EPILEPSY

Zdeněk Kundrata

EPILEPSY

- Chronic, neurological disease – affects 1% of the adult population
- Recurrence of unprovoked epileptic seizures, with epileptic seizures meaning paroxysmal disorder of behaviour, emotion, motor, sensory or autonomic functions underpinned by abnormal (excessive and hypersynchronous) activity of neurons of the cerebral cortex

Definition

- **Incidence** in developed countries between 24-53 / 100,000 individuals per year
- The **prevalence of active epilepsy** (proportional number of epilepsy patients who have had at least one epileptic seizure in the past five years) is 0.5-1% in the population (Shorvon, 2000)
- There are around 70,000 patients with active epilepsy in the Czech Republic
- A significant health and social problem in every society (Wrangled, Hacker and Marusic, 2004)

Etiopatogenesis

- Idiopathic epilepsy - GM susceptibility to seizures (at different ages, variously expressed)
- Symptomatic epilepsy - bleeding, ICMP stroke, tumor,....
- Cryptogenic epilepsy - predicted lesion cannot be detected by current dg. methods

Pathogenesis

- Sudden and transient dysfunction of nerve cells uncontrollable activity and increased electrical activity (usually at least partially isolated and with the reduction of axosomatic inhibitory synapses by GABA mediators and glycine by promoting paroxymal discharges into stem structures, ARAS, occurs to project impulses into both brain hemispheres
- Clinical manifestations reflect the area of the brain where the discharge started - epileptic fossil

Pathogenesis

Focus - a variously large population of neurons with pathological electrical activity In neurons and their membranes, respectively, action depolarization (paroxysmal depolarization shift) occurs, causing hyperexcitability and abnormal discharge in the bearing

Further manifestations of hyperautorytmicity and hypersynchrony

epileptic seizure

- Basic clinical manifestation of epilepsy
- International epilepsy league classification 2017

- Type of seizure
- Type of epilepsy
- Type of epileptic syndrome (determined by a set of features including seizure type, EEG and imaging findings) Fisher et al., 2014

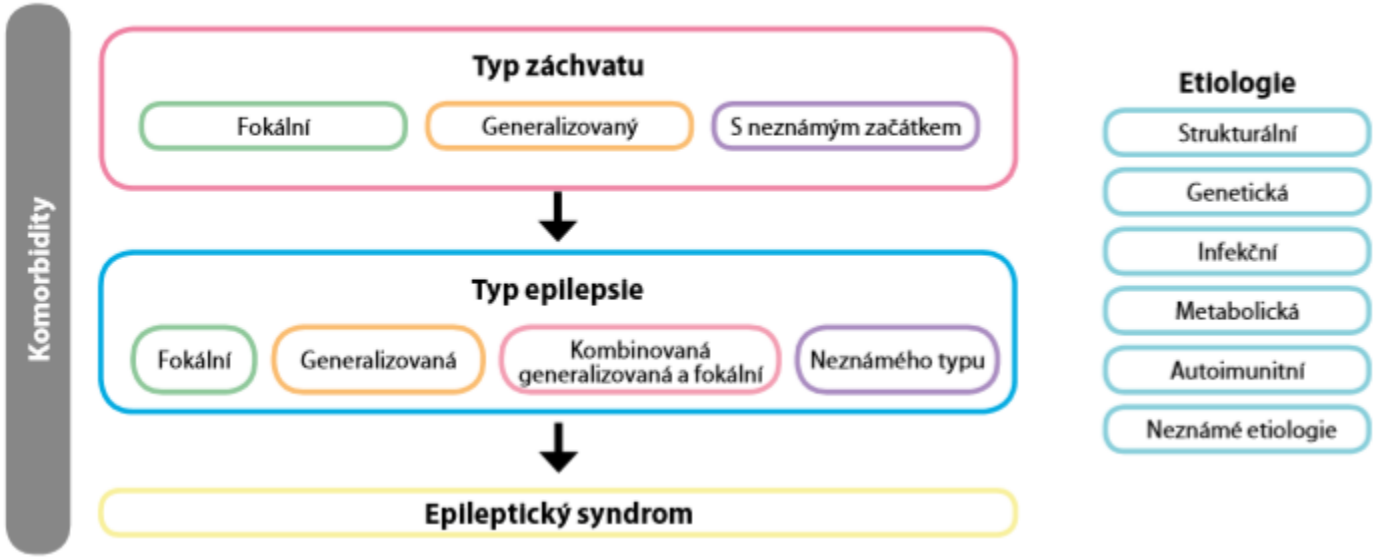
Neurol.praxi2018, 19(I):32-36

classification of epilepsy and epileptic seizures, ILAE 2017

with an unknown start

seizure type

type of epilepsy



Etiology
Structural
Genetic
Infectious
Metabolic
Autoimmune
Of unknow etiology

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focal without consciousness disorder
focal with consciousness disorder

