteristika	Počet pacientov (%)
pozitívna rodinná anamnéza	3 (27,3 %)
pozitívna osobná anamnéza	3 (27,3 %)
provokácia I. paroxysmu:	
zvýšená teplota	7 (63,6 %)
teplá voda	1 (9,1 %)
očkovanie	1 (9,1 %)
bez jasnej provokácie	2 (18,2 %)
abnormálne EEG v úvode ochorenia	2 (18,2 %)
abnormálne EEG v priebehu ochorenia	8 (72,7 %)
abnormity na MR mozgu	6 (54,5 %)
autistické prejavy	2 (18,2 %)
ataxia	2 (18,2 %)
centrálna hypotónia	5 (45,5 %)
ložiskový neurologický nález	1 (9,09 %)
problémy so správaním (hyperaktivita, porucha pozornosti)	4 (36,4 %)
oneskorený psychomotorický vývoj	5 (45,5 %)
dyslália	5 (45,5 %)
zníženie intelektu	7 (63,6 %)
mikrocefália	2 (18,2 %)

n – počet pacientov v súbore

Tab. 4. Farmakologická odpoveď u pacientov s DS (n = 11).

Medikácia s parciálnym efektom	Podiel pacientov s odpoveďou (%)
valproát	6/8 (75 %)
topiramát	6/7 (85,7 %)
clobazam	5/6 (83,3 %)
clonazepam	5/5 (100 %)
levetiracetam	3/7 (42,8 %)
stiripentol	4/4 (100 %)
zonisamid	3/3 (100 %)

Medikácia zhoršujúca klinický priebeh	Podiel pacientov s odpoveďou (%)
lamotrigin	4/4 (100 %)
fenobarbital	1/3 (33,3 %)

n – počet pacientov v súbore

Tab. 5. Interiktálne EEG (n = 11)

Abnormita ZA (áno/nie)	Výskyt hrotov (áno/nie)	Výskyt SWC (áno/nie)
7/4	5/6	1/10

n – počet pacientov v súbore; ZA – základná aktivita v EEG; SWC – komplex hrot-vlna (spike wave complex)

hyperaktivity. Nežiadúce účinky pre svoju závažnosť priamo viedli k vysadeniu stiripentolu len u jednej pacientky (predovšetkým sa jednalo o výraznú agresivitu, koproláliu, závažné poruchy spánku). U ďalšej pacientky došlo k úprave dávkovania, s klinickým efektom, bez nutnosti vysadenia. Podrobne sú spracované výsledky uvedené v tab. 2–5.

Diskusia

V hodnotenom súbore pozorujeme miernu štatistickú prevahu výskytu DS u žien – 7 žien (63,6 %), 4 muži (36,4 %). Gendrové rozdelenie podľa svetovej literatúry sa pohybuje v pomere 1 : 2 (žena : muž) [1,2]. Nekorešpondujúce rozdelenie na základe pohlavia prisudzujeme malému počtu pacientov v sledovanom súbore.

Manifestácia ochorenia bola v sledovanom súbore v priemere 6,5 mesiaca (od 1. mesiaca po 16. mesiac). Najčastejších typom záchvatov v dobe manifestácie ochorenia sú prolongované záchvaty trvajúce viac ako 10 minút (8; tj. 72,7 %). V porovnaní s údajmi z veľkých multicentrických štúdií oba údaje korelujú (Brunklaus et al uvádzajú rozvoj prvého záchvatu okolo 6. mesiaca a výskyt prolongovaných záchvatov okolo 7. mesiaca) [5,6]. Hemikonvulzívne záchvaty sa v našom súbore vyskytujú u 6, tj. 54,5 %, s priemerným rozvojom vo veku 6,5 mesiaca. Identické výsledky uvádzajú aj Brunklaus et al (72 % pacientov rozvinie hemikonvulzívne záchvaty vo veku okolo 7 mesiacov). Badateľný rozdiel v porovnaní s multicentrickými štúdiami je viditeľný v počte pacientov s myoklonickými záchvatmi a manifestácií atypických absencií. Brunklaus et al pozorujú výskyt myoklonií u 69 % pacientov a atypických absencií u 51 % subjektov [5]. V našom súbore hovoríme o 18,2 % a 36,4 %. Rozdiel v údajoch v porovnaní s publikovanými údajmi súvisí pravdepodobne s počtom pacientov v našom súbore. Významný je aj fakt, že myoklonické záchvaty sa často objavujú až po niekoľkých rokoch od klinickej manifestácie ochorenia, alebo sa vyskytovať vôbec nemusia [7].

Analýza vybraných klinických parametrov ukazuje, že väčšina záchvatov je provokovaná zvýšenou telesnou teplotou, a to u 7 (63,6 % pacientov). V práci Bayat et al sa febrílie ukazujú ako provokačný faktor u 30 % pacientov. Najčastejším provokačným faktorom v spomínanej práci bolo vyhodnotené očkovanie (40 % pacientov) [6]. V našom súbore bolo očkovanie v časovej súvislosti s rozvojom symptomatológie príčinou len u 1 pacienta (9,1 %).

Pri hodnotení neurologického nálezu sme preukázali manifestáciu neurologickej symptomatológie až po 3. roku života. Najčastejšie sme diagnostikovali centrálny hypotonický syndróm (5; čo predstavuje 45,5 %). Ataxiu sme zaznamenali u 2 subjektov (18,2 %). Percentuálne zastúpenie je v zhode s údajmi zo svetovej literatúry [5,6]. Známky autistického spektra sme zaznamenali u 2 (18,2 %). V porovnaní s prácou Brunklausa et al je tento údaj výrazne nižší (46 %). Prevalencia autizmu u pacientov s DS sa v rôznych prácach líši (Bayat et al uvádzajú len 12% prevalenciu autizmu) [5,6]. Predpokladáme niekoľko príčin nižšieho zastúpenia porúch autistického spektra v našom súbore. Významne sa podieľa nízky počet pacientov v súbore, ale aj relatívne väčší podiel pacientov mladších ako 3 roky. Porucha aktivity a pozornosti sa v našom súbore vyskytuje u 4 pacientov (36,4 %). Tento údaj korešponduje s nálezmi z multicentrických štúdií [5,6]. U jedného pacienta (9,1 %) v neurologickom náleze dominuje centrálna hemiparéza na podklade PVL. Ložiskový neurologický nález je netypický pre pacientov s DS. Toto súvisí so závažnými perinatálnymi komplikáciami a ovplyvňuje fenotyp.

Abnormity na MR mozgu boli identifikované u 6 pacientov (54,5 %). Tento údaj je podstatne vyšší ako v práci Brunklausa et al a nedokážeme ho plauzibilne interpretovať. Brunklaus et al zaznamenali v EEG fotosenzitivitu u 33 % pacientov [5]. V našom súbore sme nezaznamenali zmeny v EEG pri fotostimulácií u žiadneho z pacientov.

V terapii DS sa ukázali ako parciálne efektívne valproát, topiramát, klobazam, klonazepam, stiripentol, levetiracetam, zonisamid. Ako nevhodné sa v našom súbore preukázalo použitie lamotriginu a fenobarbitalu. Viedlo k zhoršeniu frekvencie záchvatových prejavov, a to predovšetkým pri použití lamotriginu (100 % pacientov). Fenobarbital bol použitý celkom u 4 pacientov. Traja pacienti medikovali fenobarbital v rámci dlhodobej medikácie. Pri 1 pacientovi bol použitý ako liečba epileptického statu. V perorálnej forme viedol k zhoršeniu záchvatov len u 1 pacienta (33,3 %), v intravenóznej forme nedošlo k zastaveniu epileptického statu. Vigabatrín a primidon neovplyvnili záchvatové prejavy žiadnym spôsobom.

Lamotrigín, karbamazepín, fenytoín sú nevhodné pri terapií DS. Ďalej je kontraindiko-

vané použitie vigabatrínu a neodporúčajú sa vysoké dávky fenobarbitalu [1,5,6]. Blokátory sodíkových kanálov, ako aj ďalšie neodporúčané AEDs boli použité vo všetkých prípadoch pred znalosťou diagnózy.

Štúdia autorov z Japonska popisuje 10% úmrtnosť pacientov s DS [8]. V našom súbore neevidujeme žiadne úmrtie. Vedúcim dôvodom úmrtia u DS je náhla smrť u epileptikov (sudden unexpected death in epilepsy; SUDEP). Nasledujú úmrtie pri epileptickom statuse, úmrtie pri nehode [9]. Etiologická súvislosť vyššieho percenta SUDEP u pacientov s DS súvisí s mutáciami v génoch pre sodíkové kanály. Princípom je patologická regulácia v sinoatriálnom uzle autonómnym nervovým systémom (prevaha sympatika nad parasympatikom), čo následne môže viesť k život ohrozujúcim srdcovým arytmiám [10].

Ďalším parametrom, ktorý sme v našom súbore hodnotili, bol priemerný čas od rozvoja klinickej symptomatológie k stanoveniu diagnózy. Pacienti narodení pred rokom 2010 priemerne dospeli k správnej diagnóze až po 116 mesiacoch trvania ochorenia. U pacientov narodených po roku 2010 je to priemerne 19 mesiacov, čo predstavuje významné skrátenie doby trvania diagnostického procesu. Diagnostika mutácie v *SCN1A* géne je dostupná od roku 2010. Retrospektívne vyhľadávanie vhodných kandidátov je náročné a na túto eventualitu sa v mnohých prípadoch nemyslí. Diagnostika DS je aktuálne bežne dostupná, čo umožňuje urýchliť diagnostický proces a zvýšiť záchyt pacientov v skoršom veku.

Analyzovaný súbor pacientov má v 100 % prípadov preukázanú mutáciu v géne pre *SCN1A*. V súčasnej dobe je identifikovaných viac ako 600 mutácií asociovaných s DS a tieto sú náhodne distribuované v priebehu celého *SCN1A* génu. Mutácie génov pre iónové kanály hrajú významnú úlohu v etiopatogenéze, preto hovoríme o kanálopatiách [11–13].

V prípade, že sa mutácia v danom géne nepreukáže a naďalej trvá podozrenie na DS, je potrebné rozšíriť genetickú diagnostiku. Mutácia *PCDH19* (chromozóm Xq22) bola objavená u jednotky epilepsia a mentálna retardácia viazaná na ženy (EFMR). EFMR je X- viazaná choroba. Klinická manifestácia je u heterozygotných pacientok. Hemizygotní muži sú nepostihnutí. Mutácia tohto génu pri DS je len v 5 %. Dôležité je pozorovanie častej familiárnej väzby [12]. Klinicky priebeh je miernejší v porovnaní s DS spôsobeným mutáciou v *SCN1A* géne. Začína v neskoršom veku – medián 9,5 mesiacov, myoklonické záchvaty a status epilepticus sú zriedkavé. Psychomotorická retardácia je u 45 % pacientov len ľahkého stupňa a častý je výskyt autistických rysov. U malého počtu pacientov s DS bola identifikovaná mutácia v géne pre gama2 podjednotku GABAa receptoru – *GABRG2* [1,2].

Záver

DS sa radí medzi epilepsie s genetickým podkladom. Na diagnózu je nutné pomýšľať v prípade výskytu opakovaných, prolongovaných febrilných záchvatov. Genetické testovanie prináša pre pacienta množstvo benefitov. Predovšetkým sa jedná o výber vhodného a nevhodného antiepileptika, odbremenenie od zbytočných testov a procedúr, predpoklad prognózy. Nesporný význam je aj v správnom managemente pacienta a zabezpečenie komplexného multioborového prístupu vrátane zaradenia pravidelných kardiologických kontrol [14], logopédie, rehabilitácie a podobne. Svoj význam má genetické testovanie aj na prenatálnej úrovni v rámci *in vitro* fertilizácie [13]. Cieľom liečby DS je zníženie frekvencie záchvatov a záchvatmi indukovaných zranení, limitácia rozvoja mentálneho defektu, psychosociálnych problémov, zníženie rizika SUDEP [14,15].

Dané fakty sme potvrdili aj v našom súbore. U pacientov zo sledovaného súboru narodených pred rokom 2010 je celkový vývoj ochorenia menej priaznivý a má výrazný dopad na mentálny status, náročnosť ošetrovateľskej starostlivosti a budúceho života pacienta a rodiny.

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2.7 Annex 7

Danhofer P, Horák O, Fajkusová L, Pavloušková L, Ošlejšková H. **Syndrom Dravetové: těžká myoklonická epilepsie v časném dětství.** Neurol praxi 2015; 16(1): 38-42.

Summary:

Dravet syndrome is classified as a rare progressive epileptic encephalopathy. Seizure onset starts in the first year of life in so far normal developped children. Generalised or lateralized clonic-tonic seizures, often prolonged and during the febrile infect can be observed. Later on, we can see other types of seizures accompanied by deterioration of psychomotor development. In present, the genetic basis of this syndrom with mutations in SCN1A gene can be detected in 70–80 % of patients. 5 % of patients have mutation in PCDH19 gene, rarely the mutations in GABARG2 and SCN1B genes can be detected. Beneficial effect in the therapy of DS is observed in valproic acid, clobazame and as add-on therapy stiripentol. Topiramat, levetiracetam and ketogenic diet can also bring a positive effect in the seizure reduction. Early diagnostics of DS is very important from the therapeutical point of view.

Syndrom Dravetové: těžká myoklonická epilepsie v časném dětství

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Syndrom Dravetové se řadí mezi vzácné progresivní epileptické encefalopatie. Klinická manifestace začíná v prvním roce života u dosud normálně se vyvíjejících dětí. Objevují se generalizované nebo lateralizované klonické záchvaty, často protrahované a vázané na febrilní infekty. Později se objevují i jiné formy záchvatů doprovázené deteriorací psychomotorického vývoje. V současné době je možné genetické potvrzení mutace v SCN1A genu u 70–80 % pacientů. V 5 % případů se jedná o mutaci v genu PCDH19, vzácně pak jsou prokázány i mutace v GABARG2 a SCN1B genu. V terapii se uplatňuje především valproát a klobazam, jako přídatná terapie stiripentol. Dále pak topiramat, levetiracetam, ketogenní dieta. Časná diagnostika a zařazení tohoto epileptického syndromu jsou z terapeutického hlediska velmi důležité.

Klíčová slova: Dravetové syndrom, myoklonická epilepsie, epilepsie, terapie.

Dravet syndrome: severe myoclonic epilepsy in infancy.

Dravet syndrome is classified as a rare progressive epileptic encephalopathy. Seizure onset starts in the first year of life in so far normal developped children. Generalised or lateralized clonic-tonic seizures, often prolonged and during the febrile infect can be observed. Later on, we can see other types of seizures accompanied by deterioration of psychomotor development. In present, the genetic basis of this syndrom with mutations in SCN1A gene can be detected in 70–80 % of patients. 5 % of patients have mutation in PCDH19 gene, rarely the mutations in GABARG2 and SCN1B genes can be detected. Beneficial effect in the therapy of DS is observed in valproic acid, clobazame and as add-on therapy stiripentol. Topiramat, levetiracetam and ketogenic diet can also bring a positive effect in the seizure reduction. Early diagnostics of DS is very important from the therapeutical point of view.

Key words: Dravet syndrome, myoclonic epilepsy, epilepsy, therapy.

Neurol. praxi 2015; 16(1): 38–42

Úvod

Syndrom Dravetové, těžká myoklonická epilepsie v časném dětství, se řadí mezi vzácné progresivní epileptické encefalopatie (Panayiotopoulos, 2010). Klinická manifestace začíná v prvním roce života u dosud normálně se vyvíjejících dětí. Recidivující protrahované febrilní konvulzivní a hemikonvulzivní záchvaty s pozdějším vývojem jiných typů záchvatů vedou k postupné deterioraci psychomotorického vývoje a rozvoji mentální retardace různého stupně (Panayiotopoulos, 2010). Epilepsie je farmakorezistentní, některé léky mohou záchvaty zhoršovat, jiné naopak mohou jejich výskyt redukovat. Především stiripentol je schopen redukovat výskyt a délku trvání protrahovaných febrilních konvulzivních záchvatů, které jsou spojeny s mírou psychomotorické retardace (Chiron et Dulac, 2011). Časná diagnostika a vhodná léčebná strategie je tedy žádoucí. Vzhledem k dostupnosti genetické diagnostiky je v současné době syndromologické zařazení pacientů možno geneticky potvrdit a na tuto jednotku by mělo být pomýšleno.

Klasifikace

Syndrom Dravetové – těžká myoklonická epilepsie v časném dětství (Severe Myoclonic Epilepsy in Infancy – SMEI) byl popsán poprvé v roce 1978 profesorkou Charlotte Dravet ve Francii (Dravet, 1978). Dle ILAE klasifikace epileptických syndromů z roku 1989 se řadí mezi epilepsie a epileptické syndromy nezařaditelné jako ložiskové či generalizované (ILAE, 1989). Dle revize této klasifikace z roku 2010 se řadí mezi elektro-klinické syndromy časného dětství (Berg et al., 2010).

Etiologie a patofyziologie

V souladu s ILAE revizí epileptických syndromů 2010 se syndrom Dravetové z etiologického hlediska řadí mezi epilepsie s genetickým podkladem. 70–80 % pacientů je nositelem mutace v genu pro α-1 podjednotku sodíkového kanálu – SCN1A genu (Marini et al., 2011). Jedná se buď o truncating mutace, které způsobují předčasný vznik terminačního kodonu, čímž vedou k předčasnému ukončení translace (40 %) nebo o missense mutace (40 %). Zhruba 5 % ženských pacientů nese mutaci PCDH19 (Dapienne et al., 2009) a byly identifikovány i vzácné mutace v genu GABARG2 (Harkin et al., 2002) a SCN1B (Patino et al., 2009). U 20 % pacientů je etiologie syndromu neznámá. Předpokládá se její genetický podklad, mutaci se však nepodaří prokázat. U pacientů s mutacemi v SCN1A genu existuje jistá fenotypová variabilita, lze mluvit o DS-spektru (Harkin et al., 2007; Marini et al., 2011). Kromě klasického klinického obrazu syndromu Dravetové (SMEI) sem lze zařadit i tyto jednotky:

- hraniční těžká myoklonická epilepsie v časném dětství (Borderline severe myoclonic epilepsy of infancy – SMEB) – zde v klinickém obraze chybí myoklonické záchvaty nebo generalizovaná epileptiformní aktivity charakteru hrot-vlna v EEG (Harkin et al., 2007),
- rezistentní dětská epilepsie s generalizovanými tonicko-klonickými záchvaty (Intractable childhood epilepsy with generalised tonic-clonic seizures – ICEGTC) – psychomotorický vývoj se zpomaluje především v druhém roce života a míra psychomotorické retardace je významná; ve srovnání DS zde chybí jiné typy záchvatů, jako jsou myoklonické záchvaty, absence a fokální záchvaty (Fujiwara et al., 2003),
- těžká multifokální epilepsie v časném dětství (Severe infantile multifocal epilepsy – SIMFE) – zde se objevuje časný výskyt multifokálních záchvatů, zpomalení psychomotorického vývoje a multifokální epileptiformní aktivity v EEG; epilepsie má spíše obraz fokálních záchvatů, myoklonické záchvaty anebo ab-

Tabulka 1. Screeningový test rizikových faktorů DS (převzato z Hattori et al., 2008)

rizikový faktor	počet bodů
klinická manifestace epilepsie v ≤ 7 měsících věku	2
celkový počet záchvatů ≥ 5	3
lateralizované záchvaty – hemikonvulzivní	3
fokální záchvaty	1
myoklonické záchvaty	1
protrahované záchvaty	3
záchvaty indukované horkou vodou	2

sence chybí nebo jsou jen vzácné, nevyskytují se zde ani generalizované epileptiformní výboje v EEG (Harkin et al, 2007).