motor
without motor manifestations

Schéma 1. *Klasifikace epileptických záchvatů ILAE 2017. Česka verze dle Fisher et al., Epilepsia 2017. Vypracoval Výbor České ligy proti epilepsii, odborné společnosti ČLS JEP*

Fokální

Bez poruchy vědomí / **S poruchou vědomí**

Motorické
- automatismy
- atonické
- klonické
- epileptické spasmy
- hyperkinetické
- myoklonické
- tonické

Bez motorických projevů
- autonomní
- záraz v chování
- kognitivní
- emoční
- senzorický

Fokální přecházející do bilaterálního tonicko-klonického (FBTCS)

Generalizované

Motorické
- tonicko-klonické (GTCS)
- klonické
- tonické
- myoklonické
- myoklonicko-tonicko-klonické
- myoklonické-atonické
- atonické
- epileptické spasmy

Bez motorických projevů (absence)
- typické
- atypické
- myoklonické
- s myokloniemi víček

S neznámým začátkem

Motorické
- tonicko-klonické
- epileptické spasmy

Bez motorických projevů
- záraz v chování

Neklasifikované

focal to bilateral tonic-clonic

ILAE 2017 Classification of Seizure Types Expanded Version[1]

Focal Onset

Aware | Impaired Awareness

Motor Onset
- automatisms
- atonic[2]
- clonic
- epileptic spasms[2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms[2]

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified[3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.

2 These could be focal or generalized, with or without alteration of awareness

3 Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

- **Generalized seizures affect both hemispheres simultaneously** - sudden fall of consciousness with fall, tonic contraction of limb muscles, masticatory muscles and chest muscles - forsied expiratory - moaning to shout → seconds → clonic phase - rhythmic twitching of limbs (frequency decreases, amplitude increases) → atony postmaxis disorientation

Focal with consciousness disorder
Focal without consciousness disorder
Focal to bilateral tonic-clonic

Seizure types

Motor - dominated by motor manifestations
Atonic - sudden decrease in muscle tone (head, jaw, fall to the ground)
Automatismy
Clonic (frequency decreases, amplitude increases)
Epileptic **spasms** - muscle contractions of different duration, predominantly axial muscles
Hyperkinetic - often bizarre, fast
Myoclonic - sudden, short muscle twitches, bilateral and unilateral, rhythmically not repeated
Tonic - longer-lasting contractions
Without motor manifestations
Autonomous - tachycardia, ictal discoloration, tachypnoe, redness
Behavioral accent
Cognitive
Sensory - illusion, paraesthesia, pain, pseudohalucination

Seizure types

- **Generalized without motor manifestations - ABSENCE**
  childhood and adolescence
  facial stiffness, gaze, lasting seconds
  different depth of consciousness disorder (transient cognitive disorders)
- **Not classifiable** - the available data is not enough to distinguish whether it was a focal or generalized attack
- **With an unknown beginning**

Seizures

- **Unprovoked**, emerging within epilepsy (Annegers et al., 1995; Beghi et al., 2010; Hesdorffer et al., 2009)
- **Provoked or acute symptomatic** (provoked s.), occurrence in close temporal association with the ongoing CNS involvement of structural, toxic, metabolic, inflammatory nature
  acute symptomatic seizures ≈≈≈ provoked seizures
- Seizures induced by sleep deprivation - seizures unprovoked, it has not been proven yet that sleep deprivation could be a self-inducing factor in the onset of provoked s. (Beghi et al., 2010)
- Provoked s. is time related to insult formation (1-2 weeks)

Frontal lobe epilepsy, symptoms

- Clonic, myoclonic, Jackson marsh (spreading manifestations in head-hand-leg direction), postictal paresis of part of the body
- Expression in speech, vocalization
- Hyperkinetic / hypermotoric
- Seeing, falling, accented thinking
- Olfactory hallucinations, autonomous manifestations, incontinence
- Head pressure, version, tonic seizures

parietal lobe epilepsy, symptoms

- Sensitive sensations, Jackson marsh
- Apraxia
- Akalkulia
- Postictal numbness
- Alexia
- Dysmorphopsies
- Autoscopy

occipital lobe epilepsy, main symptoms

- Visual hallucinations
- Feeling eye movement
- Visual disturbances
- Nystagmus
- Opsoclonus
- Winking flutter eyelids

insula

- Throat tightening, epigastric pressure, chewing, licking, salivation, swallowing, changes in BP, HR
- Paresthesia, pain, taste unpleasant sensation, feeling of warmth on the nose and upper limbs

diagnostics

- **Neurological examinations**, including detailed medical history with focus on possible causes of acute symptomatic seizures and non-epileptic seizures
- **Internal study, pediatric (optimally including ECG)**
- **Basic laboratory exam.** (glycemia, ionotype, CRP, urea, creatinine, ALT, AST, GMT, blood count)
- **EEG** examination (optimally within 24 hours after the attack), activation methods, SD
- **V-EEG, video-EEG monitoring**
- **Imaging** of the brain in adults always - in non-acute situations we prefer MR over CT, in children according to the decision of a pediatric neurologist

diagnostics

- MR scan of the brain
  basic protocol MR examination in patients with epilepsy T1w, axial FLAIR, T2w mm3 mm, coronary FLAIR and T2w, DWI on hemosiderin
  Administration of a contrast agent (gadolinium)
- Functional imaging (SPECT, PET, functional MR and MR spectroscopy) is performed in patients included in the epilepsy surgery program
- **Ultrasound examination of blood vessels** and cerebral vessels, event. CT- or MR-Ag
- **Clinical-psychological examination**
- **Psychiatric examination**
- Internal and cardiological as needed (eventually ECG Holter, ECHOkg, orthostatic tests, head-up tilt table test)
- Where appropriate, metabolic, endocrinological examination

differential diagnosis of epileptic seizure

- Sometimes very difficult
- Relatively frequent co-occurrence of non-epileptic and epileptic seizures in the same patient
- The incidence of non-epileptic seizures is particularly high in the population of patients treated as pharmacoresistant epilepsy
- If there is no certainty in the origin of the seizures, consultation at a specialized workplace with the possibility of video-EEG monitoring is indicated

Somatically conditioned non-epileptic seizures

- Syncopes of various etiology (especially convulsive and cardiogenic)
- Sleep Disorders (Parasomnia)
- Paroxysmal dystonia and paroxysmal kinesigenic chorea
- Physiological myoclonus in relation to sleep, other non-epileptic myoclonies
- Tetanie
- Migraines (especially if headaches are minimal or absent)
- Benign paroxysmal vertigo
- Transient ischemic attacks of TIA
- Transient global amnesia TGA
- Paroxysmal endocrine imbalance (pheochromocytoma)
- and more…..

PNES, psychogenically related non-epileptic seizures

- Dissociative seizures
- Panic attacks
- Consciously induced (simulated) seizures
- Personality and behavior disorders
- Münchhausen's syndrome (the person pretending to be a physical or mental disorder for which he / she is subsequently treated)
- Münchhausen's syndrome would be proxy "on behalf of" (the person pretending to be a dependent person, usually a child) the affected person does not have the motivation to pretend the disease, the pretense is sick

ETIOLOGY

- Structural etiology acquired (stroke, trauma, infection), genetic disorder of structure (developmental malformation of cerebral cortex)
- Genetic etiology, epilepsy is a direct consequence of a known or suspected genetic mutation in which seizures are a basic manifestation: "Benign familial neonatal epilepsy" syndrome has most family members of the KCNQ2 and KCNQ3 potassium ion channel genes, ADNFLE syndrome frontal seizures) a particular mutation currently known to only a small proportion of individuals does not mean that it is an "inherited" epilepsy
- Idiopathic generalized epilepsy of infant absence, juvenile absence, juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures only
- Infectious etiology of epilepsy X attacks of acute symptomatic (provoked) in a situation of acute neuroinfection (HSV, TB, HIV, cerebral malaria, subacute sclerosing panencephalitis, brain toxoplasmosis and congenital infections such as Zika and cytomegalovirus)
- Metabolic etiology means that epilepsy is a direct consequence of a known or suspected metabolic disease in which seizures are one of the main symptoms (porphyria, uraemia, amino acid metabolism disorders or pyridoxine-dependent seizures)
- Autoimmune etiology is classified in cases where epilepsy is a direct consequence of immune-mediated CNS inflammation (encephalitis with NMDA receptor antibodies or anti-LGI1 limbic encephalitis)
- Epilepsy of unknown etiology (the cause of epilepsy is not yet known, of course depends on the availability and extent of examinations)

treatment of epileptic seizure

- 1. occurrence of epileptic s.≈ in up to 50% manifestation of acute brain damage
- Diazepam i.v. 10mg
- Alternative without i.v. entry, midazolam i.m. 10mg, orally, per rectum
- Repeat after 5 minutes
- CAVE: HYPOVENTILATION, HYPOTENSIS
- When i.v. administration must be available symptomatic therapy !! (artificial lung ventilation, volumotherapy) KIND flumazenil !!!!