Patofyziologická podstata mutace v genu pro sodíkový kanál přepokládá snížení excitability GABAergních interneuronů v neokortexu a hipokampu (Yu et al., 2006), což má za následek snížení výbojů v těchto inhibičních interneuronech. Dojde tak ke zvýšení excitability v neuronální síti a rozvoji epileptické encefalopatie.

Klinický obraz

Klinická manifestace začíná již v prvním roce života s vrcholem kolem 5. měsíce u dosud normálně se vyvíjejících kojenců. Incidence je udávána 1 : 30 000 dětí (Panayiotopoulos, 2010), častěji jsou postiženi chlapci v poměru 2 : 1. Typickým klinickým projevem jsou tyto typy záchvatů: časné infantilní febrilní klonické křeče, myoklonické záchvaty, atypické absence a fokální záchvaty s poruchou vědomí. Míra vyjádření jednotlivých typů záchvatů je různá, některý z uvedených typů záchvatů být přítomen nemusí. Častý je výskyt epileptických statů, tonické záchvaty jsou jen výjimečné. Klinický průběh lze rozdělit do tří stadií (Panayiotopoulos, 2010):

1) Pre-seizmické stadium

Trvá 2 týdny až 6 měsíců a je charakteristické pro výskyt febrilních klonických záchvatů, často unilaterálních, stranově se střídajících. Záchvaty jsou delšího trvání, často protrahované až ve formě epileptických statů. U tří čtvrtin pacientů jsou záchvaty provokované zvýšenou teplotou (infekce, očkování, horká vana).

2) Seizmické stadium

Objevují se další typy záchvatů uvedené výše a neurokognitivní deteriorace. Deteriorace psychomotorického vývoje se objevuje mezi 2.–6. rokem života, je vyjádřena v různé míře, ale často je těžšího stupně. Dále pak již zůstává stabilní. V neurologickém nálezu se objevují nejčastěji ataxie, centrální hypotonie a pozitivní pyramidové iritační jevy.

3) Post-seizmické stadium

Toto stadium je již stabilizované, záchvaty mohou odeznívat, zůstává však v závažném stupni vyjádřena mentální deteriorace.

Za zmínku stojí i klinický obraz pacientů s mutací v PCDH19 genu. Jedná se o mutaci kódující protocadherin 19 (Dapienne et al., 2009), jehož funkce není úplně jasná, ale předpokládá se jeho zapojení v neuronálních sítích. Klinicky tato mutace způsobuje epilepsii limitovanou na ženy s mentální retardací (Epilepsy limited to females with mental retardation – EFMR) (Dapienne et al., 2009). Velmi připomíná syndrom Dravetové, ale začíná zpravidla později, kolem 9,5 měsíce věku, je zde menší výskyt protrahovaných záchvatů a záchvatů charakteru epileptických statů. Jen zřídka se vyskytují myoklonické záchvaty. Důležité je, že u 45 % pacientů je mentální retardace jen mírného stupně, časté jsou autistické rysy. A jak již z názvu vyplývá, postižení je limitováno na dívky, jedná se o X vázanou dědičnost.

Diagnostika

Z diagnostického hlediska je důležitý negativní nález na MRI mozku, u některých pacientů se ale vyskytuje lehká mozková nebo mozečková atrofie. Vyšetření dědičných poruch metabolizmu je v normě. Zásadní je pak genetické potvrzení dané mutace.

V EEG je zpočátku normální nález, u 20 % pacientů lze nalézt generalizovanou fotoparoxyzmální odpověď (Panayiotopoulos, 2010). V průběhu roku se stává EEG u 2/3 pacientů hrubě abnormní. Dochází ke zpomalení a desorganizaci základní aktivity. Objevují se krátké, asymetrické výboje vícečetných hrotů/hrotů-pomalých vln a různé multifokální a fokální abnormity. Patologie v EEG je často aktivována ve spánku. Fotoparoxyzmální odpověď lze nalézt u 40 % pacientů (Panayiotopoulos, 2010). Iktální nález pak odpovídá jednotlivým typům záchvatů.

Jak bylo uvedeno výše, DS se manifestuje nejčastěji febrilními záchvaty v prvním roce života u dosud normálně se vyvíjejících dětí. Z tohoto hlediska je na počátku obtížné jej odlišit od febrilních křečí. Vzhledem k tomu, že terapie DS nese jistá specifika a časná intenzivní léčba je žádoucí, je nutné na DS myslet co nejdříve a z tohoto důvodu byl vyvinut screeningový test rizikových faktorů (Hattori et al., 2008). Pokud je součet rizikových faktorů v tomto testu ≥ 6 (tabulka 1), je doporučeno provést analýzu SCN1A genu.

Vyšetření SCN1A genu v ČR lze provést v Brně a v Praze. V Brně vyšetření provádí Centrum molekulární biologie a genové terapie Interní hematoonkologické kliniky LF MU a FN Brno (kontakt: RNDr. Lenka Fajkusová, CSc., lfajkusova@fnbrno.cz). V Praze se lze obrátit na Ústav biologie a lékařské genetiky 2. LF UK a FN Motol (kontakt: RNDr. Petra Hedvičáková, petra.hedvicakova@lfmotol.cuni.cz). V případě podezření na DS je vhodné provést genetickou konzultaci na výše uvedených pracovištích a po domluvě s genetikem indikovat vyšetření SCN1A genu.

Prognóza

Prognóza u DS je velmi závažná, mentální retardace je vyjádřena v různé míře, méně než 10 % pacientů si vytvoří a uchová komunikační schopnosti (Panayiotopoulos, 2010). Závažné je i vyšší riziko náhlé smrti (SUDEP), a to u 15 % pacientů (Panayiotopoulos, 2010) ve srovnání s 5 % v ostatní populaci pacientů s epilepsií.

DS v dospělosti

Další vývoj ukazuje souhrnně práce prezentována v roce 2006 na 7. evropském epileptologickém kongresu profesorkou Ch. Dravet na souboru 24 dospělých pacientů s DS ve věku 18–46 let (Dravet et al., 2006; Nikanorova et al., 2009). U všech pacientů byl přítomen mentální deficit, od lehkého po těžký stupeň. Řeč byla převážně pomalá, bez větné struktury s přítomnou dysartrií, u některých pacientů se řečové funkce nevyvinuly vůbec. V objektivním neurologickém nálezu byl často přítomen myoklonus, ataxie, neobratnost v jemné i hrubé motorice, významné jsou i skeletální deformity (kyfoskolióza, ploché nohy, kladívkové prsty), pacienti byli často schopni chůze. V dospělém věku dominují noční generalizované tonicko-klonické záchvaty, často stále vázané na febrilie. Jiné typy záchvatů (myoklonické záchvaty a absence) jsou jen ojedinělé. Na MRI mozku lze nalézt mozkovou atrofii (významněji byla popsána u pacientů užívajících vysoké dávky fenobarbitalu) a hipokampální sklerózu. Pět pacientů ze souboru (20 %) zemřelo náhlou smrtí – SUDEP.

Terapie (viz tabulka 2 a 3)

Antiepileptika indikována v terapii DS

Terapeutické možnosti u DS jsou omezené. Jedná se o vysoce farmakorezistentní epilepsii. Lékem první volby jsou VPA a benzodiazepiny (CLB, CZP), často je ale jejich efekt nedostatečný (Chiron, 2011).

Dalším lékem, jenž lze využít v terapii DS je TPM. Ve dvou retrospektivních studiích byl

Tabulka 2. Přehled studií prokazujících efekt farmakoterapie a nefarmakologických možností u DS

lék	autor	design studie	počet pacientů	výsledky	indikace v terapii DS
topiramat	Coppola et al., 2002; Nieto-Barrera et al., 2000	retrospektivní add-on	18	56 % repondérů, 3 bez záchvatů	příznivý efekt
bromid	Lotte et al., 2000	prospektivní observační add-on	32	81 % respondérů po 3 měsících, 47 % po 1 roce	příznivý efekt
	Tanabe et al., 2008	retrospektivní	99	41,7 % úspěšný v prevenci rozvoje SE	příznivý efekt
levetiracetam	Striano et al., 2007	prospektivní add-on	28	64 % respondérů (GTCS), 62 % respondérů (myoklonické záchvaty)	příznivý efekt
	Chhun et al., 2011	prospektivní add-on	9	11 % respondérů ve 3 a 6 měsících léčby	příznivý efekt
stiripentol (add-on k VPA+CLB)	STICLO Study Group Francie a Itálie - Chiron et al., 2000; Kassai et al., 2008	prospektivní randomizované placebem kontrolované studie			příznivý efekt
		Francie	41	71 % respondérů (vs. 5 % placebo), 45 % bez záchvatů	
		Itálie	23	66,7 % repondérů (vs. 9 = placebo), 27 % bez záchvatů	
lamotrigine	Guerrini et al., 1998	retrospektivní	21	80 % pacientů zhoršeno	kontraindikován
karbamazepin	Thanh et al., 2002	retrospektivní	46	61 % pacientů zhoršeno	kontraindikován
vigabatrin	Thanh et al., 2002	retrospektivní	46	64 % pacientů zhoršeno	kontraindikován
rufinamid	Mueller et al., 2011	retrospektivní	20	20 % respondérů, 30 % zhoršeno	rozporuplné výsledky – není indikován
fenobarbital – vysoké dávky intravenózně	Chipaux et al., 2010	retrospektivní		atrofie mozku na MRI a zhoršení neurologického nálezu	rozporuplné výsledky – vysoké dávky a i.v. aplikace kontraindikovány
ketogenní dieta	Caraballo et al., 2011	prospektivní observační	24/ hodnoceno 16 pacientů po 24 měsících léčby	12,5 % bez záchvatů, u 62,5 % pacientů redukce záchvatů o 75 %, u 25 % redukce záchvatů o více než 50 %	příznivý efekt
VNS	Zamponi et al., 2011	prospektivní observační	8	50 % respondérů, zlepšení kontaktu a komunikačních schopností	příznivý efekt

TPM nasazen jako přídatná terapie u pacientů s DS. U 56 % pacientů došlo k redukci záchvatů o více jak 50 % a 16,7 % pacientů bylo bez záchvatů (Coppola et al., 2002; Nieto-Barrera et al., 2000).

Další možností v terapii DS může být LEV. Výsledky studií jsou zde však rozporuplné. Byla prokázána jeho účinnost v prospektivní add-on studii, a to především na generalizované tonicko-klonické záchvaty (64 % respondérů) a myoklonické záchvaty (62 % respondérů) (Striano et al., 2007). Naproti tomu Chhun et al. publikovali v roce 2011 výsledky prospektivní studie, kde byl LEV užit jako přídatný lék v terapii DS u 9 pacientů. Jen jeden z nich (11 %) byl klasifikován jako respondér ve 3 a 6 měsících léčby.

Příznivé výsledky ukazují studie s využitím bromidu v terapii DS. U 32 dětí s DS byl využit jako přídatná terapie, zde dokonce 81 % pacientů byli označeni jako respondéři po 3 měsících léčby (47 % po jednom roce léčby). Poměrně vysoké však bylo procento nežádoucích reakcí (56 %), v 16 % byla léčba z tohoto důvodu ukončena (Lotte et al., 2012). Tanabe et al. publikovali v roce 2008 retrospektivní studii se souborem 99 dětí s DS odpovídajících na bromid jako lék v prevenci epileptického statu.

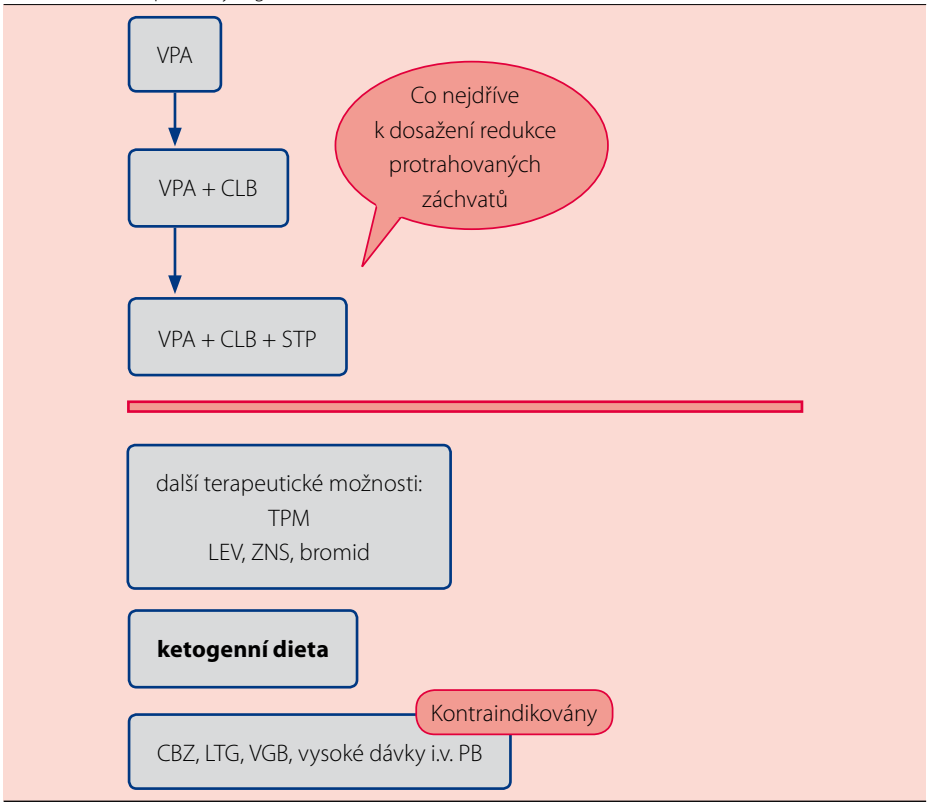
Stiripentol (Diacomit), orphan-drug v terapii DS je schválen jako přídatná terapie k VPA+CLB. V terapii DS je v Evropě schválen od roku 2007. STP není strukturálně podobný jinému dosud užívanému antiepileptiku. V in vitro studiích byl u něj zjištěn GABAergní efekt. Působí jako přímý allosterický modulátor GABA-A receptorů především přes vývojovou alfa-3 podjednotku. (Fischer, 2009). U lidí inhibuje také cytochrom-oxidázový systém P450 v játrech, což vede ke zvýšení koncentrací jiných antiepileptik, které jsou touto cestou metabolizovány. Tato farmakokinetická interakce je významná především u CLB, a to přes CYP 2C19 (Giraud et al., 2006). Dosud byly realizovány 2 randomizované placebem kontrolované studie, které sledují efekt STP jako přídatné terapie ke kombinaci VPA+CLB. Za tímto účelem byla zformována studijní skupina STICLO (STICLO Study Group) ve Francii a Itálii. Výsledky francouzské skupiny byly publikovány Catherine Chiron v roce 2000. Výsledky italské skupiny publikovány dosud nebyly, jsou však zahrnuty v metaanalýze (Kassai et al., 2008). Výsledky ukázaly 71 % (Kassai et al., 2008) resp. 67 % (Chiron et al, 2000) respondérů ve srovnání s placebem 5 % (Kassai et al., 2008) resp. 9 % (Chiron et al., 2000). Japonská studie (Inoue et al., 2009) ukázala, že STP může být efektivní i v jiné kombinaci než s VPA+CLB. Přinesl efekt u 61 % pacientů i na terapii CZP, PB, bromidem a ZNS. STP je schopen především redukovat délku protrahovaných záchvatů. Vzhledem k tomu, že právě frekvence a délka těchto záchvatů v prvním roce života je dávána do souvislosti s mírou následné psychomotorické retardace, je vhodné zahájit léčbu STP co nejdříve a snažit se tak tyto záchvaty co nejvíce redukovat. (Chiron, 2011; Chiron et Dulac, 2011)

Po nasazení STP dojde ke zvýšení hladin VPA a CLB. Tato skutečnost je zodpovědná za nejčastější nežádoucí účinky STP (ospalost, zpomalení mentálních funkcí, ataxie, diplopie, nechutenství, snížení hmotnosti, nauzea, bolesti břicha, asymptomatická neutropenie). Proto je po jeho nasazení často nutné snížit dávky VPA na 20 mg/kg/den a CLB na 0,5 mg/kg/den (Chiron et Dulac, 2011).

Antiepileptika nevhodná v terapii DS

Při výběru nejvhodnějšího antiepileptika je nutno myslet na existenci léků, které epilepsii u pacientů s DS mohou zhoršovat. Jedná se především o LTG, CBZ, VGB a vysoké dávky PB. Těmto je třeba se v terapii DS vyvarovat. Ve studii 21 pacientů s DS bylo zhoršení záchvatů v souvis-

Tabulka 3. Terapeutický algoritmus u DS



losti s LTG pozorováno u téměř 80 % pacientů, a to jak zhoršení GTCS (40 %), tak myoklonických záchvatů (33 %) (Guerrini et al., 1998). Zhoršení záchvatů bylo pozorováno ve studii se 46 pacienty u 61 % pacientů na CBZ a 64 % pacientů na VGB (Thanh et al., 2002). U pacientů, kteří užívali vysoké dávky intravenózního PB v terapii konvulzivních epileptických statů, byla zjištěna souvislost s mozkovou atrofií a zhoršením neurologického nálezu. (Chipaux et al., 2010). Mueller et al. publikovali v roce 2011 studii 20 dětí s DS užívajících RFM. 20 % pacientů bylo klasifikováno jako respondéři, ve 30 % došlo ke zhoršení záchvatových projevů. RFM není doporučen v terapii DS.

Další, nefarmakologické možnosti v terapii DS

Vhodnou léčebnou volbu představuje také ketogenní dieta, která má právě u syndromu Dravetové (i ve srovnání s jinými epileptickými syndromy) relativně vysokou účinnost. Caraballo (2011) publikoval soubor 24 pacientů se syndromem Dravetové, z nichž 16 (66,5 %) setrvalo na ketogenní dietě déle než 24 měsíců – 2 pacienti (12,5 %) byli zcela bez záchvatů, 10 pacientů (62,5 %) dosáhlo větší něž 75% a zbývající 4 pacienti (25 %) větší než 50% redukci záchvatů. KD by proto měla být zvažována již po selhání 3 až 4 antiepileptik, a nikoliv ponechávána jako poslední léčebná možnost. Zatím je stále preferována klasická KD s poměrem 4 : 1 s/bez úvodního hladovění, zkouší se i Modifikovaná Atkinsonova dieta, jejíž účinnost je však ještě třeba ověřit na větších studiích.

Příznivé výsledky ukazuje v terapii DS i implantace vagového stimulátoru. Zamponi et al. v roce 2011 publikovali výsledky stimulace bloudivého nervu u 8 pacientů s DS (průměrný věk 10,28 let, rozmezí 5–25 let). Po jednom roce stimulace bylo u 4 pacientů (50 %) pozorováno snížení frekvence záchvatů o 50–79 %, u jednoho pacienta méně než 50 % a u 3 pacientů nedošlo ke změně ve frekvenci záchvatů. Poukazují, že i u pacientů, u kterých nedošlo k výrazné redukci záchvatů, bylo zjištěno zlepšení v kontaktu a komunikačních schopnostech.