therapy, supportive measures

- **Removing objects that may cause injury**, underlay head, loosen clothing around the neck
- **Do not prevent twitches or tonic spasm, do not prevent automatism** unless there is a risk of injury or damage to things, do not open your mouth by force, and wait until the end of the seizure
- In case **of persistent impairment of consciousness stabilized position**, to open the mouth, to clean the oral cavity, to advance the lower jaw, to wait for the return to full consciousness
- **In postparoxysmal disorientation verbally calm the patient, not physically restrict** the patient in motion unless it is absolutely necessary
- **Wounded**? (especially the head, tongue or vertebrae)
- Find out the medical history of the treated patient and there is no injury requiring treatment, no disorientation persists, no transport to hospital required
- Indications for hospital transport: first seizure, seizure cumulation (except for typical cumulations that the patient or family routinely manage), status epilepticus (see below), disorientation persists, injury requiring treatment

therapy, principles of rational therapy

- “Heal blind” error, start treatment with confidence diagnosis
- Epileptic etiopathogenesis of seizures → proceed to the so-called therapeutic test with the use of a broad-spectrum antiepileptic drug in appropriate doses
- Initial treatment should be started with monotherapy of the first choice „start low and go slow“, in the absence of effect we increase up to the so-called maximum tolerated dose (MTD) - a dose that does not cause unacceptable side effects for the patient
- …initial monotherapy leads to complete disappearance of seizures in almost half of patients…
- Upon failure of the first drug, its replacement for another antiepileptic drug in monotherapy leads to remission (achieving seizure) in another approximately 13 percent of the subjects treated (Kwan and Brodie, 2000) (alternatively, use another 1st or 2nd drug)
  If seizures persist, initiate combination pharmacotherapy by adding a new anti-epileptic drug to an existing add-on drug
- If seizures persist, initiate combination pharmacotherapy by adding a new anti-epileptic drug to an existing add-on drug
- A combination of a maximum of 3 AEDs, potentiating the effect, without adverse pharmacokinetic interactions, is considered rational
- Early detection of pharmacoresistance and assessment of the suitability of surgical treatment (pharmacoresistance - satisfactory seizure control is not achieved within two years from the start of treatment using at least two and preferably three correctly selected antiepileptic drugs administered in MTD!

antiepileptics (AED), "symptomatic therapy"

- Classic ("old") - proven, cheap (carbamazepine, valproate)
- New, since 1989 - created on the basis of theoretical and experimental models, common part of clinical practice, first-line drugs (lamotrigine, levetiracetam)
- Latest generation of antiepileptic drugs - indication for adjunctive therapy of partial seizures with or without secondary generalization (eslicarbamazepine, lacosamide, perampanel)

antiepileptics

- CBZ: Na channel inhibition
- VAL: increases the activity of the main inhibitory neurotransmitter, γ-aminobutyric acid (GABA)
- LTG: blockade of Na +, Ca ++ channels, decreased excitatory amino acid activity, positive psychotropic effect - mood stabilizer, !! slow titration !!
- TPM: blockade of Na +, Ca ++ channels, kainate / AMPA glutamate receptors, potentiation of GABAergic inhibition
- LEV: binding to SV2A synaptic vesicular protein, minimal interaction, good tolerance
- PGB: modulation of α2-δ subunit of Ca ++ channels → decreased Ca ++ influx presynaptically → decreased release of excitatory neurotransmitters into the synaptic cleft
- ZNS: blockade of Na +, Ca ++ channels, inhibition of carbonic anhydrase, modulation of dopaminergic and serotoninergic systems
- LCM: selective effect on slow (not fast) inactivation of Na + channels, reduces hyperexcitability without affecting physiological aktivity
- PER: selective, non-competitive ionotropic glutamate AMPA receptor antagonist
- ESL: Na + channels, prevents channels from returning to the activated phase