Závěr

Syndrom Dravetové se řadí mezi prognosticky závažné epilepsie manifestující se v časném dětství. Diagnózu DS lze stanovit již na základě klinického obrazu. Na možnost DS je nutné myslet v těchto případech:

- rozvoj epilepsie u dosud normálně se vyvíjejících kojenců,
- generalizované resp. lateralizované tonicko-klonické záchvaty,
- protrahovaný průběh záchvatů, opakované SE,
- především febrilní záchvaty,
- iniciálně normální EEG,
- v dalším průběhu rozvoj myoklonických záchvatů, atypických absencí, fokálních záchvatů,
- rozvoj psychomotorické deteriorace.

Potvrzení klinické diagnózy je možné i geneticky, zhruba ve 20 % případů DS je však genetika negativní. V terapii se jako lék volby uplatňuje VPA v kombinaci s CLB, jako přídatná terapie se užívá STP. STP je schopen redukovat výskyt protrahovaných generalizovaných tonicko-klonických záchvatů, které jsou dávány do souvislosti s rozvojem psychomotorické retardace. Rychlá syndromologická diagnostika a nasazení adekvátní terapie je tedy žádoucí.

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2.8 Annex 8

Danhofer P, Brunová K, Ošlejšková H. **Syndrom Dravetové (těžká infantilní myoklonická epilepsie): charakteristiky onemocnění v dospělém věku**. Neurol praxi 2017; 18 (2): 113-6.

Summary:

Dravet syndrome (DS) is ranked among severe epileptic syndromes with occurence in the first year of life in normal children. It can be diagnosed according to the clinical course, genetics can be very helpful by assessing the mutation in SCN1A gene, which is responsible for 70–80 % of cases with DS. Other mutations were identified more rarely (SCN2A, SCN3A, SCN7A, SCN8A a SCN9A, GABARG2, SCN1B and PCDH19). Dravet syndrom in adulthood is characterised by cognitive and behavioral changes in patients with various rate of mental retardation, language deficit and cerebellar symptomatic. The course of epilepsy is milder, the rate of seizure freedom is still low. Patients often suffer from nocturnal partial complex seizures with secondary generalisation, often with frontal origin. Present possibilities of genetic confirmation of DS are very important from the therapeutical point of view. This allows to improve the prognosis of the disease and the quality of life of patients with DS.

Syndrom Dravetové (těžká infantilní myoklonická epilepsie): charakteristiky onemocnění v dospělém věku

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Dravetové syndrom se řadí mezi závažné epileptické syndromy s rozvojem v kojeneckém věku u dosud zdravých dětí. Diagnózu lze stanovit na podkladě klinického obrazu, v současné době lze využít i genetického stanovení mutace v SCN1A genu, která je zodpovědná za 70–80 % případů a diagnózu tak potvrzuje. Vzácněji byly identifikovány u pacientů s DS i mutace v dalších genech (SCN2A, SCN3A, SCN7A, SCN8A a SCN9A, GABARG2, SCN1B a PCDH19). DS se v dospělém věku vyznačuje především kognitivními a behaviorálními změnami u pacientů s různou mírou mentální retardace, závažné jsou řečové poruchy a mozečková symptomatika. Epilepsie je již mírnější, plné kompenzace však dosáhne malé procento pacientů. Dominují noční záchvaty parciální komplexní se sekundární generalizací často s frontálním počátkem. Současné možnosti genetické diagnostiky DS jsou velmi důležité z hlediska zahájení časné a správné léčby, která umožní zlepšit prognózu, a tím i kvalitu života pacientů s tímto onemocněním.

Klíčová slova: dravetové syndrom, myoklonická epilepsie, dospělost, terapie.

Dravet syndrome (severe myoclonic epilepsy of infancy – SMEI): characteristics of adulthood

Dravet syndrome (DS) is ranked among severe epileptic syndromes with occurence in the first year of life in normal children. It can be diagnosed according to the clinical course, genetics can be very helpful by assessing the mutation in SCN1A gene, which is responsible for 70–80 % of cases with DS. Other mutations were identified more rarely (SCN2A, SCN3A, SCN7A, SCN8A a SCN9A, GABARG2, SCN1B and PCDH19). Dravet syndrom in adulthood is characterised by cognitive and behavioral changes in patients with various rate of mental retardation, language deficit and cerebellar symptomatic. The course of epilepsy is milder, the rate of seizure freedom is still low. Patients often suffer from nocturnal partial complex seizures with secondary generalisation, often with frontal origin. Present possibilities of genetic confirmation of DS are very important from the therapeutical point of view. This allows to improve the prognosis of the disease and the quality of life of patients with DS.

Key words: dravet syndrome, myoclonic epilepsy, adulthood, therapy.

Úvod

Dravetové syndrom (DS) byl poprvé popsán v roce 1978 profesorkou Charlottou Dravetovou ve Francii (Dravet, 1978). Dle ILAE klasifikace epileptických syndromů z roku 1989 se řadí mezi epilepsie a epileptické syndromy nezařaditelné jako ložiskové či generalizované (ILAE, 1989). Dle revize této klasifikace z roku 2010 mezi elektroklinické syndromy časného dětství (Berg et al., 2010). V souladu s ILAE revizí epileptických syndromů 2010 se z etiologického hlediska zařazuje mezi epilepsie na genetickém podkladě.

Patofyziologické aspekty a genetika u pacientů s DS

Převážná část pacientů jsou nositelé mutace v genu pro alfa1 podjednotku sodíkového kanálu (gen SCN1A), tato mutace se vyskytuje u 70–80 % pacientů (Marini et al., 2011). Dochází zde ke snížení excitability GABAergních interneuronů v neokortexu a hipokampu (Yu et al, 2006), čímž dojde ke zvýšení excitability v neuronální síti a rozvoji SCN1A epileptické encefalopatie. Snížení exprese napětově řízených sodíkových kanálů typu 1.1 v Purkyňových buňkách vedoucí k abnormálnímu influxu sodíku má za následek ataxii na zkoumaných zvířecích modelech (Yu et al., 2006).

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Tab. 1. *Charakteristika pacientů s DS v dětském věku a dospělosti*

	DS v dětském věku	DS v dospělém věku
Typy záchvatů	iniciálně: febrilní/afebrilní SE hemiklonický nebo generalizovaný	generalizované tonicko-klonické záchvaty resp. parciální komplexní záchvaty s nebo bez sekundární generalizace, často s frontálním počátkem
	dále (1–4 roky): myoklonické záchvaty, atypické absence a fokální záchvaty	vazba na noční spánek
Provokace záchvatů	vysoká teplota, horká vana, infekce, očkování, emoce	provokace vysokou teplotou již mírnější, ale trvá
EEG	zpočátku normální nález, u 20 % pacientů fotoparoxyzmální odpověď; v dalším roce zpomalení a desorganizace základní aktivity, výboje vícečetných hrotů/hrotů – pomalých vln a různé multifokální a fokální abnormity	zpomalení a desorganizace základní aktivity, multifokální heterogenní abnormity, výrazná redukce až vymizení fotoparoxyzmální odpovědi
MRI	normální nebo lehká mozková nebo mozečková atrofie	normální nebo lehká mozková nebo mozečková atrofie
Objektivní neurologický nález	iniciálně normální	mozečková symptomatika – ataxie, dysartrie, intenční tremor; pyramidová symptomatika nebo extrapyramidové jevy, ortopedické obtíže – skolióza, kyfoskolióza, plochonoží nebo kladívkovité prsty
Neuropsychologické vyšetření	iniciálně normální PMV, od 2. roku zpomalení či zástava vývoje	lehká až těžká mentální retardace, behaviorální a kognitivní poruchy, řečové dysfunkce, autistické rysy

Mutace v SCN1A genu jsou odpovědné za rozvoj velmi variabilního fenotypového vyjádření, tzv. GEFS+ (Generalized epilepsy and febrile seizures plus – generalizovaná epilepsie s febrilními záchvaty plus) spektra. Na „benigním" konci spektra se vyskytují pacienti se syndromem GEFS+, na druhém konci spektra se nachází pacienti s DS. Mutace u pacientů s DS jsou ve 40 % tzv. truncating mutace, které způsobují předčasný vznik terminačního kodonu, čímž vedou k předčasnému ukončení translace a nebo v dalších 40 % případů se jedná o tzv. missense mutace (mutace měnící smysl – způsobují změnu jedné báze za druhou). Většina mutací vzniká de novo, v 5–10 % případů se setkáváme s familiárním výskytem onemocnění v rámci rodin s GEFS+ s autosomálně dominantním typem dědičnosti. V těchto případech je pozorováno, že pokud je v důsledku missense mutace postižen transmembránový segment proteinu, vzniká fenotyp DS. Pokud je postižení mimo tento důležitý segment, vzniká spíše epilepsie z druhého konce GEFS+ spektra (Dravet et Guerrini, 2011). Přítomnost fenotypové variability v rámci jedné rodiny lze zčásti vysvětlit mozaicizmem v SCN1A genu (Guerrini, 2012). Příčina je však pravděpodobně komplexní, uplatňuje se jak genetické pozadí, tzv. modifikující geny, tak vliv prostředí.

SCN1A negativní pacienti mohou mít mutaci přesahující uložení SCN1A genu. Z tohoto hlediska jsou významné sousedící geny pro jiné části alfa podjednotky napěťově řízeného sodíkového kanálu jako SCN2A, SCN3A, SCN7A, SCN8A a SCN9A. Tím dochází ke zvýšení variability fenotypového vyjádření onemocnění v rámci GEFS+ spektra (Marini et al., 2011). Vzácně byly identifikovány u pacientů s DS i mutace v genu GABARG2 (Harkin et al., 2002) a SCN1B (Patino et al., 2009).

Zhruba 5 % pacientů s fenotypovým vyjádřením DS, i když s určitými odlišnostmi, nese mutaci v genu PCDH19 s X-vázanou dědičností (Depienne et al., 2009). Postižené jsou heterozygotní ženy, hemizygotní muži jsou zdraví. Jedná se o gen kódující protocadherin 19, jehož funkce nebyla dosud plně objasněna, ale předpokládá se jeho zapojení v neuronálních sítích. Mutace způsobuje Epilepsii limitovanou na ženy s mentální retardací (Epilepsy limited to females with mental retardation – EFMR). Charakteristickým rysem je zde pozdější začátek onemocnění, menší výskyt epileptických statů a jen zřídka se objevují myoklonické záchvaty. U 45 % pacientů je mentální retardace jen mírného stupně, časté jsou autistické rysy.

V současné době je v České republice genetické vyšetření možné provést v Brně a v Praze. Jedná se o vyšetření celého panelu mutací u pacientů s fenotypovým vyjádřením GEFS+ spektra a DS. V Brně vyšetření provádí Centrum molekulární biologie a genové terapie Interní hematoonkologické kliniky LF MU a FN Brno (kontakt: RNDr. Lenka Fajkusová, CSc., lfajkusova@fnbrno.cz). V Praze se lze obrátit na Ústav biologie a lékařské genetiky 2. LF UK a FN Motol (kontakt: RNDr. Petra Hedvičáková, petra.hedvicakova@lfmotol.cuni.cz). V případě podezření na toto onemocnění je vhodné provést genetickou konzultaci na výše uvedených pracovištích.

Pro zájemce o podrobnější informace o genetice DS autoři odkazují na připravovaný článek „Genetické aspekty Dravetové syndromu", který bude v brzké době publikován v České neurologii a neurochirurgii kolektivem autorů z Kliniky dětské neurologie LF MU a FN Brno.

Klinický obraz a terapie DS v dětském věku

V klinickém obraze dochází k rozvoji epileptických záchvatů v kojeneckém věku s vrcholem kolem 5. měsíce u dosud normálně se vyvíjejících dětí. Incidence je dle nejnovějších údajů udávána 1:22 000 (výskyt DS v dánské populaci – Bayat et al., 2015), častěji jsou postiženi chlapci v poměru 2:1 (Panayiotopoulos, 2002). Objevují se tyto typy záchvatů: generalizované tonicko-klonické záchvaty (resp. často lateralizované stranově střídající), myoklonické záchvaty, atypické absence a fokální záchvaty s poruchou vědomí. Velmi častý je výskyt status epilepticus (SE), především v počátečním období, a to převážně u febrilních záchvatů. V klinickém obraze existuje určitá variabilita, mluvíme o DS-spektru, kam se řadí Borderline severe myoclonic epilepsy in infancy (SMEB), kde se nesetkáváme s myoklonickými záchvaty, Intractable child epilepsy with generalised tonic-clonic seizures (ICEGTC), kde se vyskytují převážně jen GTCS a Severe infantile multifocal epilepsy (SIMFE), kde dominují multifokální záchvaty.

V terapii DS jsou lékem volby valproát a benzodiazepiny (Chiron, 2011), především klobazam. Při jejich nedostatečném efektu je indikován stiripentol. Stiripentol (Diacomit) je řazen mezi orphan-drug v terapii DS a je schválen jako přídatná terapie k valproátu+klobazamu. V terapii DS je v Evropě schválen od roku 2007. Dosud byly realizovány dvě randomizované placebem kontrolované studie, které sledují efekt stiripentolu jako přídatné terapie ke kombinaci VPA+CLB. Výsledky ukázaly 71 % (Kassai et al., 2008) resp. 67 % (Chiron et al., 2000) respondérů ve srovnání s placebem. Zásadním poznatkem je, že stiripentol má nejvyšší efekt především na generalizova-

né tonicko-klonické záchvaty, které jsou v časném dětství zodpovědné za dramatický obraz této epileptické encefalopatie a nepřímo tak vedou k rozvoji mentální retardace u pacientů s DS, nasadit stiripentol je vhodné tedy co nejdříve.

Další terapeutickou možností jsou topiramat a levetiracetam (účinný především na myoklonické záchvaty), které lze využít jako přídatné léky. Z patofyziologie DS vyplývá, že inhibitory napětově řízených kanálů (fenytoin, lamotrigine, karbamazepin a vysoké dávky fenobarbitalu) mohou záchvaty zhoršovat a je žádoucí se jich v léčbě vyvarovat. V neposlední řadě je nutno zmínit i ketogenní dietu, která má v terapii DS relativně vysokou účinnost ve srovnání s jinými epileptickými encefalopatiemi (Caraballo, 2011). Příznivé výsledky ukazuje v terapii DS i implantace vagového stimulátoru (Zamponi et al., 2011).

DS v dospělém věku

Existuje jen limitovaný počet studií, které se zabývají klinickým obrazem a dalšími charakteristikami DS u dospělých pacientů. Je to dáno především tím, že tento syndrom je řazen mezi vzácná onemocnění a pacientů tedy obecně není mnoho. Dalším důvodem může být to, že je znám teprve z konce 70. let minulého století, možnosti genetické diagnostiky DS jsou ještě mnohem mladší a u řady dospělých pacientů je tedy stále poddiagnostikován a jsou vedeni často jako pacienti s farmakorezistentní epilepsií a mentální retardací, blíže nezařazení.

Níže jsou shrnuty výsledky studií, které se zabývají popisem klinického obrazu u pacientů s DS v dospělém věku (tab. 1). V souhrnu se autoři těchto studií shodují v tom, že záchvaty a především SE v raném dětském věku a dále frekventní epileptiformní výboje v EEG jsou považovány za hlavní příčinu kognitivních a behaviorálních změn u pacientů s DS v dětském a dospělém věku (Dravet et al., 2005). Dnes víme mnohem více o patofyziologii tohoto onemocnění a pacienty jsme schopni časně diagnostikovat. Jak záchvaty, tak EEG abnormity jsou potencionálně léčitelné a jejich kontrola může zlepšit outcome u pacientů s DS (Scheffer et al., 2009).

Epilepsie u dospělých pacientů s DS

Epileptické záchvaty jsou u dospělých pacientů s DS méně časté a mírnější. Plné kompenzace však dosahuje malé procento pacientů – 16,1 % (Akiyama et al., 2010), 8,3 % (Genton et al., 2011), 0 % (Jansen et al., 2006). Míra kompenzace záchvatů souvisí nepřímou úměrou s četností a závažností epileptických statů v dětství a s četností výskytu epileptiformních grafoelementů v EEG během dalšího vývoje (Akiyama et al., 2010). Citlivost na zvýšenou teplotu přetrvává i v dospělém věku, ale její dopad na frekvenci a závažnost epileptických záchvatů je menší (Genton et al., 2011).

V klinickém obraze dominují generalizované konvulzivní záchvaty a často jsou jediným typem záchvatů u těchto pacientů (Dravet et al., 2009; Jansen et al., 2006). 35 pacientů ze 40 (87,5 %) anamnesticky popisovali generalizované konvulzivní záchvaty, jejich typické záchvaty však byly zachyceny na iktálním EEG jako parciální záchvaty často s frontálním počátkem a s nebo bez sekundární generalizace (Akiyama et al., 2010). Typický je výskyt záchvatů s vazbou na noční spánek (Genton et al., 2011; Dravet et al., 2009). Další typy záchvatů, jako jsou myoklonické záchvaty, atypické absence nebo komplexní parciální záchvaty, jsou v dospělém věku málo časté (Genton et al., 2011). Pokud se vyskytují, tak spíše v nakupení před rozvojem GTCS (Dravet et al., 2009). Se SE se u dospělých pacientů setkáváme méně často. Akiyama et al. ukazují dramatický pokles výskytu SE, kdy po 10. roce již žádný zaznamenán nebyl (Akiyama et al., 2010). V dospělém věku se však vyskytovat mohou, jak je patrné ze studie 24 pacientů s DS, kde byl SE zaznamenán u 3 z nich, a to ve věku 24, 26 a 28 let (Genton et al., 2011). Pacienti, kteří trpí myoklonickými záchvaty nebo atypickými absencemi, mohou mít nonkonvulzivní SE v rámci nakupení těchto záchvatů.

Změny v EEG se s věkem také mění, stále dominují ale výboje multifokální a jsou velmi heterogenní, jak v interiktálním, tak iktálním obraze. Fotosenzitivita již v dospělém věku není tak výrazná, má tendenci vymizet před dosažením 20. roku (Genton et al., 2011).

Objektivní neurologický nález u dospělých pacientů s DS

Motorické abnormity v neurologickém nálezu jsou časté. Nejčastěji se vyskytuje mozečková symptomatika jako ataxie, dysartrie a intenční tremor, tento obraz je patrný u 30 % pacientů (Genton et al., 2011) resp. 28,5 % pacientů (Jansen et al., 2006). Méně často lze nalézt pyramidovou symptomatiku nebo extrapyramidové jevy (16 % resp. 12,5 % – Genton et al., 2011). U části pacientů s DS se v druhé dekádě života začíná rozvíjet progresivní porucha chůze – tzv. „crouch gait" (crouch = krčit se). Typicky zde nacházíme ortopedické abnormity, jako je zvýšená anteverze krčku stehenních kostí, vnější torze holenních kostí a pedes valgi. Tyto změny mají výrazný negativní dopad na schopnost samostatné chůze u pacientů s DS (Rodda et al., 2012). Velmi časté jsou další ortopedické obtíže jako skolióza, kyfoskolióza, plochonoží nebo kladívkovité prsty. Začínají se rozvíjet v dětském věku a zhoršují se v adolescenci i přes intenzivní fyzioterapii (Genton et al., 2011).