Therapy

- Focal **LEV, LTG** ESL, LCM, TPM,ZNS, GBP + BRV, PRG
- Generalized **LEV, LTG** TPM,VAL +LEV, ZNS
- Absence **ESM,LTG** LEV,TPM +ZNS
- Myoklonic **LEV, VAL** LTG +TPM

LEV – levetiracetam, VAL – valproate, CBZ – carbamazepin,

LTG – lamotrigin, ESL – eslicarbamazepin, TPM – topiramat,

LCM- lacosamid, GBP gabapentin, BRV – brivaracetam, PRG – pregabalin,

ESM – etosuximid

therapy, regime measures

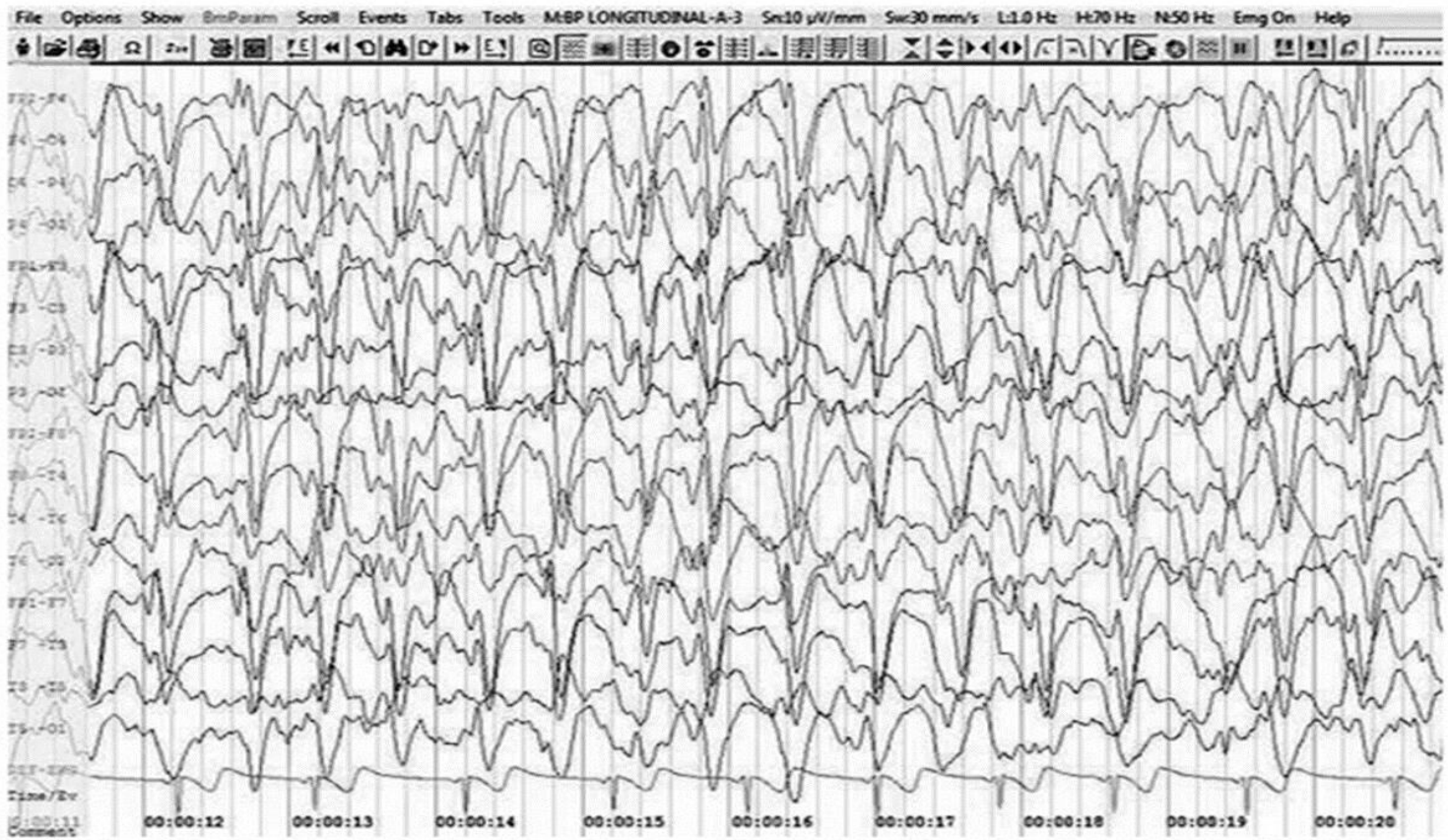
- Driving ban (certain groups, no. 271/2015 Coll.)
- Similarly, the firearms license
- CAVE alcohol, sleep deprivation, photostimulation
- No work on shifts, no open fire, for exposed rotating and electrical live equipment
- No swimming alone