Neuropsychologický profil u dospělých pacientů s DS

Obecně lze konstatovat, že velká míra pacientů prokazuje deficit v jedné nebo několika sférách neuropsychologického vyšetření. Mentální retardace se vyskytuje od lehké po těžkou formu (Genton et al., 2011). V australské studii byla prokázána lehká mentální retardace u 5 z 11 pacientů (45,5 %) a těžká u 6 z 11 pacientů (54,5 %) (Jansen et al., 2006). Berkvens et al. prokazují těžkou nebo hlubokou mentální retardaci u 9 pacientů ze 13 (69,2 %) (Berkvens et al., 2015).

Závažný je deficit v oblasti řečových funkcí. Ve studii 21 dospělých pacientů s DS byl závažný řečový deficit prokázán u 14 z nich (66,6 %), z toho 3 (14,3 %) nemluvili vůbec a slabé komunikační schopnosti mělo 7 (33,3 %) z nich (Genton et al., 2011). V další studii s 31 dospělými pacienty byl závažný řečový deficit prokázán u 30 (96,7 %) pacientů. Sedm (22,6 %) jich nemluvilo vůbec, 23 (74,2%) z nich mělo slabé komunikační schopnosti a jen jeden (3,3 %) pacient měl jen lehký řečový deficit, u tohoto však dominovaly psychotické projevy (Akiyama et al., 2010).

Zatímco v dětském věku jsou u pacientů s DS významně zastoupeny behaviorální poruchy, jako je hyperaktivita, porucha pozornosti, impulzivita, opoziční chování nebo emoční labilita, v dospělém věku již tyto projevy tak výrazné nejsou (Berkvens et al., 2015). Behaviorální poruchy lze vystopovat ještě v adolescentním věku, jak prokazuje studie u 20 adolescentů s DS, kde u všech tyto problémy diagnostikovány byly (Olivieri et al., 2016). Poruchy autistického spektra byly popsány u osmi dospělých pacientů z 13 (61,5 %), automutilační tendence u čtyř pacientů ze 13 (30,8 %) a behaviorální poruchy u žádného z nich (Berkvens et al., 2015). Lze říci, že v dospělém věku dominují

poruchy autistického spektra, které však jsou také patrny již v dětském věku. Zajímavým rysem je, že pacienti s DS často prokazují nedostatek sociální odtažitosti a bývají nadměrně familiární k cizím osobám, jejich socializační schopnosti jsou výrazně lépe vyvinuty, než jak jsou popsány u poruch autistického spektra. Často tak ani jako autisté klasifikováni nejsou (Berkvens et al., 2015).

Závislost na okolí je konstantním rysem u dospělých pacientů, a to v 85,7–96,7% případů (Genton et al., 2011; Jansen et al., 2006; Akiyama et al., 2010).

Terapie dospělých pacientů s DS

V současné době je jen málo studií, které se zabývají terapií DS v dospělém věku. Uplatňují se obecné terapeutické principy léčby jednotlivých typů záchvatů podle toho, které v klinickém obraze dominují a využívají se obdobná terapeutická schémata identická pro léčbu DS v dětském věku. Lékem volby jsou tedy valproát a benzodiazepiny, pokud je jejich efekt nedostatečný, lze přidat stiripentol, případně topiramát, levetiracetam nebo zonisamid. Je třeba se vyvarovat blokátorů napěťově řízených kanálů, jak bylo uvedeno v části o terapii DS v dětském věku.

Ohledně efektu stiripentolu v dospělém věku byla publikována studie 13 dospělých pacientů s DS. V průběhu 36měsíčního sledovacího období byla zaznamenána redukce záchvatů o více než 50 % u tří pacientů (23,1 %), zhoršení záchvatů u tří pacientů (23,1 %) a beze změny zůstali tři pacienti (23,1 %). Nežádoucí reakce referovalo sedm pacientů (53,8 %), nejčastěji se jednalo o nechutenství, ztrátu hmotnosti a únavu. Tři z těchto pacientů STP pro nežádoucí reakce vysadili. Studie ukazuje nižší účinnost STP a obdobnou snášenlivost ve srovnání s dětskými pacienty (Balestrini et al., 2016).

Mortalita u dospělých pacientů s DS

DS je asociován se zvýšenou mírou úmrtnosti a úmrtí se může vyskytnout v jakémkoliv věku, častěji však během dětství (Genton et al., 2011). Průměrný věk úmrtí pacientů je 11 let (15,9 % pacientů ze souboru) (Dravet et al., 2009) resp. 65 měsíců (14,3 % pacientů ze souboru) (Oguni et al., 2001). Nejčastější příčinou úmrtí je SE u malých dětí, u starších dětí a dospělých pacientů pak SUDEP (Sudden Unexpected Death in EPilepsy – Náhlé neočekávané úmrtí u pacientů s epilepsií).

Závěr

Pro diagnostiku DS v dospělém věku je zásadní především důkladná anamnéza z období manifestace záchvatů, klinický obraz těchto pacientů v dospělém věku je sice popsán, ale nevykazuje typické rysy, na základě kterých bychom pacienty mohli diagnostikovat. Definitivní diagnóza je však pro pacienty důležitá, ukončí často náročné vyšetřování a umožní se zaměřit na specifika léčby a zlepšit tak kvalitu života pacientů s tímto závažným onemocněním.

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2.9 Annex 9

Danhofer P, Zech M, Bálintová Z, Baláž M, Jech R, Ošlejšková H. **Brittle Biballism-Dystonia in a Pediatric Patient with GNAO1 Mutation Managed Using Pallidal Deep Brain Stimulation.** Mov Disord Clin Pract. 2021;8(1):153–5. doi: 10.1002/mdc3.13118.

Summary:

In this work, the author presents a case report of a patient with a pathogenic variant in the GNAO1 gene, in which the movement disorder dominated in the clinical manifestation. The patient was kept under a diagnosis of dyskinetic cerebral palsy with epilepsy for a long time, until the cause of his condition was clarified by genetic examination. During the respiratory infection, there was a significant deterioration of the clinical condition up to the image of brittle dystonia. The patient was implanted with DBS with excellent effect. The author discusses the possible effect of DBS in these patients.

Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Brittle Biballism-Dystonia in a Pediatric Patient with GNAO1 Mutation Managed Using Pallidal Deep Brain Stimulation

Pavlína Danhofer, PhD,[1,*] Michael Zech, PhD,[2,3] Zdenka Bálintová,[1] Marek Baláž, PhD,[4] Robert Jech, PhD,[5] and Hana Ošlejšková, PhD[1]

Early onset movement disorders are a clinically and genetically heterogenous group of disorders. Mutations in GNAO1 were first reported in patients with Ohtahara syndrome and early infantile epileptic encephalopathy 17 (EIEE17).[1,2] GNAO1 (guanine nucleotide-binding protein 1) encodes the α-subunit of a heterotrimeric guanine nucleotide-binding protein (Gαo) which is the most abundant membrane protein in the mammalian central nervous system.[3] The early recognition of worsening extrapyramidal symptoms may facilitate intervention or prevent progression to status dystonicus.[4] A dystonia severity and action plan (DSAP, grades 1–5) can be very useful in assessing the threat of status dystonicus.[4]

We report a case of a 12-year-old boy with GNAO1 mutation who presented with severe biballistic symptomatology with dystonic features (DSAP 3) and required emergency deep brain stimulation (DBS) to avoid life-threatening symptoms. The boy was first examined at the Department of Pediatric Neurology at the age of 2 years. The clinical course is summarized in Table 1. At the age of 12 years, the patient deteriorated after respiratory infection and worsening of extrapyramidal symptomatology with dominating biballism and dystonic features developed with the threat of status dystonicus (Video S1). He experienced almost continuous generalized ballistic movements combined with dystonic postures, which were very painful and limited his normal activity, feeding, or sleep (DSAP 3). The patient was hospitalized in the ICU with the necessity of muscle relaxation. The course of treatment is summarized in Table 1. Taking into consideration the seriousness of this condition, DBS of bilateral globus pallidus internus (DBS-GPi) was performed. The sedative medication was gradually tapered off over the next 14 days and his condition rapidly improved to DSAP 1 (Video S2). Half a year after DBS, motor functions returned to the condition before the brittle biballism-dystonia developed. Whole exome sequencing (WES) identified a heterozygous missense variant in GNAO1 gene *c.625 C > T; p. (Arg209Cys)* previously described in the study by Koy et al. (2018)[5] and considered as pathogenic. The mutation was absent in the patient's parents and considered as de novo.

When pre-status dystonicus persists despite orally active antidystonia drugs and unsuccessful weaning from sedative or anesthetic agents, intrathecal baclofen or deep brain stimulation should be considered.[4] Several case reports and one small series have been published in which DBS was effective in patients with a GNAO1 mutation.[3,5] DBS may be effective due to its general effects in modulating aberrant synchronization in the basal ganglia-thalamo-cortical loops. The effect of DBS in our patient was very fast, with the improvement to DSAP 1 in 14 days. The patient tolerated the stimulation very well; however, only 3 months after initiation he developed generalized epileptic seizure. It is uncertain whether this occurred as a result of DBS (potentially triggered by tapering off the medication during the switching on and adjusting the DBS parameters) or was merely a coincidence in a patient with a history of epilepsy. In any case, stimulation should be increased cautiously and mildly in patients with epilepsy. After the introduction of levetiracetam, no further seizures occurred.

In patients with GNAO1 mutation and severe dystonia, GPi-DBS could be a treatment option with life-saving potential.

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TABLE 1 *Clinical course and therapy*

Age	Clinical characteristics	Neurological and psychological examination	Therapy	Effect	Note
3 months	episodes of apnoe and cyanosis - gastroesophageal reflux	normal	none	spontaneous remission	
2 years	epilepsy - generalised tonic–clonic seizures (GTCSs)		valproic acid	seizure freedom	discontinuation at the age of 10
		severe central hypotonia, developmental delay, speech delay	physiotherapy, speech therapy		
3 years		generalised spasticity with persistent axial hypotonia, dystonic postures, developmental delay, speech delay	physiotherapy, speech therapy		
5 years	severe dystonic storm after thiethylperazin (DSAP 4)		i.v. continuous clonazepam	partial with sedation	
			i.v. continuous midazolam	partial with sedation	
			baclofen p.o.	good effect	
12 years	brittle biballism-dystonia (DSAP 3) after respiratory infection		i.v. continuous clonazepam	partial with sedation	
			i.v. continuous midazolam	partial with sedation	
			i.v. pulses of phenobarbital	partial with sedation	
			i.v. pulses of propofol	very good effect	used with precaution for the risk of propofol infusion syndrome
			tetrabenazine p.o.	worsened	
			i.v. tiapride	no effect	
			i.v. valproic acid	no effect	
			gabapentin p.o.	no effect	
			GPi-DBS[a]	very good effect	initial stimulation: 0.5 V/130 Hz/90usec actual parametres: 3.2 V/130 Hz/120usec
12 years - 3 months after DBS	GTCS		levetiracetam	seizure freedom	

[a]GPi-DBS electrodes position: contacts 0 and 9, with distal contacts of electrodes on the right side: 1.6 mm anteriorly, 3.1 mm caudally and 18.1 mm laterally from mid-commisural point. On the left side: 2.6 mm anteriorly, 3.7 mm caudally and 19.8 mm laterally from mid-commisural point.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

PD: 1A, 1B, 1C, 2A, 2B, 3A
MZ: 1C, 2C, 3B
ZB: 1A, 2B, 2C, 3B
MB: 1C, 2B, 3B
RJ: 1C, 2C, 3B
HO: 1C, 2C, 3B

Disclosures

Ethical Compliance Statement: The study was approved by the Ethical Committee of the institutions concerned and both parents and the patient agreed with the publication after receiving all information relevant to the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Video 1. Clinical condition before DBS implantation. Deterioration into the picture of brittle biballism-dystonia and impending status dystonicus. Almost continuous biballistic movements with dystonic postures that impede normal movement, they are painful and exhaust the patient.

Video 2. Clinical condition of the patient 2 months after DBS implantation. He is able to climb independently on all fours. Motor skills and coordination of movements are improved.

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2.10 Annex 10:

Česká K, Aulická Š, Horák D, Danhofer P, Říha P, Mareček R, Šenkyřík J, Rektor I, Brázdil M, Ošlejšková H. **Autosomal dominant temporal lobe epilepsy associated with heterozygous reelin mutation: 3 T brain MRI study with advanced neuroimaging methods.** Epilepsy Behav Case Reports 2019; 11: 39-42. doi: 10.1016/j.ebcr.2018.10.003

This publication provides more information on the genetics of epilepsy. Authors present a patient with MR-negative focal temporal lobe epilepsy. Only genetic examination using the NGS panel clarified the etiology. Genetics plays an important role in the diagnosis of epilepsy and may end further investigations within the epileptosurgery program.

Summary:

Purpose: Autosomal dominant lateral temporal epilepsy (ADLTE) is a genetic focal epilepsy syndrome characterized by focal seizures with dominant auditory symptomatology. We present a case report of an 18-year-old patient with acute onset of seizures associated with epilepsy. Based on the clinical course of the disease and the results of the investigation, the diagnosis of ADLTE with a proven mutation in the RELN gene, which is considered causative, was subsequently confirmed. The aim of this study was to use 3 Tesla (3 T) magnetic resonance imaging (MRI) and advanced neuroimaging methods in a patient with a confirmed diagnosis of ADTLE.

Methods: 3 T MRI brain scan and advanced neuroimaging methods were used in the standard protocols to analyzse voxel-based MRI, cortical thickness, and functional connectivity.

Results: Morphometric MRI analysis (blurred grey-white matter junctions, voxel-based morphometry, and cortical thickness analysis) did not provide any informative results. The functional connectivity analysis revealed higher local synchrony in the patient in the left temporal (middle temporal gyrus), left frontal (supplementary motor area, superior frontal gyrus), and left parietal (gyrus angularis, gyrus supramarginalis) regions and the cingulate (middle cingulate gyrus) as compared to healthy controls.

Conclusions: Evidence of multiple areas of functional connectivity supports the theory of epileptogenic networks in ADTLE. Further studies are needed to elucidate this theory.

The following two papers are important mainly in terms of epilepsy and comorbidities. In her dissertation, the author dealt with the incidence of ADHD in patients with Rolandic epilepsy and prepared a review on co-occurence of ADHD and epilepsy **(Annex 12).** As already mentioned in the text, the new ILAE 2017 Classification of epilepsies takes this aspect into account in children with „benign“ focal epilepsies. The term „benign“ is replaced by the term „self-limited“.

Autistic symptoms are often observed in children with epilepsy, and Autism Spectrum Disorder (ASD) is a significant comorbidity associated with epilepsy in children. The author prepared a review on this topic **(Annex 12).**

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Case Report

Autosomal dominant temporal lobe epilepsy associated with heterozygous reelin mutation: 3 T brain MRI study with advanced neuroimaging methods

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ABSTRACT

Purpose: Autosomal dominant lateral temporal epilepsy (ADLTE) is a genetic focal epilepsy syndrome characterized by focal seizures with dominant auditory symptomatology. We present a case report of an 18-year-old patient with acute onset of seizures associated with epilepsy. Based on the clinical course of the disease and the results of the investigation, the diagnosis of ADLTE with a proven mutation in the RELN gene, which is considered causative, was subsequently confirmed. The aim of this study was to use 3 Tesla (3 T) magnetic resonance imaging (MRI) and advanced neuroimaging methods in a patient with a confirmed diagnosis of ADTLE.

Methods: 3 T MRI brain scan and advanced neuroimaging methods were used in the standard protocols to analyzse voxel-based MRI, cortical thickness, and functional connectivity.

Results: Morphometric MRI analysis (blurred grey-white matter junctions, voxel-based morphometry, and cortical thickness analysis) did not provide any informative results. The functional connectivity analysis revealed higher local synchrony in the patient in the left temporal (middle temporal gyrus), left frontal (supplementary motor area, superior frontal gyrus), and left parietal (gyrus angularis, gyrus supramarginalis) regions and the cingulate (middle cingulate gyrus) as compared to healthy controls.

Conclusions: Evidence of multiple areas of functional connectivity supports the theory of epileptogenic networks in ADTLE. Further studies are needed to elucidate this theory.

1. Introduction

Autosomal dominant lateral temporal epilepsy (ADLTE), also known as autosomal dominant partial epilepsy with auditory features (ADPEAF), is a genetic focal epilepsy syndrome. It is characterized by focal seizures with or without a loss of consciousness, inconstantly with secondary generalization. Focal seizures are mainly characterized by auditory symptoms. Auditory auras are the most common symptom, and occur in isolation or precede some kind of receptive aphasia. Other symptoms following the auditory phenomena include vertigo, paroxysmal headache, déjà-vu, and epigastric discomfort [2]. Sensory symptomatology (e.g., visual, olfactory) and autonomic motor symptomatology are less common. Neurological findings and the mental status of patients are normal. The manifestation of the syndrome occurs between the ages of four and 50 years, with the maximal occurrence in the adolescent period [3]. Structural examinations of the brain (CT, MRI) at standard resolutions most often return normal findings. Routine and sleep electroencephalography (EEG) may be normal, but findings of focal/slow wave abnormality in the temporal areas are not uncommon, occurring in approximately 20% of patients [2,3]. The disease heredity is autosomal dominant with varying penetration (about 70%) [1]. The diagnosis is based on personal and family history, seizure semiology, and normal MRI brain scan. Approximately 33% of patients show a pathogenic variant in the LGI1 gene [2]. In a smaller percentage of ADLTE cases, mutation in the reelin (RELN) gene is shown in heterozygous

Abbreviations: ADLTE, Autosomal dominant lateral temporal epilepsy; ADPEAF, Autosomal dominant partial epilepsy with auditory features; LGI1, Leucine-rich, glioma inactivated 1; RELN, Reelin; MRI, Magnetic resonance imaging; CT, Computer tomography; EEG, Electroencephalography; CBZ, Carbamazepine; CLB, Clobazam; 3 T, three Tesla; 1.5 T, one Tesla; TLE, Temporal Lobe Epilepsy; HDEEG, high density resting-state EEG; GMC, grey matter concentration; GMV, grey matter volume; WMC, white matter concentration; WMV, white matter volume; LS, Local synchrony.

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form [2]. The RELN gene is primarily expressed in brain tissue. The protein product of the RELN gene is called reelin. Reelin regulates the correct formation of laminated structures during embryonic development and postnatally modulates dendritic growth and synaptic plasticity [2]. Homozygous variants of the RELN mutation cause lissencephaly with cerebellar hypoplasia, severe neuronal migration defects, delayed cognitive development, and epileptic seizures [5]. Heterozygous mutation of the RELN mutation can cause small changes in the cortex corresponding to neuronal migration disorders [2]. The prognosis of the disease is benign and, in most cases, there is a very good response to treatment with properly selected anti-seizure drugs (valproate, phenytoin, and carbamazepine are recommended).

2. Case report

We present a case report of an 18-year-old man who was admitted to the Department of Pediatric Neurology of the University Hospital Brno in 2017. According to his personal history, he was born in the 32nd week of gestation (the reason is unknown) and his psychomotor development was normal. The family history showed no neurological disease or epilepsy. At the age of 17, the patient suddenly began to experience epileptic seizures without clear provocation. The clinical manifestation was dominated by focal auditory seizures, without the loss of consciousness. The seizures (auras) were described as a short-term loss of hearing and simultaneous sensations of warmth lasting up to 30 s. The auras consistently progressed into focal seizures with right-handed facial-brachial motor symptomatology. Focal to bilateral tonic-clonic seizures occurred inconsistently. The seizures were daily, and the frequency at initial onset was very high. The auditory and vegetative auras occurred several times a day and convulsive seizures following auras occurred five to six times per week. On admission, the patient was already being treated with valproic acid monotherapy at a total dose of 1500mg per day with a suitable serum concentration. This medication had no significant effect. A CT and MRI (1.5 T) scan, performed at another institution, were described as normal. A routine EEG showed a non-specific finding of theta activity in the left fronto-centro-temporal region. The patient was admitted to our department urgently after a generalized tonic–clonic seizure. A complete neurological examination and routine laboratory tests as well as EEG returned normal findings. Due to the clinical course of the disease and the seizure semiology, a genetic examination with high suspicion for ADLTE (a requirement for the LGI1 gene and the RELN gene) was performed. For therapeutic purposes, the patient was switched from valproate to carbamazepine (CBZ), at a total dose of 600 mg per day, with a partial effect on seizures (there was a reduction in seizure intensity, not a reduction in frequency). Clobazam (CLB) was added to the carbamazepine at a dose of 40 mg per day, with a pronounced effect on seizures: convulsive seizures disappeared and auditory seizures decreased to 20%. Overall, the patient's quality of life improved, as reported by the patient and his family.

The causal mutation in the RELN gene (c.877G>A p. (Asp293Asn)) in the heterozygous state was confirmed. Despite the patient's negative family history, an investigation of the patient's parents' DNA was recommended. An identical mutation was found in the patient's mother through genetic testing. The patient's mother's EEG was normal and further treatment of the mother was not pursued.

3. Methods

The magnetic resonance data was acquired on a 3 T Siemens Prisma machine. The protocol contained: T1 MPRAGE, T2 FLAIR, T1 MP2RAGE; T2 TSE; T2 FLASH; T1 TIR; T2 TIRM; T1 TIR; T2 TIRM; and T2 TSE sequences.

The high density resting-state EEG (HDEEG) data was acquired using the GES 400 amplifier (Electrical Geodesics, Inc.) with a 256-channel EEG cap. The subject was instructed to sit still with closed eyes during 20 min of recordings.

4. Image analysis

4.1. Morphometry

The T1 MPRAGE and T2 FLAIR images were preprocessed using the SPM12 and CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat/index.html) running under MATLAB (Mathworks, Inc.). We obtained images showing the spatial distribution of the local grey matter volume/concentration (GMV/GMC). The resulting GMV and GMC images were voxel-wise compared to a set of GMV/GMC images and white matter volume/concentration (WMV/WMC) images acquired with the same MR protocol and resulting from the same preprocessing process applied to data from healthy subjects (HC) ($N = 48$). The data were intensity normalized by estimating the total intracranial volume to correct for bias introduced by variability in head size [6]. The GMC and WMC images were used to localize abnormalities in grey/white matter junctions [7]. The patient's junction image was compared with the HC using a two-sample T-test with age and gender as nuisance covariates.

The CAT12 output contains an estimate of cortical thickness [13], which makes it possible to localize abnormalities in grey matter with higher sensitivity than VBM. The patient data were compared to HC data in the same way as junctions and GMC/GMV images.

4.2. Functional connectivity

The HDEEG data were segmented into 1 s epochs. We select 300 epochs with clean EEG. The sensor-space data from 256 channels were projected using sLORETA into the source space using Cartool [9]. Using the Corrected Imaginary Coherence metric, we estimated the spatial distribution of local synchrony (LS) in source-space. The increased local synchrony was shown to be a potential marker of epileptogenicity [10]. We compared the patient's LS image with LS images from 26 healthy controls using a two-sample T-test.

5. Results

5.1. MRI findings

Brain 3 T MRI was used with our patient. We found discrete changes (subtle cortical thickness in T2-weighted sequences and very mild decrease of signal intensity in T1-weighted sequences) in the left superior temporal gyrus on 3 T MRI. Subtle cortical dysplasia in this site was. Consequently, advanced neuroimaging methods (voxel-based 3D MRI analysis, cortical thickness analysis, and functional connectivity) were used. Morphometric MRI analysis (blurred grey-white matter junctions, voxel-based morphometry, and cortical thickness analysis) did not provide any informative results. The functional connectivity analysis revealed higher local synchrony in the left temporal (middle temporal gyrus), left frontal (supplementary motor area, superior frontal gyrus), left parietal (gyrus angularis, gyrus supramarginalis) region and the cingulate (middle cingulate gyrus) gyrus of the patient as compared to healthy controls (See Fig. 1 and Table 1).

6. Discussion

We present a case of an 18-year-old patient with an acute manifestation of severe epileptic seizures that had a significant impact on the quality of life of the patient and his family. The age at seizure onset, clinical course of the disease, seizure semiology and the results of the paraclinical examinations indicated possible ADLTE. The diagnosis was supported by genetic testing, which revealed a heterozygous mutation in the RELN gene. In 30–50% of cases, ADLTE is caused by a mutation in the LGI1 gene; around 17% of patients carry a mutation in the RELN gene [2,3]. Nearly 50% of patients are not tested for causal mutation. Due to the similar clinical course of the disease in both mutations, it is recommended to test for both genes for ADLTE in suspected patients

[2]. To our knowledge, seven families have thus far been identified with a proven mutation in the RELN gene [1,2]. Dazza et al. reported that the dominant type of focal auditory seizures is present in 71% of patients. However, these seizures occur mostly at a low frequency (weekly or yearly). Seizure freedom was achieved with the first antiepileptic drug in 63% of patients; 31% of patients continued to experience sporadic auditory auras on established antiepileptic therapy. Tonic–clonic seizures disappeared in all studied patients [1]. The patient in this case report was not seizure free even after trying several anti-seizure drugs. He continued to experience sporadic auditory auras. However, the quality of life of the patient and the whole family has improved. As a significant success of therapy, the patient reports that the seizure frequency has decreased to 20%, and the tonic–clonic seizures have disappeared on the combination of CBZ and CLB. The patient's EEG was abnormal only at the onset of the disease. Dazza et al. observed routine and/or sleep EEG revealing epileptiform abnormality or deceleration in 12 patients out of a total of 15 (80%); 20% of those patients had normal EEG or non-specific abnormalities [1]. The family history of some individuals with ADLTE may appear negative due to the early unrelated death of a parent, later manifestations of epilepsy (perhaps manifested in the 50th year of life), or reduced penetration. Approximately 33% of patients with a pathogenic variant of the gene remain asymptomatic [3]. If the genetic examination in the proband parents is negative, there are two explanations for the result: germinal mosaicism in the parents or de novo mutation in the proband. The possibility of de novo mutation in this type of epilepsy is assumed to be less than 1% [3].

The homozygous form of mutation in the RELN gene can cause serious brain damage, such as lissencephaly and cerebellar hypoplasia, as well as severe neuronal migration disorders. It can thus be assumed that in the heterozygous form of mutation, small changes in the cortex corresponding to neuronal migration disorders may result [2]. These

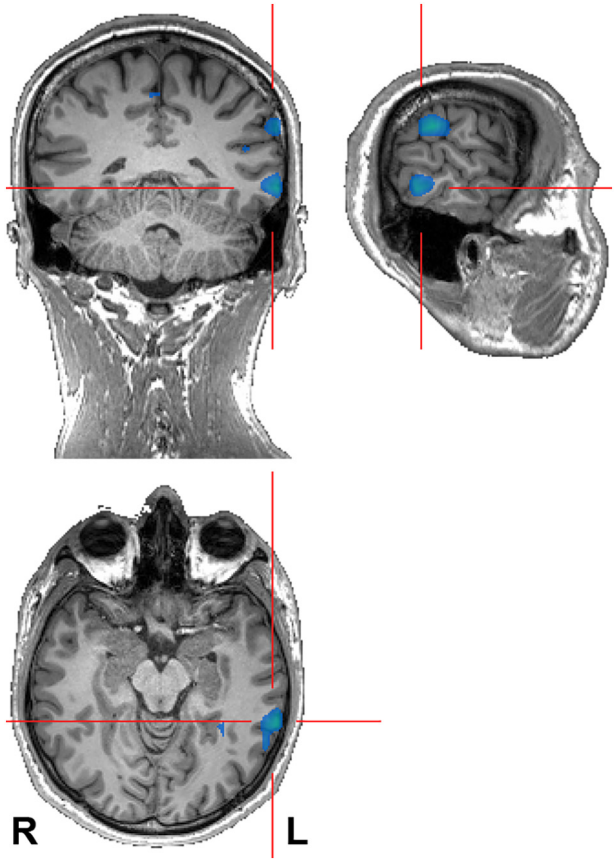

Fig. 1. The regions showing increased local synchrony in the patient as compared to HC (N = 26; p < 0.001).

Table 1
The regions that show increased local synchrony in the patient as compared to the HC (N = 26; p < 0.001). The underlined regions are depicted in Fig. 1.

Region	# voxels	Z-value[a]	Coordinate[a] [mm]
L SMA	19	7.02	−6 18 72
L supramarginal g	14	6.12	−66 −30 30
L angular g	40	5.84	−48 −66 42
L middle temporal g	13	5.31	−66 −48 −6
L middle cingulate g	31	5.26	−6 12 36
R superior frontal g	5	4.29	24 36 54

[a] Cluster maximum; L – left; g – gyrus; SMA – supplementary motor area; voxel size = (6 × 6 × 6) mm^3.

subtle changes cannot be detected on commonly available low resolution MRI devices. Brain 3 T MRI and advanced neuroimaging methods (voxel-based MRI analysis, cortical thickness analysis, and functional connectivity) were used with our patient. The 3 T MRI findings in the left superior temporal gyrus were felt to be insignificant . Advanced neuroimaging methods including morphometric MRI analysis (blurred grey-white matter junctions, voxel-based morphometry, and cortical thickness analysis) did not provide any informative results. The functional connectivity analysis revealed higher local synchrony in the left temporal, left frontal, and left parietal regions and the cingulate when the patient was compared to healthy controls (see Fig. 1 and Table 1).

The evaluation of brain networks using functional connectivity fMRI is a relatively new technique that has been used successfully to identify brain networks in several conditions, including autism, depression, and schizophrenia [11]. Evidence of multiple areas of functional connectivity confirms the theory of epileptogenic networks in ADTLE. Connectivity abnormalities have potential for clinical relevance and correlation. They may assist with diagnosis, they may provide insights into neurologic deficits associated with TLE, and they may benefit invasive treatments through a more accurate understanding of the functional anatomy of TLE [11]. The epileptogenic network concept is a key factor in identifying the anatomic distribution of the epileptogenic process, which is particularly important in the context of epilepsy surgery [12].

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

None of the authors has any conflict of interest to disclose.

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2.11 Annex 11:

Cahová P, Pejčochová J, Ošlejšková H. **Hyperkinetická porucha/ „Attention Deficit Hyperactivity Disorder“ u dětských pacientů s epilepsií.** Cesk Slov Neurol N 2011; 74/107(2): 157-162.

Summary:

Hyperkinetic disorder, also known as attention deficit hyperactivity disorder (HKD/ADHD), is a neurodevelopmental disorder characterised by an age-related and inappropriate rate of hyperactivity with impulsivity together with an inability to remain focused on tasks or activi- ties. HKP/ADHD incidence in children with epilepsy is estimated to be as high as 30%–40%. Several studies show that in children with ADHD the presence of epileptiform discharges can be found in 6%–51% of cases. The hypothesis that the comorbid incidence of epilepsy and ADHD may be merely coincidental is not accepted. Cognitive and behavioural changes in patients with epilepsy used to be explained as the consequences of recurrent seizures, the influence of antiepileptic medication and the substantial substrate of epilepsy. However, in the majority of ADHD and epilepsy children, the onset of ADHD symptomatology precedes the onset of clinical seizures. The onset of spontaneous seizures arises out of a complex process of epileptogenesis that involves a cascade of transcriptional changes involving the processes of plasticity, apoptosis and neurogenesis. All of these changes may influence the behavioural and cognitive profile before seizure onset. The pathophysiology of ADHD is explained by disturbances in the prefrontal-thalamo-striato-cortical neuronal circuits. It is the frontal lobe that is important to the understanding of the common neurobiological substrate of ADHD and epilepsy.

Hyperkinetická porucha/ „Attention Deficit Hyperactivity Disorder“ u dětských pacientů s epilepsií

Hyperkinetic Disorder/Attention Deficit Hyperactivity Disorder in Children with Epilepsy

Souhrn

Hyperkinetická porucha/„Attention deficit hyperactivity disorder“ (HKP/ADHD) se řadí mezi neurovývojové poruchy. Je charakterizována věku nepřiměřenou mírou nepozornosti, impulzivity a hyperaktivity. HKP/ADHD je jednou z relativně častých komorbidit u dětí s epilepsií. Symptomy této poruchy se u dětí s epilepsií vyskytují až ve 30–40 % případů. Výsledky studií ukazují, že u dětí s HKP/ADHD lze nalézt epileptiformní grafoelementy v EEG v 6–51 % případů. Co se týká komorbidního výskytu HKP/ADHD, nelze se spokojit s hypotézou pouhé náhodné koincidence. Kognitivní a behaviorální změny u pacientů s epilepsií byly dříve vysvětlovány následky opakovaných záchvatů a vlivy antiepileptické medikace. Naopak u řady pacientů symptomatika HKP/ADHD předchází časově rozvoji záchvatů. Nástup záchvatů je výsledkem komplexního procesu epileptogeneze, který zahrnuje řetězec transkripčních změn zasahujících na úrovni plasticity, apoptózy a neurogeneze. Všechny tyto změny mohou ovlivňovat behaviorální a kognitivní profil ještě před rozvojem klinických záchvatů. Patofyziologie HKP/ADHD je vysvětlována poruchou na úrovni prefronto-thalamo-striato-kortikálních neuronálních okruhů. A právě frontální lalok je důležitý pro pochopení společného neurobiologického substrátu HKP/ADHD a epilepsie.

Abstract

Hyperkinetic disorder, also known as attention deficit hyperactivity disorder (HKD/ADHD), is a neurodevelopmental disorder characterised by an age-related and inappropriate rate of hyperactivity with impulsivity together with an inability to remain focused on tasks or activities. HKP/ADHD incidence in children with epilepsy is estimated to be as high as 30%–40%. Several studies show that in children with ADHD the presence of epileptiform discharges can be found in 6%–51% of cases. The hypothesis that the comorbid incidence of epilepsy and ADHD may be merely coincidental is not accepted. Cognitive and behavioural changes in patients with epilepsy used to be explained as the consequences of recurrent seizures, the influence of antiepileptic medication and the substantial substrate of epilepsy. However, in the majority of ADHD and epilepsy children, the onset of ADHD symptomatology precedes the onset of clinical seizures. The onset of spontaneous seizures arises out of a complex process of epileptogenesis that involves a cascade of transcriptional changes involving the processes of plasticity, apoptosis and neurogenesis. All of these changes may influence the behavioural and cognitive profile before seizure onset. The pathophysiology of ADHD is explained by disturbances in the prefrontal-thalamo-striato-cortical neuronal circuits. It is the frontal lobe that is important to the understanding of the common neurobiological substrate of ADHD and epilepsy.

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Klíčová slova

hyperkinetická porucha – ADHD – epilepsie – epilepsie frontálního laloku – dětské absence – BERS

Key words

hyperkinetic disorder – ADHD – epilepsy – frontal lobe epilepsy – childhood absence epilepsy – BECTS

Úvod

Hyperkinetická porucha/Attention Deficit Hyperactivity Disorder (HKP/ADHD) se řadí mezi neurovývojové poruchy. Je charakterizována věku nepřiměřenou mírou nepozornosti, impulzivity a hyperaktivity. Postihuje děti již od raného věku a ve 40–50 % [1] přechází do dospělého věku. HKP/ADHD je jedna z častých komorbidit u dětí s epilepsií. Komorbidní výskyt obou těchto diagnóz není jasně vysvětlen. Vzhledem k jejich četnosti se nelze spokojit s hypotézou náhodné koincidence. Patofyziologicky lze předpokládat genetickou poruchu na úrovni vyzrávání CNS vedoucí jak k epileptiformní aktivitě v EEG, tak ke kognitivním a behaviorálním změnám [2]. Výskyt HKP/ADHD u pacientů s epilepsií nesmí být opomíjen. HKP/ADHD významně snižuje kvalitu života těchto pacientů a negativně ovlivňuje úroveň jejich dosažených školních výsledků a dovedností.

Autoři textu se snaží blíže vysvětlit patofyziologické souvislosti koincidenčního výskytu HKP/ADHD a epilepsie, dále se zaměřují na epileptické syndromy, které bývají nejčastěji spojeny s HKP/ADHD.

Diagnostická kritéria HKP/ADHD

Diagnostická kritéria hyperkinetické poruchy vychází z MKN-10 [3], kde jsou rozlišovány dva subtypy: porucha pozornosti a hyperaktivita (F90.0) a hyperkinetická porucha chování (F90.1) (tab.1, 2). Pro diagnózu je nutné, aby byly přítomny všechny jádrové příznaky, a to porucha pozornosti, hyperaktivita a impulzivita. Porucha se musí manifestovat před sedmým rokem věku a musí trvat alespoň šest měsíců. Pokud se k jádrovým příznakům hyperkinetické poruchy přidají i poruchy chování (agresivita, kriminální činy, sociální nepřizpůsobivost atd.), mluvíme o hyperkinetické poruše chování (F90.1), která vyžaduje odlišný terapeutický algoritmus a z pohledu sociální adaptace je závažnější.

V současnosti hojně používaný termín ADHD (Attention Deficit Hyperactivity Disorder) vychází z amerických diagnostických manuálů. Ve svých diagnostických kritériích využívá jiné členění subtypů a v tomto směru je diagnostika ADHD o něco méně „přísná" ve srovnání s HKP. DSM-IV [4] definuje ADHD odlišně a rozlišuje tři subtypy: ADHD s převládající poruchou pozornosti (ADHD Inattentive type), ADHD s převládající hyperaktivitou a impulzivitou (ADHD Hyperactivity/Impulsivity type) a ADHD smíšený typ (ADHD Combined type) (tab. 1–3). Zásadní rozdíl oproti klasifikaci dle MKN-10 je, že pro diagnostiku není nutná přítomnost všech jádrových příznaků. Podmínkou diagnózy je nutnost výskytu některých jádrových příznaků již před sedmým rokem věku, některé příznaky se objevují na dvou či více místech (např. doma či ve škole) a musí být zohledňován i aspekt sociální. DSM-IV klasifikace ADHD se oproti MKN-10 klasifikaci HKP liší i tím, že nezahrnuje poruchy chování jako součást ADHD, neexistuje tedy analogie diagnózy F90.1 jako v MKN-10 klasifikaci a pacienti s ADHD a poruchami chování jsou vedeni pod dvojí diagnózou. Právě odlišnosti v tomto členění jsou příčinou vyšší incidence ADHD

Tab. 1. Diagnostická kritéria HKP (MKN-10) vs ADHD (DSM-IV).