STATUS EPILEPTICUS, SE

- SE is a seizure and / or recurrent seizures between which are not fully adjusted, lasting longer than 5 minutes (in case of convulsive SE) or more than 10 minutes (in case of focal SE with consciousness disorder) Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus-Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015;56:1515–1523.

- SE
- NCSE, non convulsive SE - ***EEG-based diagnostics only***

- In case of benzodiazepine failure (5 min. From the 2nd dose)
- **DEVELOPED SE**: phenytoin (Epanutin) 20mg / kg, max 1500mg, 50ml / min. do not dilute to glucose, BP and HR monitoring !!! (bradyarrhythmias, asystole)
- Alternative i.v. valproate (Depakine) 40mg / kg, max 3000mg
  i.v. levetiracetan (Keppra 60mg / kg, max 4500mg)
- **REFRACTIONAL SE**: Ventilation! EEG monitoring!
  Thiopental bolus 2-7 mg / kg (rate up to 50 mg / min), continuous infusion usually 0.5-5 mg / kg / h (often more) with EEG (burst suppression) adjustment
  Midazolam bolus 0.2 mg / kg (rate 2 mg / min), continuously 0.05-0.2 mg / kg / h with EEG monitoring
  Propofol bolus 1-2 mg / kg (rate 20 µg / kg / min) followed by 30–200 µg / kg / min (caution at doses> 80 µg / kg / min)



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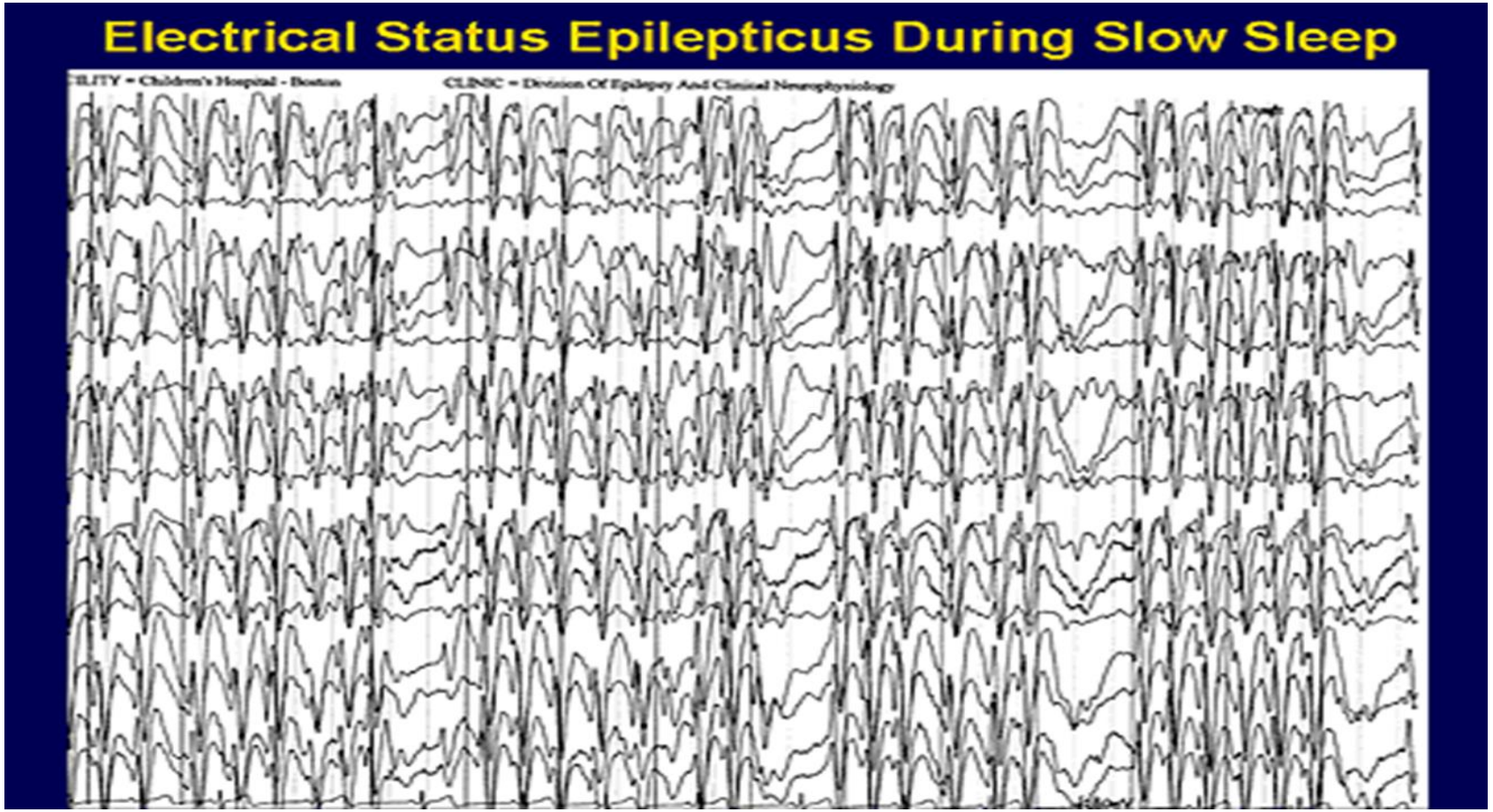