Diagnostická kritéria HKP dle MKN-10	**Diagnostická kritéria ADHD dle DSM-IV**
symptomy poruchy pozornosti:	**• kritéria A1: 6 nebo více příznaků trvajících minimálně 6 měsíců**
• alespoň 6 příznaků po dobu 6 měsíců	**porucha pozornosti:**
obtížná koncentrace pozornosti	nepozornost při školních úkolech, opomíjení detailů, chyby z nepozornosti
neposlouchá	neudrží pozornost při hře
nedokončuje úkoly	neposlouchá během rozhovoru
vyhýbá se úkolům vyžadujících mentální úsilí	neposlouchá instrukce, není schopno dokončit úkol
nepořádný, desorganizovaný	organizační problémy
ztrácí věci	nesnáší úkoly vyžadující mentální úsilí, vyhýbá se jim
roztržitý	ztrácí věci
zapomnětlivý	dá se snadno rozptýlit vnějšími podněty
	často zapomnětlivost
symptomy hyperaktivity:	**• kritéria A2: 6 nebo více příznaků hyperaktivity-impulzivity trvajících minimálně 6 měsíců, nepřiměřených vývojovému stupni**
• alespoň 3 příznaky po dobu 6 měsíců	**Hyperaktivita:**
neposedí, vrtí se	neklid rukou, nohou, vrtí se na židli
pobíhá kolem	vstává ve třídě, když má sedět
vyrušuje, je hlučný, obtížně zachovává klid	často pobíhá v nevhodných situacích
v neustálém pohybu	neumí si hrát tiše
excesivně mnohomluvný	trvale příliš vysoká motorická aktivita
symptomy impulzivity:	nadměrně mnohomluvný
• alespoň 1 příznak po dobu 6 měsíců	**Impulzivita:**
nezdrženlivě mnohomluvný	často vyhrkne odpověď na otázky, které ještě nebyly dokončeny
vyhrkne odpověď bez přemýšlení	často není schopno čekat ve frontě nebo až přijde na řadu ve hře či komunikaci
nedokáže čekat	často přerušuje ostatní nebo se jim vnucuje
přerušuje ostatní	často příliš mluví bez ohledu na sociální zábrany

Tab. 2. Klasifikace HKP (MKN-10) vs ADHD (DSM-IV).

Hyperkinetická porucha (MKN-10)	Attention Deficit Hyperactivity Disorder – ADHD (DSM-IV)
Porucha pozornosti a hyperaktivita (F90.0)	ADHD typ s převahou poruchy pozornosti
	ADHD typ hyperaktivně-impulzivní
	ADHD typ smíšený
Hyperkinetická porucha chování (F90.1)	ADHD typ nespecifický
	ADHD v časné remisi

Tab. 3. Klasifikace ADHD (DSM-IV) dle diagnostických kritérií.

Subtypy ADHD (DSM-IV)

ADHD typ s převahou poruchy pozornosti
kritéria A1 alespoň 6 měsíců

ADHD typ hyperaktivně impulzivní
kritéria A2 alepsoň 6 měsíců

ADHD typ kombinovaný
kritéria A1 a A2 alespoň 6 měsíců

ADHD typ nespecifický
prominentí symptomy nepozornosti, hyperaktivity-impulzivity, které však nesplňují kritéria ADHD

ADHD v časné remisi
současné symptomy již nesplňují všechna kritéria

ve Spojených státech amerických a způsobují jisté rozpaky a nepřesnosti při srovnávání výsledků našich studií s výsledky studií designovaných dle kritérií DSM-IV.

Autoři se dále soustředí na výskyt a klinické rysy epilepsie bez ohledu na využití klasifikačního schématu HKP, resp. ADHD. Proto je termín HKP/ADHD používán současně. V citacích je terminologie zachována dle záměru autora původní práce.

Epidemiologie současného výskytu HKP/ADHD a epilepsie

Již v roce 1955 publikoval Ounsted [5] práci, kde dává do souvislosti výskyt poruchy pozornosti jako součásti hyperkinetické poruchy a epilepsie. S dalším rozvojem pohledu a klasifikačních schémat ADHD se objevily další práce [6,7], jež využívají u pacientů s ADHD klasifikačního schématu DSM-IV a zjišťují signifikantně vyšší výskyt ADHD v této skupině pacientů s nejpočetnějším zastoupením subtypu s poruchou pozornosti.

Dle výsledků různých studií jsou symptomy HKP/ADHD přítomny u 30–40 % pacientů s epilepsií [7–9]. Dle Salpekara et al [10] se dokonce ADHD řadí mezi nejčastější psychiatrickou komorbiditu u pacientů s epilepsií. U pacientů s HKP/ADHD lze nalézt epileptiformní aktivitu v EEG v 6–53 % [11–13]. Prediktivní hodnota epileptiformní EEG abnormality ve vztahu k následnému rozvoji klinických záchvatů u pacientů s ADHD je 14 % [11].

Neurobiologické aspekty v patogenezi HKP/ADHD a epilepsie

V současné době je pro pochopení patofyziologie HKP/ADHD přijímána hypotéza prefronto-striato-thalamo-kortikálního okruhu. Z pohledu exekutivních funkcí rozlišujeme v neuroanatamicko-fyziologickém pojetí v zapojení frontálního laloku s oblastí bazálních ganglií tři okruhy [14]:

- **dorzolaterální okruh** (dorzolaterální prefrontální kortex – nucleus caudatus dorsolateralis – globus pallidum lat. dorsomedialis – thalamus ventralis anterior a mediodorsalis), jehož poškození vede k rozvoji dorzolaterálního syndromu (postižení exekutivních kognitivních funkcí s projevy mentální a motorické perseverace, poruchy provádění komplexních cílených činností, motorického programování, snížená plynulost řeči, poruchy řešení problému, poruchy paměti a učení).
- **orbitofrontální okruh** (laterální orbitální kortex – nucleus caudatus ventromedialis – globus pallidum med. dorsomedialis – thalamus ventralis anterior a mediodorsalis), jehož poškození vede k rozvoji prefrontálního syndromu s emoční labilitou a desinhibicí v chování.
- **přední cingulátový (mediofrontální) okruh** (přední cingulum – nucleus accumbens – globus pallidum rostrolateralis – thalamus mediodorsalis), jehož poškození vede k rozvoji apatie až akinetického mutizmu.

Právě poruchy neurotransmise vyskytující se v zapojení prefronto-stirato-thalamo-kortikálního okruhu hrají významnou roli v etiopatogenezi HKP/ADHD. V roce 1970 byla vyslovena Kortenskym katecholaminová hypotéza hyperaktivity. Noradrenalin a dopamin se ukázaly hlavními neurotransmitery uplatňujícími se v patogenezi HKP/ADHD. Tato hypotéza byla upevňována výsledky celé řady studií využívajících funkční zobrazení CNS a podpořena také efektem dopaminergních a noradrenergních psychofarmak v terapii HKP/ADHD. Výsledky zobrazovacích a funkčních studií poukazují na hypofunkční katecholaminovou projekci z oblasti bazálních ganglií do prefrontálního kortexu. V neurotransmiterové oblasti se tato dysfunkce projevuje jako relativní hypoaktivita kortikálního dopaminového systému s relativní hyperaktivitou striatálního dopaminu. Jedinci s HKP/ADHD mají hypoaktivitu kortikálního dopaminového systému (nižší tonický dopamin) a hyperaktivitu striatálního dopaminu (zvýšený fyzický dopamin).

Prefrontální oblasti a funkce s těmito oblastmi asociované, jako je kontrola pozornosti či impulzivity, nedozrávají dříve než v období rané dospělosti [15]. Tento fakt je zásadní pro pochopení neurovývojového aspektu HKP/ADHD. HKP/ADHD jako porucha nastupuje před sedmým rokem věku, první známky lze pozorovat již v kojeneckém období. Průběh HKP/ADHD mění svůj klinický obraz i tíži vyjádření současně se zráním mozku jedince. U poloviny případů HKP/ADHD dochází ke spontánnímu ústupu kolem 12. roku věku. Ve 40–60 % případů však porucha přetrvává do dospělosti [16].

Tato „čistá forma" HKP/ADHD se nezabývá aspekty EEG či výskytu klinicky manifestních epileptických záchvatů. Prevalence HKP/ADHD v dětské populaci je 3–7 % [17], a jak bylo uvedeno výše, u 30–40 % pacientů s epilepsií je pozorována symptomatika HKP/ADHD. Vzhledem k této četnosti komorbidního výskytu HKP/ADHD a epilepsie by bylo odvážné považovat jejich současný výskyt za pouhou náhodnou koincidenci. Jaký je ale

vztah mezi symptomy HKP/ADHD a epilepsií, zůstává otázkou.

Epileptická aktivita, která se vyskytuje v kortikálních oblastech funkčně asociovaných s exekutivními funkcemi, může zapříčiňovat rozvoj symptomů HKP/ADHD. Pokud nastupuje v kritickém vývojovém stadiu CNS, může interferovat se zráním mozku a poškozovat vyvíjející se kortikální sítě [18]. Tuto hypotézu podporují i výsledky studií, které hodnotí lokalizaci EEG patologie u pacientů s HKP/ADHD. Silvestri et al [13] prokazují u pacientů s ADHD výskyt epileptiformní aktivity v EEG nejčetněji v centrotemporální oblasti (28,2 %), dále frontálně (12,5 %), zastoupena je i lokalizace fokusu v oblasti okcipitální (9,3 %) a generalizoavné výboje byly zastoupeny 2,3 %. Na Klinice dětské neurologie FN Brno bylo retrospektivně hodnoceno 135 pacientů ve věku 6–18 let s HKP a s výskytem či bez výskytu komorbidní epilepsie. U 60 z nich byla zachycena specifická epileptická aktivita v EEG. V této skupině byl nejčetnější výskyt generalizovaných výbojů u 18 pacientů (30 %), dále u 17 pacientů (28 %) frontálně, u osmi pacientů (13 %) centrotemporálně, u 16 pacientů (27 %) temporálně a u jednoho pacienta (2 %) okcipitálně [19]. Vysvětlení, proč lze u pacientů s HKP/ADHD nalézt fokální epileptiformní grafoelementy i v jiných oblastech než temporálních či okcipitálních, může být složitější. Lze předpokládat, že šíření epileptické aktivity ovlivňuje komplexnější neuronální okruhy a ty jsou schopny zahrnout i oblast frontálního laloku, event. lze přijmout i hypotézu, že určitá část komorbidních epilepsií s HKP/ADHD může být opravdu koincidencí.

Druhou otázkou zůstává, jaký je vztah manifestní epilepsie a HKP/ADHD symptomatiky. Dlouhou dobu byly kognitivní a behaviorální změny typické pro klinický obraz HKP/ADHD u pacientů s epilepsií připisovány především následkům opakovaných epileptických záchvatů, vlivu antiepileptické medikace či podstatě epilepsie jako onemocnění samotného [20,21]. Proti těmto tvrzením byl podán důkaz, že antiepileptika nejsou hlavní příčinou kognitivních a behaviorálních změn u pacientů s epilepsií [22] a že délka klinicky vyjádřené epilepsie či doba vzniku prvního záchvatu neovlivňuje obraz ADHD [23]. Symptomy ADHD předcházejí klinickou manifestaci epilepsie až u 82 % dětí [8]. Existují neurovývojové abnormality, jež předcházejí rozvoj záchvatů a mají vztah k vývoji ADHD a asociovaných komorbidit [8]. Cortez et al předložili důkaz, že nástup spontánních epileptických záchvatů je výsledkem komplexního procesu epileptogeneze, jež zahrnuje kaskádu transkripčních změn odstartovanou interakcí genetických faktorů a faktorů prostředí. Tyto transkripční změny zasahují do procesů plasticity, apoptózy a neurogeneze. Tyto všechny mohou ovlivnit kognitivní a behaviorální změny již před vlastním rozvojem klinických záchvatů [24].

Z výše uvedeného vyplývá, že klinická manifestace symptomů HKP/ADHD je častěji vázána s epileptickými syndromy asociovanými s frontálním lalokem. Jedná se především o epilepsii frontálního laloku (FLE) a benigní epilepsii s centrotemporálními hroty (BERS, BECTS). Další významnou skupinou jsou idiopatické generalizované epilepsie (IGE). Zde se předpokládá patofyziologický podíl abnormálních thalamo-kortikálních okruhů, které aktivují patologické oscilační rytmy a generují generalizované epileptiformní EEG výboje. Předpokládá se propojení thalamu s kortikálními oblastmi (thalamokortikální okruhy) právě v oblasti frontálního laloku [25].

V poslední době se objevuje celá řada studií, jež předpokládají patofyziologický podíl mozečku v rozvoji HKP/ADHD. U dětí s ADHD byl zjištěn signifikantně menší objem mozečkových hemisfér [26] a snížený objem vermis cerebella [27,28]. Podíl mozečku na patofyziologii ADHD je nesporný a ukazuje se, že mozeček je silně zapojen do kognitivních a afektivních procesů [29–31]. Jak ve skupině pacientů s ADHD, tak ve skupině pacientů s ADHD a epilepsií byla zjištěna nižší frakční anizotropie (FA) (pomocí difuzní MR) v oblasti pravého středního mozečkového pedunklu, tedy oblasti která je funkčně zapojena do kortiko-ponto-cerebelárního okruhu [32]. Tento deficit může vést k defektní transmisi signálu z prefrontálních oblastí do mozečku, vedoucí k symptomatice ADHD. Protože ve skupině ADHD i ADHD/epilepsie byla zjištěna nižší FA v identických oblastech mozečku, lze předpokládat, že podíl mozečku na patofyziologii ADHD je u obou skupin pacientů stejný. Výsledky této studie ukazují, že podíl mozečku na procesu epileptogeneze u pacientů s ADHD prokázán nebyl.

Epileptické syndromy asociované s HKP/ADHD

Epilepsie frontálního laloku (FLE)

Prefrontální oblasti hrají klíčovou úlohu v neuronálních okruzích zodpovědných za exekutivní funkce a chování. Epileptiformní výboje lokalizované v oblasti frontálního laloku mohou interferovat s vývojem těchto funkčních okruhů [33]. Ve studii 16 pacientů s epilepsií frontálního laloku ve věku 8–16 let byl prokázán kognitivní a behaviorální deficit kvalitativně srovnatelný s FLE u dospělých. Děti s FLE vykazovaly obtíže v otázkách motorické koordinace, plánování komplexních motorických úkolů, ve vizuo-prostorové organizaci, tenacitě pozornosti, inhibici odpovědi, plánování a schopnosti řešit úkoly [34]. Prevost et al [35] prokazují symptomy ADHD u 14 dětských pacientů s FLE v souboru 21 dětí. Významným faktem je, že celá řada pacientů s nonlezionální FLE může vykazovat poruchy v těchto oblastech a u těchto pacientů kontrola záchvatů nezaručí i zlepšení v oblasti symptomů ADHD [35].

Idiopatické generalizované epilepsie – dětské absence (CAE)

Dětské absence se řadí mezi benigní dětské epileptické syndromy, míra spontánní remise je vysoká. Z hlediska neurokognitivního a behaviorálního je CAE prognosticky závažnější. U dětí s absencemi jsou pozorovány potíže v pozornosti verbální i vizuální, zejména ve složce vytrvalosti [36–38]. Caplan et al [39] prokázali v souboru 69 dětí s CAE výskyt lehkého kognitivního deficitu v 25 %, poruch řeči v 43 % a 61 % pacientů splnilo diagnostická kritéria dle DSM-IV pro ADHD či úzkostnou poruchu. Symptomy těchto poruch byly v korelaci s délkou trvání a frekvencí absencí. Jen malá část pacientů s ADHD či úzkostnou poruchou měla adekvátní psychiatrickou terapii. Nejčastější subtyp ADHD u dětí s CAE je ADHD – subtyp s poruchou pozornosti [7,39]. Kognitivní a behaviorální změny jsou závažnější u pacientů s nástupem CAE před čtvrtým rokem věku [38].

Epilepsie s centrotemporálními hroty („rolandické epilepsie“)

Skupina epilepsií s centrotemporálními hroty je zvolena čistě topograficky, nevychází z aktuálně platné ILAE klasifikace epileptických syndromů. Zahrnuje

pacienty s epileptickými syndromy či pacienty s EEG patologií, pro něž je společná lokalizace EEG patologie v oblasti centrotemporální (rolandické). U těchto pacientů bývá často vyjádřen kognitivní deficit a behaviorální změny [40–45]. Výskyt centrotemporálních hrotů v EEG u pacientů s HKP/ADHD je popisován v 3,7–5,6 % případů [40]. Jejich epileptogenicita je nízká, 2–10 % nositelů této patologie vyvine klinické záchvaty [43]. Kromě pacientů s „náhodným nálezem" EEG patologie v centrotemporální oblasti, která se nemanifestuje klinicky epileptickými záchvaty, je nutno uvést i pacienty s epileptickými syndromy, pro které je lokalizace v rolandické oblasti typická až patognomická. Hroty v centrotemporální oblasti nacházíme u pacientů s benigní dětskou epilepsií s rolandickými hroty (BERS/ /BECTS), která je v ILAE klasifikaci řazena do skupiny fokálních, idiopatických věkově vázaných epilepsií. Další významnou skupinou jsou pacienti s atypickou benigní parciální epilepsií (Pseudo-Lennox syndromem), která dosud v ILAE klasifikaci své místo nemá. A v neposlední řadě je třeba uvést pacienty s Landau-Kleffner syndromem (dle ILAE klasifikace epileptických syndromů je řazen do skupiny epilepsií nezařazených – fokálních či generalizovaných), se syndromem fragilního chromozomu X a Rettovým syndromem, kde lze v EEG patologii lokalizovat do centrotemporální oblasti [43].

Benigní dětská epilepsie s rolandickými hroty (BERS/ /BECTS)

Benigní epilepsie s rolandickými hroty se řadí mezi nejčastější epileptické syndromy v dětském věku. Podle International Classification of Epilepsies and Epileptic Syndromes (Commission on Classification and terminology of the ILAE 1989) [46] je BERS řazena mezi věkově vázané epileptické syndromy manifestující se mezi 3–13 lety věku dítěte s normálním psychomotorickým vývojem. Považuje se díky dobré prognóze za benigní epilepsii, je dobře kontrolovatelná antiepileptickou medikací a spontánně remituje v adolescenci.

U pacientů s BERS je ADHD diagnostikováno signifikantně dříve než u pacientů bez centrotemporálních hrotů, vykazují více vyjádřenou hyperaktivně-impuzivní symptomatiku. Předpokládá se, že centrotemporální EEG patologie může nejasným mechanizmem snižovat práh citlivosti, způsobovat tak časnější nástup a těžší průběh ADHD. U pacientů s BERS je také zjištěn signifikantní deficit pozornosti. Důležité je, že míra poruchy pozornosti není závislá na frekvencí epileptiformních výbojů v bdělém stavu či četnosti záchvatů [42,44]. Naopak lateralizační aspekt může být významný a právě lokalizace centrotemporálních hrotů pravostranně či bilaterálně je častěji spojena s poruchou pozornosti [42]. Předpokládá se funkční dysbalance mezi hemisférami způsobená epileptiformními výboji. Lateralizační aspekty je však nutno brát obezřetně, poněvadž právě u pacientů s BERS je často pozorována alterace fokusu z jedné hemisféry na druhou.

Aktivace epileptiformní aktivity v EEG ve spánku a její možná sekundární generalizace u pacientů s BERS může významně ovlivňovat kognitivní deficit a vizuálně-percepční schopnosti. Je zodpovědná za signifikantně nižší celkový inteligenční skór dle WISC-III testu, slabší vizuomotorickou koordinaci, nonverbální krátkodobou paměť a udržení pozornosti [45]. Snížení frekvence epileptiformní aktivity ve spánku, ať již spontánně, či po nasazení antiepileptické medikace, může zlepšit neuropsychologický profil pacientů s BERS, a to dokonce do takové míry, že je poté srovnatelný s kontrolní skupinou [45].