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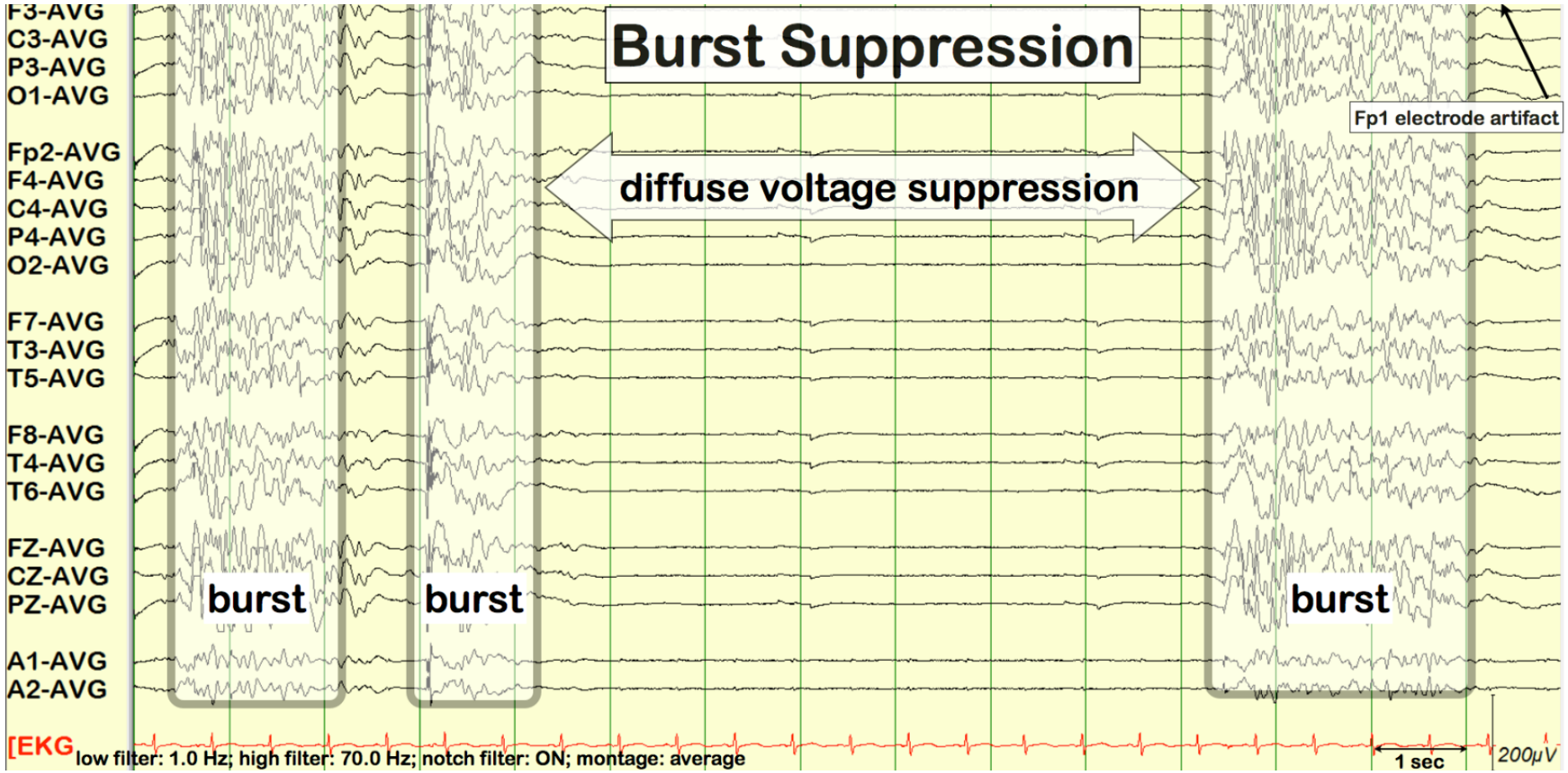