Spánkové epileptické syndromy

Spánek může být významným aktivátorem epileptiformních grafoelementů v EEG. Právě aktivace specifické patologie u pacientů s BERS může být spoluzodpovědná za kognitivní deficit a behaviorální změny, jak bylo již uvedeno v předchozím odstavci. Frekventní epileptiformní výboje ve spánku, které lze zaznamenat např. u pacientů s CSWS (se syndromem s kontinuálními komplexy hrot-vlna v synchronním spánku) mohou narušovat neurální okruhy a zasahovat do procesů učení a kognitivních funkcí [46]. Další významnou skupinou jsou pacienti s noční epilepsií frontálního laloku (NFLE). Ta vychází z orbitofrontálních a mediálních oblastí frontálního laloku a je často asociována s ADHD [47].

Nelze opomenout ani fakt, že spánková EEG patologie a noční epileptické záchvaty snižují kvalitu spánku, oddalují nástup první REM fáze a vedou k defragmentaci spánku [48]. Tyto faktory bezesporu vedou k denní ospalosti, jež se může především u dětí manifestovat paradoxně hyperaktivitou a také poruchou pozornosti.

Závěr

U pacientů s epilepsií se nezřídka setkáváme se symptomy hyperkinetické poruchy/ADHD. Není dosud jednoznačně vysvětleno, jaké jsou společné patofyziologické mechanizmy. Současné znalosti a výsledky výzkumů nás vedou k pochopení prefronto-striato-thalamo-kortikálních okruhů jako možných příčinných mechanizmů a řada epileptických syndromů s frontálním lalokem spojených tuto hypotézu podporuje. Jaký je podíl epilepsie či EEG patologie na klinickém vyjádření a prognóze HKP/ADHD, je v současné době předmětem zájmu mnoha studií. Právě pochopení komplexnosti těchto patofyziologických spojitostí nám umožní správně diagnostikovat a vést terapii, která může být pro pacienta s HKP/ADHD a epilepsií zásadní a v nemalé míře se podílí na socioekonomických aspektech těchto komorbidních diagnóz.

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2.12 Annex 12

Danhofer P, Horák O, Aulická Š, Česká K, Pejčochová J, Fajkusová L, Ošlejšková H. **Genetické a neurobio logické aspekty komorbidního výskytu poruch autistického spektra a epilepsie.** Cesk Slov Neurol N 2019; 82(2): 148-54. doi: 10.14735/ amcsnn2019148.

Summary:

Autism spectrum disorder (ASD) is ranked among neurodevelopmental and neuropsychiatric disorders with clinical onset in childhood. In recent years, this disorder has come to the forefront of scientific interest, mainly due to increasing prevalence of up to 1/68 in 2014. The genetic causes of the disorder and the pathophysiological mechanisms that might be involved in the development of ASD are revealed. Comorbid occurrence with epilepsy is quite common, in up to 46% of cases. This article summarizes the current knowledge in this field with a focus on the hypothesis of excitatory-inhibitory imbalance. Some genetic causes of ASD and current diagnostic options are also discussed. The pathophysiology of the co-morbidity of ASD and epilepsy is discussed in terms of possible therapeutic interventions.

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Genetické a neurobiologické aspekty komorbidního výskytu poruch autistického spektra a epilepsie

Genetic and neurobiological aspects of comorbid occurence of autism spectrum disorder and epilepsy

Souhrn

Poruchy autistického spektra (PAS) se řadí mezi neurovývojové a neuropsychiatrické poruchy s klinickou manifestací v dětském věku. V posledních letech se tato porucha dostává do popředí vědeckého zájmu, a to především z důvodu narůstající prevalence až na 1/68 v roce 2014. Odhalují se genetické příčiny poruchy a patofyziologické mechanizmy, které by se na rozvoji PAS mohly podílet. Komorbidní výskyt s epilepsií je poměrně častý, a to až ve 46 % případů. Práce shrnuje dosavadní poznatky v této oblasti se zaměřením na hypotézu excitačně-inhibiční nerovnováhy. Jsou probrány i některé genetické příčiny PAS a současné možnosti diagnostiky. Patofyziologie komorbidního výskytu PAS a epilepsie je diskutována z pohledu možných terapeutických intervencí.

Abstract

Autism spectrum disorder (ASD) is ranked among neurodevelopmental and neuropsychiatric disorders with clinical onset in childhood. In recent years, this disorder has come to the forefront of scientific interest, mainly due to increasing prevalence of up to 1/68 in 2014. The genetic causes of the disorder and the pathophysiological mechanisms that might be involved in the development of ASD are revealed. Comorbid occurrence with epilepsy is quite common, in up to 46% of cases. This article summarizes the current knowledge in this field with a focus on the hypothesis of excitatory-inhibitory imbalance. Some genetic causes of ASD and current diagnostic options are also discussed. The pathophysiology of the co-morbidity of ASD and epilepsy is discussed in terms of possible therapeutic interventions.

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Key words

autism – epilepsy – autism spectrum disorder – genetics – ASD

Poruchy autistického spektra

Poruchy autistického spektra (PAS) se řadí mezi neurovývojové a neuropsychiatrické poruchy s klinickou manifestací v dětském věku charakterizované potížemi v sociální interakci a komunikaci, omezenými zájmy a repetitivními prvky v chování. Příznaky přetrvávají celoživotně a děti s PAS proto po 18. roce věku přecházejí do péče lékařů pro dospělép acienty.

Častěji se PAS vyskytují u mužů v poměru 4 : 1. Odhadovaná prevalence PAS v populaci se zvýšila z 1/476–1/323 v 90. letech 20. století [1,2] na 1/68 v roce 2014 [3]. Takový značný nárůst prevalence může být dán zčásti zvýšenou informovaností a povědomím populace o této poruše, zčásti i změnami v diagnostických postupech. Svůj podíl mohou

mít i faktory ze strany matky a faktory prostředí. Infekce plodu v prenatálním období může negativně zasáhnout do vývoje imunoregulačních mechanizmů [4], podstatný vliv je přikládán febriliím [5]. Dále jsou studovány např. zvýšená koncentrace toxických látek v ovzduší [6] a vliv těžkých kovů, kde výsledky jsou kontroverzní [7,8].

V oblasti klasifikace PAS byla během posledních let provedena celá řada změn. Autizmus lze dělit na vysokofunkční a nízkofunkční (na podkladě kognitivního profilu), autizmus s regresí nebo bez ní (s ohledem na vývojové aspekty), syndromický nebo nesyndromický aj. U nesyndromického autizmu je PAS primární diagnózou a není součástí komplexní poruchy, která je charakterizována vývojovými abnormitami a malformacemi. Naproti tomu u syndromického (atypického) autizmu je znám genetický syndrom, v rámci něhož část pacientů vykazuje PAS (např. Angelmanův syndrom, syndrom fragilního chromozomu X, Rettův syndrom).

Pro klinické účely vycházejí v ČR diagnostická kritéria PAS z mezinárodní klasifikace nemocí MKN-10. Zde se autizmus řadí mezi pervazivní neurovývojové poruchy (F84.0–F84.9). Praktičtější je, a to především z pohledu možnosti srovnání pacientů se soubory publikovanými ve světovém písemnictví, využití klasifikace DSM (diagnostický a statistický manuál). Tato klasifikace nemocí zařadila PAS do svého obsahu ve svém třetím vydání a od té doby prošla celou řadou změn. Kritéria PAS v DSM-III [9] vycházela z původních Kannerových případů [10] a byla poměrně přísná. DSM-IV [11] poté spektrum autizmu rozšířilo o případy méně závažně (pervazivní vývojové poruchy jinak nespecifikované [PDD-NOS] a Aspergerův syndrom). Poslední revize DSM-V z roku 2013 [12] kombinuje všechny podskupiny do jedné diagnózy poruch autistického spektra. PAS se již nedělí do jednotlivých subkategorií, ale diferencují se pouze varianty autizmu [12].

Současným zlatým standardem v diagnostice autizmu je podrobná psychologicko-psychiatrická anamnéza a testování alespoň dvěma škálami – celosvětově uznávaným nástrojem je The Autism Diagnostic Interview – Revised (ADI-R) a The Autism Diagnostic Observation Schedule (ADOS). Testování musí provádět specialista na PAS. ADI-R je velmi podrobná dotazníková škála založená na strukturovaném pohovoru s rodiči. ADOS je standardizovaný diagnostický test, který skóruje na základě přímé observace dítěte a zohledňuje i jeho vývojový stupeň a věk. Je doporučován jako vhodný standardizovaný diagnostický observační nástroj. Vyšetřující nabízí dítěti interaktivní aktivity, které jsou navrženy tak, aby bylo možno hodnotit sociální interakci a komunikaci i repetitivní prvky v chování, jež jsou podkladem diagnostiky PAS [13].

Na Klinice dětské neurologie LF MU a FN Brno byla v roce 2007 provedena retrospektivní studie 204 dětí s PAS s cílem zjistit, zda je diagnóza stanovena časně nebo dochází ke zpoždění v diagnostickém procesu. Závěrem této studie bylo, že diagnostika autizmu je často provedena pozdě, a tím je znemožněno zahájení časných edukačních, behaviorálních a léčebných intervencí [14]. Zvýšené povědomí o PAS, lepší informovanost široké veřejnosti a formování týmů specialistů, kteří se zabývají diagnostikou této poruchy, přináší v tomto ohledu slibné výsledky a v současné době lze konstatovat, že u většiny pacientů je diagnostika PAS dokončena před dosažením 5. roku věku [15].

Epilepsie u pacientů s PAS

Komorbidní výskyt autizmu a epilepsie byl znám již od doby, kdy byl autizmus poprvé popsán Leo Kannerem v roce 1943 [10]. Je všeobecně známo, že u pacientů s autizmem je výskyt epilepsie vyšší než v běžné populaci. Prevalence však kolísá v poměrně širokém rozmezí – 2 [16] až 46 % [17]. Na Klinice dětské neurologie LF MU a FN Brno bylo hodnoceno 205 dětí s PAS ve vztahu ke komorbidnímu výskytu epilepsie nebo epileptiformní aktivity v EEG. PAS byly spojeny s epileptickými záchvaty ve 40 % případů a s epileptiformní aktivitou v EEG bez manifestních záchvatů ve 20 % případů. Nejvyšší výskyt epilepsie byl ve skupině dětí s dětským autizmem (66 %) a atypickým autizmem (30,1 %). Nejnižší výskyt byl zjištěn u dětí s Aspergerovým syndromem (3,9 %) [18]. Výsledky studií jsou značně nekonzistentní [16,17]. Je to dáno především opakovanými změnami v klasifikačních schématech a různými diagnostickými postupy. Velký podíl nese i spektrum vyšetřovaných pacientů. Obecně lze říci, že soubory z terciárních center soustřeďující „komplikovanější" pacienty (tj. často farmakorezistentní s četnějšími komorbiditami) vykazují vyšší výskyt komorbidního výskytu PAS a epilepsie ve srovnání se soubory „běžných" pacientů s PAS dispenzarizovaných v sektorovém ambulantním provozu.

Faktory diskutované v souvislosti s výskytem epilepsie u pacientů s PAS

Deficit intelektu

Přítomnost intelektového deficitu u PAS (tj. IQ < 70) je běžně asociována se zvýšenou mírou výskytu komorbidní epilepsie. Metaanalýza z roku 2008, která studovala data z publikovaných studií z let 1963–2006, ukazuje prevalenci epilepsie u dětí s PAS mladších 12 let 21,4 % v případě přítomného intelektového deficitu ve srovnání s 8 % u dětí bez deficitu v intelektu [19]. Další metaanalýza – z roku 2012, která zahrnula jen studie, kde follow-up byl delší než 12 měsíců, ukázala prevalenci 23,7, resp. 1,8 % [20]. Silná asociace mezi intelektovým deficitem a epilepsií u dětí s PAS vysvětluje nižší výskyt epilepsie u pacientů s Aspergerovým syndromem, kde je intelekt normální.

Pohlaví

Existuje zvýšené riziko epilepsie u dívek s PAS ve srovnání s chlapci [21].

Etiologie onemocnění

Výskyt epilepsie u pacientů s nesyndromickým neboli idiopatickým autizmem je nižší než u pacientů se syndromickým (atypickým) autizmem. Například dle výsledků jedné studie 20 % u nesyndromické formy ve srovnání s 33 % u syndromických PAS [22]. I přesto je ale i u pacientů s idiopatickou formou PAS výskyt epilepsie vyšší než v běžné populaci. Syndromické formy PAS spojené s epilepsií jsou popsány např. u Rettova syndromu, Rett-like syndromů (mutace v genu pro methyl CpG binding protein 2 [MECP2], mutace v genu pro cyclin-dependent kinase-like 5 [CDKL5]), Angelmanova syndromu (mutace v genu pro ubiquitin-protein ligázu E3A [UBE3A]), tuberózní sklerózy (mutace v genu pro tuberous sclerosis complex [TSC] 1 a TSC2), neurofibromatózy typu I (mutace v genu pro neurofibromin 1 [NF1]), Dravetova syndromu (mutace v genu pro sodium voltage-gated channel alpha subunit 1 [SCN1A]), tedy syndromů, se kterými se v praxi setkáváme nejčastěji.

Vývojový regres

Vývojový regres je definován jako ztráta již dříve naučených dovedností. Odhaduje se, že zhruba 30 % pacientů s PAS prochází vývojovým regresem, který se typicky objevuje mezi 18. a 24. měsícem věku [23]. Výskyt epilepsie a/nebo epileptiformní patologie v EEG je považován za rizikový faktor pro přítomnost vývojového regresu [23,24].

Vliv epilepsie a/nebo epileptiformní aktivity v EEG na rozvoj PAS

Předpokládá se, že epileptiformní abnormita se může spolupodílet na rozvoji neuropsychologického deficitu u pacientů s PAS.

Studie 77 dětí s PAS prokázala, že epileptiformní výboje v EEG jsou signifikantně více spojeny s abnormálním vývojem v 1. roce života [24]. Například u Rettova syndromu, syndromu fragilního X, Angelmanova syndromu nebo Prader-Williho syndromu lze současně nalézt jak patologii v EEG, tak i příznaky PAS. Je však nutné brát v úvahu, že nejsme schopni přesně vystopovat, kdy se epileptiformní aktivita v EEG u daného pacienta objevila poprvé. Je ovšem možné, že epileptiformní výboje v EEG, které se objeví v kritickém období vývoje, jsou částečně odpovědné za rozvoj autistických symptomů [25] nebo se mohou asociovat s autistickým regresem u těchto dětí [24].

Epileptiformní výboje mohou mít negativní dopad na senzorické, paměťové a vyšší kognitivní funkce, a to především pokud se vyskytují ve spánku, který je považován za klíčový v procesech učení a paměti. Toto je patrno zvláště u pacientů s Landau-Kleffnerovým syndromem, kde se ve spánku setkáváme s kontinuálními výboji v EEG. Pacienti mají těžký kognitivní deficit a často i PAS [26]. Potlačení výbojů antiepileptickou medikací však nepřináší vždy jednoznačný a předvídatelný efekt [27].

Vidíme tedy, že epileptiformní výboje v EEG mají dopad na kognitivní funkce pacienta, ale potlačení výbojů nevede k předpokládanému zlepšení neuropsychologického profilu. V takovém případě je nutné zvažovat i jiné faktory, které se dostávají do hry, jak je probíráno dále v textu.

Zvířecí modely ukazují, že pokud je epilepsie provokována epileptickým statem (status epilepticus; SE), lze pozorovat rozvoj aseptického zánětu, objevují se poruchy buněčného metabolizmu a poruchy na úrovni iontových kanálů a receptorů. Rozvíjí se poruchy vedení vzruchu, tvoří se aberantní neuronální sítě. Nakonec může dojít až k apoptóze buněk. Zároveň jsou poškozeny neuronální okruhy citlivé na rozvoj dalších záchvatů a nejsou schopny udržet normální kognitivní funkce [28]. Pravda je, že samotný SE se často objevuje jako důsledek zánětu, infekce nebo traumatu. Pak je obtížné rozlišit, jaký je podíl samotného etiologického procesu a jak se v rozvoji kognitivního deficitu uplatňuje následný SE. Potlačení záchvatů však vede jen k minimálnímu zlepšení kognitivního profilu pacientů. Proto je možné, že samotná příčina epilepsie může vést přímo k poškození neuropsychologických funkcí autistických pacientů [25] více než další epileptický proces.

Etiopatogeneze komorbidního výskytu epilepsie a PAS

Genetické aspekty v patogenezi komorbidního výskytu epilepsie a PAS

Studie s dvojčaty ukazují, že dědičnost PAS je zhruba 85–92 % [29,30]. I v případě, že se nepodaří identifikovat mutaci odpovědnou za rozvoj PAS, je riziko pro další potomky vyšší [31]. V etiopatogenezi PAS se předpokládá role jak vzácných, tak běžných variant genů. S pokrokem na poli molekulárně-genetických technologií (jako jsou chromozomální microarray technologie nebo celoexomové sekvenování – whole exome sequencing) bylo identifikováno více než 800 chromozomálních lokusů a genů, které by mohly být asociovány s PAS, což poukazuje na vysoce heterogenní genetickou architektoniku této poruchy [3]. Geny a jejich příslušné proteiny se uplatňují v celé řadě biologických procesů, např. remodelaci chromatinu, regulaci genové transkripce, buněčném růstu a proliferaci a v neuronálně specifických procesech, jako jsou např. synaptická organizace a aktivita, dendritická morfologie a axonogeneze [3].

Přehlednou databází genů asociovaných s PAS je Simons Foundation Autism Research Initiative (SFARI) gene [32]. Databáze podává informace o hladině významnosti dané mutace na podkladě výsledků zvířecích a humánních studií. Všechny geny, pro které existuje hladina úrovně důkazu v diagnostice PAS, jsou skórovány v databázi: 1 – vysoce důvěryhodný a 2 – silný kandidátní gen. Je jich 51 (aktuální počet v roce 2018) a jsou uvedeny souhrnně v tab. 1.

Co se týká komorbidního výskytu PAS a epilepsie, riziko rozvoje epilepsie u dětí s PAS je 12,8 %, u jejich sourozenců 2,3 %, což je 2× vyšší riziko než v běžné populaci. Genetické pozadí se tedy týká nejen PAS, ale i epilepsie v rodinách s mnohočetným výskytem autizmu [33,34]. Vztah mezi PAS a epilepsií zůstává nejasný; může zde být kauzální vztah mezi těmito dvěma poruchami (především v případě epileptických encefalopatií či syndromického autizmu) nebo jsou obě výsledkem stejného neuropatofyziologického procesu. V každém případě se předpokládá, že na rozvoj PAS a epilepsie mají vliv nejen dědičné, ale i další faktory [25], jak bude detailněji probráno dále.

Imunitní faktory v patogenezi komorbidního výskytu epilepsie a PAS

Zánětlivé procesy v CNS hrají poměrně významnou roli ve společné patogenezi epilepsie a PAS. Jejich dopadem mohou být

Tab. 1. Přehled genů se skóre 1 a 2 z databáze genů asociovaných s autismem SFARI gene: „1" – vysoce důvěryhodný a „2" – silný kandidátní gen.

Gen	Chromozom	Název genu	Skóre
ADNP	20q13.13	activity-dependent neuroprotector homeobox	1
ANK2	4q25-q26	ankyrin 2, neuronal	1
ARID1B	6q25.3	adenin thymin rich interactive domain 1B (SWI1-like)	1
ASH1L	18q12.1	Ash1 (absent, small, or homeotic)-like (Drosophila)	1
ASXL3	18q12.1	additional sex combs like 3 (Drosophila)	1
CACNA1H	16p13.3	calcium channel, voltage-dependent, alpha 1H subunit	2
CACNA2D3	3p21.1-p14.3	calcium channel, voltage-dependent, alpha 2/delta subunit 3	2
CHD8	14q11.2	chromodomain helicase DNA binding protein 8	1
CNTN4	3p26.3-p26.2	contactin 4	2
CTNND2	5p15.2	catenin (cadherin-associated protein), delta 2	2
CUL3	2q36.2	cullin 3	1
DSCAM	21q22.2	Down syndrome cell adhesion molecule	1
DYRK1A	21q22.13	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	1
GABRB3	15q12	gamma-aminobutyric acid (GABA) A receptor, beta 3	2
GIGYF2	2q37.1	growth factor receptor-bound protein 10 (GRB10) interacting glycine-tyrosine-phenylalanine domain protein 2	2

Tab. 1 – pokračování. Přehled genů se skóre 1 a 2 z databáze genů asociovaných s autismem SFARI gene: „1" – vysoce důvěryhodný a „2" – silný kandidátní gen.

Gen	Chromozom	Název genu	Skóre
GRIN2B	12p13.1	glutamate receptor, inotropic, N-methyl D-apartate 2B	1
GRIP1	12q14.3	glutamate receptor interacting protein 1	2
ILF2	1q21.3	interleukin enhancer binding factor 2Â	2
INTS6	13q14.3	integrator complex subunit 6	2
IRF2BPL	14q24.3	interferon regulatory factor 2 binding protein-likeÂ	2
KAT2B	3p24.3	lysine (K) acetyltransferase 2BÂ	2
KATNAL2	18q21.1	katanin p60 subunit A-like 2	1
KDM5B	1q32.1	lysine (K)-specific demethylase 5B	2
KMT2C	7q36.1	lysine (K)-specific methyltransferase 2CÂ	2
KMT5B	11q13.2	lysine methyltransferase 5B	1
MED13L	12q24.21	mediator complex subunit 13-like	2
MET	7q31.2	met proto-oncogene (hepatocyte growth factor receptor)	2
MSNP1AS	5p14.1	moesin pseudogene 1, antisense	2
MYT1L	2p25.3	myelin transcription factor 1-like	1
NAA15	4q31.1	N(alpha)-acetyltransferase 15, NatA auxiliary subunit	1
NCKAP1	2q32.1	non-catalytic region of tyrosine kinase adaptor-associated protein 1	1
NLGN3	Xq13.1	neuroligin 3	2
NRXN1	2p16.3	neurexin 1	2
POGZ	1q21.3	pogo transposable element with zinc finger domain	1
PTEN	10q23.31	phosphatase and tensin homolog (mutated in multiple advanced cancers 1)	1
RANBP17	5q35.1	ras-related nuclear binding protein 17	2
RELN	7q22.1	reelin	1
RIMS1	6q13	regulating synaptic membrane exocytosis 1	2
SCN2A	2q24.3	sodium channel, voltage-gated, type II, alpha subunit	1
SCN9A	2q24.3	sodium voltage-gated channel alpha subunit 9	2
SETD5	3p25.3	Su(var)3-9, enhancer-of-zeste and trithorax (SET) domain containing 5	1
SHANK2	11q13.3-q13.4	Src homology 3 and multiple ankyrin repeat domains 2	2
SHANK3	22q13.33	Src homology 3 and multiple ankyrin repeat domains 3	1
SLC6A1	3p25.3	solute carrier family 6 (neurotransmitter transporter), member 1	2
SPAST	2p22.3	spastin	2
SYNGAP1	6p21.32	synaptic Ras guanosin tri phosphate (GTP)ase activating protein 1	1
TBR1	2q24.2	T-box, brain, 1	1
TNRC6B	22q13.1	trinucleotide repeat containing 6B	2
TRIP12	2q36.3	thyroid hormone receptor interactor 12	1
USP7	16p13.2	ubiquitin specific peptidase 7 (herpes virus-associated)	2
WDFY3	4q21.23	tryptophan-aspartic acid repeat and FYVE domain containing 3	2

FYVE – Fab 1 (yeast orthologue of PIKfyve), YOTB, Vac 1 (vesicle transport protein), and EEA1
SFARI – Simons Foundation Autism Research Initiative

změny indukované mediátory zánětu v excitačních neuronálních sítích.

U komorbidního výskytu PAS a epilepsie nacházíme zvýšení HMBG-1 (high mobility group box protein 1), klíčové zánětlivé molekuly, která aktivuje signální cestu přes interleukin (IL)-1 a IL-1ß. U pacientů s PAS toto zvýšení koreluje s postižením v sociální interakci [35]. Stejně tak zvýšení exprese HMBG-1 bylo detekováno v hipokampu pacientů s epilepsií temporálního laloku (TLE) [36] a dětí s febrilními křečemi [37]. Poznatky opět ukazují na aktivaci IL-1 signální kaskády vedoucí k zánětlivé reakci se zvýšenou excitabilitou v neuronálních sítích. Ukazuje se, že antagonisté HMBG-1 jsou v preklinických studiích účinné v kontrole záchvatů [36].

U pacientů s PAS bylo detekováno zvýšení Th1 prozánětlivých cytokinů (např. IL-6, tumor necrosis factor α [TNF-α] a interferon γ [IFN-γ]), hladina protizánětlivých Th2 cytokinů (např. IL-4, IL-5, IL-10) zůstává nezměněna. U pacientů tím dochází ke zvýšení poměru Th1/Th2 (T-helper lymphocytes 1/T-helper lymphocytes 2). Periferní lymfocyty u pacientů s PAS vykazují 2× vyšší hladiny prozánětlivých cytokinů ve srovnání s kontrolami. Pokud byl TNF-α vyšetřen u všech nepostižených sourozenců pacientů s PAS, byla zjištěna opět signifikantně vyšší hladina této molekuly, což svědčí pro určitý podíl genetiky v nastavení zánětlivých signálních kaskád [38]. Stejně tak byla zjištěna elevace prozánětlivých cytokinů (TNF-α, IL-1β a IL-6) u pacientů s TLE. Tyto cytokiny mají *in vivo* i *in vitro* prokázaný prokonvulzivní efekt [39].

Dalšími společnými patofyziologickými vodítky mezi PAS a epilepsií mohou být porucha integrity hematoencefalické bariéry (HEB), mikrogliální aktivace a zánět indukovaný stresem. Mastocyty lokalizované v hypotalamu mohou být aktivovány stresem, jak bylo pozorováno u pacientů s PAS, a mohou vést k poruše HEB. Aktivace mastocytů vede ke spuštění prozánětlivých kaskád (např. exprese IL-6, vaskulárního endoteliálního růstového faktoru – vascular endothelial growth factor [VEGF]), které mají dopad na úrovni tight junctions HEB, což způsobuje poruchu její integrity [40]. Porucha integrity HEB byla zjištěna i na modelech chronické epilepsie, kde je opět důsledkem aktivace prozánětlivých signálních kaskád [41].

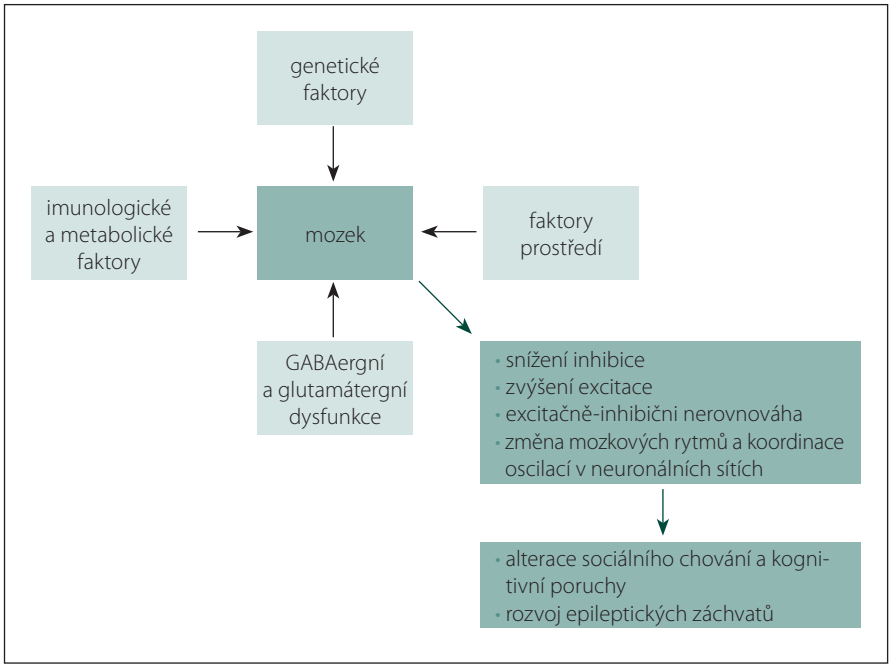
Společným důsledkem aktivace zánětlivého procesu u pacientů s PAS a epilepsií je zvýšení excitability mozku a progrese klinického vyjádření obou syndromů. Následkem

zvýšení excitability v mozkových neuronálních okruzích nastane porucha excitačně-inhibiční (E/I) rovnováhy, která představuje velmi křehké ekvilibrium mezi excitačními a inhibičními vlivy mozku. Dochází pak k nekontrolovatelným neuronálním výbojům a rozvoji záchvatů, jak bude blíže vysvětleno v další kapitole [25]. U pacientů s PAS a epilepsií byla v post mortem studiích zjištěna astroglióza, odpovědná za poruchu zpětného vychytávání glutamátu, což vede ke zvýšení jeho extracelulárních hladin a zvýšení excitability. Aktivace mikroglie (opět pozorována u obou procesů) zvýšení glutamátu ještě podporuje. Stejný efekt má aktivace IL-6, která stimuluje tvorbu excitačních synapsí [42].

Hypotéza společného patofyziologického mechanizmu komorbidní epilepsie a PAS

Shrnutím výše uvedených pozorování a výsledků lze předpokládat, že autizmus a epilepsie mohou mít alespoň v některých případech společný neurobiologický podklad. Jak bylo uvedeno v úvodu, existují syndromy, pro které je společný výskyt těchto dvou diagnóz typický. Právě v těchto případech je patrné a všeobecně přijímané, že jak PAS, tak epilepsie mohou mít společnou genetickou příčinu, která postihuje synaptické funkce a vývoj mozku. Jedna z nejrozšířenějších hypotéz, která popisuje komorbidní výskyt PAS a epilepsie, předpokládá, že neurovývojový defekt různého původu (např. genetického, metabolického, imunitního nebo působením faktorů vnějšího prostředí) vede ke změně struktury excitačních a inhibičních okruhů, což má za následek rozvoj perzistující E/I nerovnováhy [42]. Tento vztah ilustruje obr. 1 [43].

Podkladem hypotézy E/I rovnováhy je předpoklad, že normální mozkové funkce závisí na dokonalé rovnováze mezi excitačními a inhibičními vstupy do klíčových mozkových buněk. Pokud je přítomna nadměrná excitace nebo nedostatečná inhibice, dojde k hyperexcitabilitě neuronální sítě a rozvoji záchvatů. U celé řady epileptických syndromů může být za rozvoj záchvatů odpovědná nedostatečná inhibice, např. alterace receptorů pro gama aminomáselnou kyselinu (GABA) nebo funkce interneuronů. Může také dojít k nadměrné excitaci např. na úrovni excitačních receptorů nebo excitačních neuronálních okruhů. V souladu s teorií E/I rovnováhy je i princip terapie antiepileptiky, který známe z běžné neurologické praxe: použití



Obr. 1. Schematické znázornění patofyziologického modelu komorbidního výskytu poruch autistického spektra a epilepsie – hypotéza excitačně-inhibični nerovnováhy. Převzato a modifikováno z [43].

GABA – gama aminomáselná kyselina

Fig. 1. Schematic representation of the pathophysiological model of the comorbid occurence of autism spectrum disorder and epilepsy – hypothesis of excitatory-inhibitory dysbalance. Taken and modified from [43].

GABA – gamma-aminobutyric acid

GABAergních agonistů ke zvýšení inhibice nebo snižování excitačních vlivů blokátory sodíkových nebo vápníkových kanálů.

V oblasti rozvoje PAS je hypotéza excitačně-inhibiční rovnováhy přijímána již více než 10 let. Pokud E/I nerovnováha vede k rozvoji záchvatů, pak samotná přítomnost záchvatů může indikovat rozvoj E/I nerovnováhy i u pacientů s PAS [25]. Ztráta inhibice cestou alterace GABAergní transmise, dysfunkce interneuronů nebo abnormální migrace byla dokumentována i u pacientů s PAS. Bylo zjištěno snížení hladin GABA v kortikálních oblastech mozku u těchto pacientů [44] a snížení $GABA_A$ receptorů v oblasti frontálního kortexu [45]. Post mortem studie ukazují redukci parvalbuminových interneuronů v mediálním prefrontálním kortexu [46]. E/I nerovnováha může být vysvětlením v patogenezi i u celé řady genetických syndromů, které spojují epilepsii a PAS – mutace v genu pro SCN1A, mutace v genu pro podjednotku epsilon-1 glutamátového receptoru (GRIN2A) nebo mutace v genu pro phosphatase and tensin homolog (PTEN) [25].

Logickým důsledkem této hypotézy je úvaha, že antiepileptika by mohla zlepšit kognitivně-behaviorální komorbidity u autistických pacientů. Zvířecí modely nabízí velmi slibné výsledky, např. u SCN1A +/- myší bylo prokázáno zlepšení sociálních a paměťových funkcí po léčbě klonazepamem [47]. Bohužel antiepileptika v případě podání pacientům s autizmem tento efekt nevykazují [48,49]. Naše zkušenosti ukazují, že podání klonazepamu pacientům se syndromem Dravetové nevede ke zlepšení kognitivních a behaviorálních funkcí (vlastní nepublikované pozorování).

Z předchozího vyplývá, že problematika autistických projevů u pacientů s epilepsií nebude jen důsledkem samotné epilepsie nebo E/I nerovnováhy. Do hry vstupují další faktory. E/I rovnováhu nelze chápat jako statické ekvilibrium. Dokonce i v klidovém stavu jsou mozkové struktury aktivní a informace v mozku jsou zpracovávány prostřednictvím specifických rytmů. Právě tyto mozkové rytmy jsou schopny koordinovat neuronální výboje, a tak je umožněn přenos informací. Základní roli v uvedených procesech hraje GABAergní inervace. GABAergní inhibice vytváří rytmickou aktivitu oscilací a „rytmické ticho" neuronů během oscilací způsobuje okno, ve kte-

rém jsou informace rozmělňovány na „sousta", která mohou být účinně přenášena a interpretována [50]. Díky alterované GABAergní transmisi u pacientů s PAS jsou pozměněny mozkové rytmy a koordinace oscilací [25]. Objevuje se celá řada důkazů, že u těchto pacientů jsou redukovány γ a α rytmy a fázová synchronizace po zrakovém nebo sluchovém stimulu. Maturační profil oscilací a synchronizací neuronálních sítí během klidového stavu je u dětí a adolescentů s PAS abnormální [51]. E/I nerovnováha tedy vede ke změně mozkových rytmů a špatné koordinaci v oblasti neuronálních sítí. Funkční konektivita je poškozena a to může mít za následek rozvoj senzorických, percepčních a sociálních potíží u pacientů s PAS [52] (obr. 1).

Terapeutické perspektivy

Pochopení patofyziologického substrátu komorbidního výskytu PAS a epilepsie je stěžejní z pohledu možných terapeutických intervencí. Hypotéza porušené E/I rovnováhy nabízí hned několik cílových molekul v léčebných možnostech těchto onemocnění.

GABA agonisté

Pokusy na SCN1A myších modelech ukázaly zlepšení chování po léčbě klonazepamem [47]. Chybí však konzistentní data na dalších zvířecích modelech a je nutno také brát v potaz možnou paradoxní reakci léků ovlivňujících $GABA_A$ receptory u pacientů s PAS díky perzistující excitační GABA aktivitě. Ostatně příkladem může být zvýšení úzkosti u některých pacientů s PAS po léčbě diazepamem [53]. Naproti tomu $GABA_B$ agonista R-baklofen (arbaclofen, STX209) byl účinný v léčbě zvířecích modelů s PAS [54]. Dokonce jsou již výsledky klinických studií na pacientech s fragilním syndromem X. Ukazuje se, že STX209 může zlepšit symptomatiku u pacientů s PAS [55]. Co se týká ostatní GABAergních látek v klinické praxi, jako např. riluzol, tiagabin, vigabatrin, zlepšení symptomatiky PAS je rozporuplné a nepřesvědčivé [56].

Neurosteroidy

Řadí se mezi pozitivní modulátory $GABA_A$ receptorů. Příkladem je syntetický derivát progesteronového metabolitu allopregnanolonu, ganaxolon. Ukázal se efektivní v redukci záchvatů na myších modelech epileptických spazmů [57] a chování u myší s PAS [58]. Výzkum ganaxolonu se nachází ve fázi II u pacientů s refrakterní epilepsií a u pacientů s PAS a syndromem fragilního X.

Antagonisté glutamátového receptoru

Předpokládá se jejich efekt na snížení hyperexcitability u pacientů s PAS a komorbidní epilepsií a byla provedena celá řada studií u pacientů s PAS a syndromem fragilního X. Výsledky jsou opět nekonzistentní a rozporuplné. Antagonista N-metyl-D-aspartát receptoru memantin ukázal pozitivní efekt na myších modelech [59] a dokonce i v klinické studii u pacientů s autizmem [60].

Mammalian Target of Rapamycin (mTOR) inhibitory

Zapojení mTOR inhibitorů je klíčové v regulaci řady buněčných procesů – růstu, proliferaci a translaci proteinů. Komponenty mTOR signální cesty v mozku jsou lokalizovány na synapsích, kde kontrolují synaptogenezi. mTOR inhibitor rapamycin je schopen zlepšit neurobehaviorální deficit u myší s PAS [61]. Probíhají klinické studie s mTOR inhibitory u pacientů s tuberózní sklerózou a refrakterní epilepsií, kde měly pozitivní vliv na redukci záchvatů, jak ukazuji výsledky III. fáze klinické studie [62].

Závěr

Komorbidní výskyt PAS a epilepsie není zřejmě pouhou koincidencí, ale jedná se o velmi komplexní a vícesubstrátový proces. Porozumění patofyziologickému substrátu tohoto komorbidního výskytu je stěžejní nejen pro pochopení procesů probíhajících v mozku u pacientů, ale může být zásadní i z pohledu možných terapeutických intervencí. Hypotéza porušené E/I rovnováhy nabízí hned několik cílových molekul v léčebných možnostech těchto onemocnění (GABA agonisté, neurosteroidy, antagonisté glutamátových receptorů, mTOR inhibitory a další). Výsledky na zvířecích modelech jsou slibné. Jejich aplikace na člověka ale musí projít ještě složitou cestou, která je vzhledem k závažnosti těchto diagnóz a limitovaným terapeutickým možnostem velkou výzvou v celosvětovém vědeckém měřítku.

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