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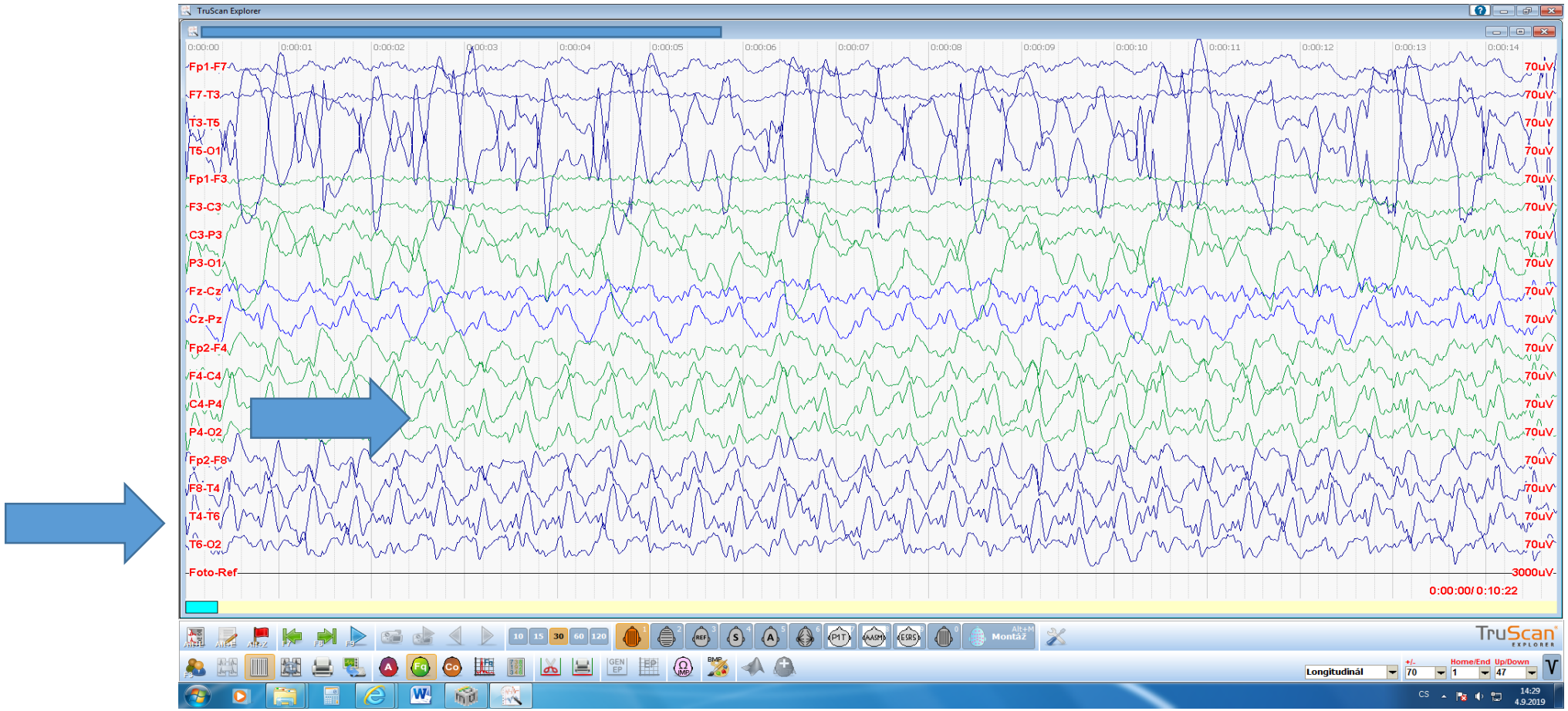
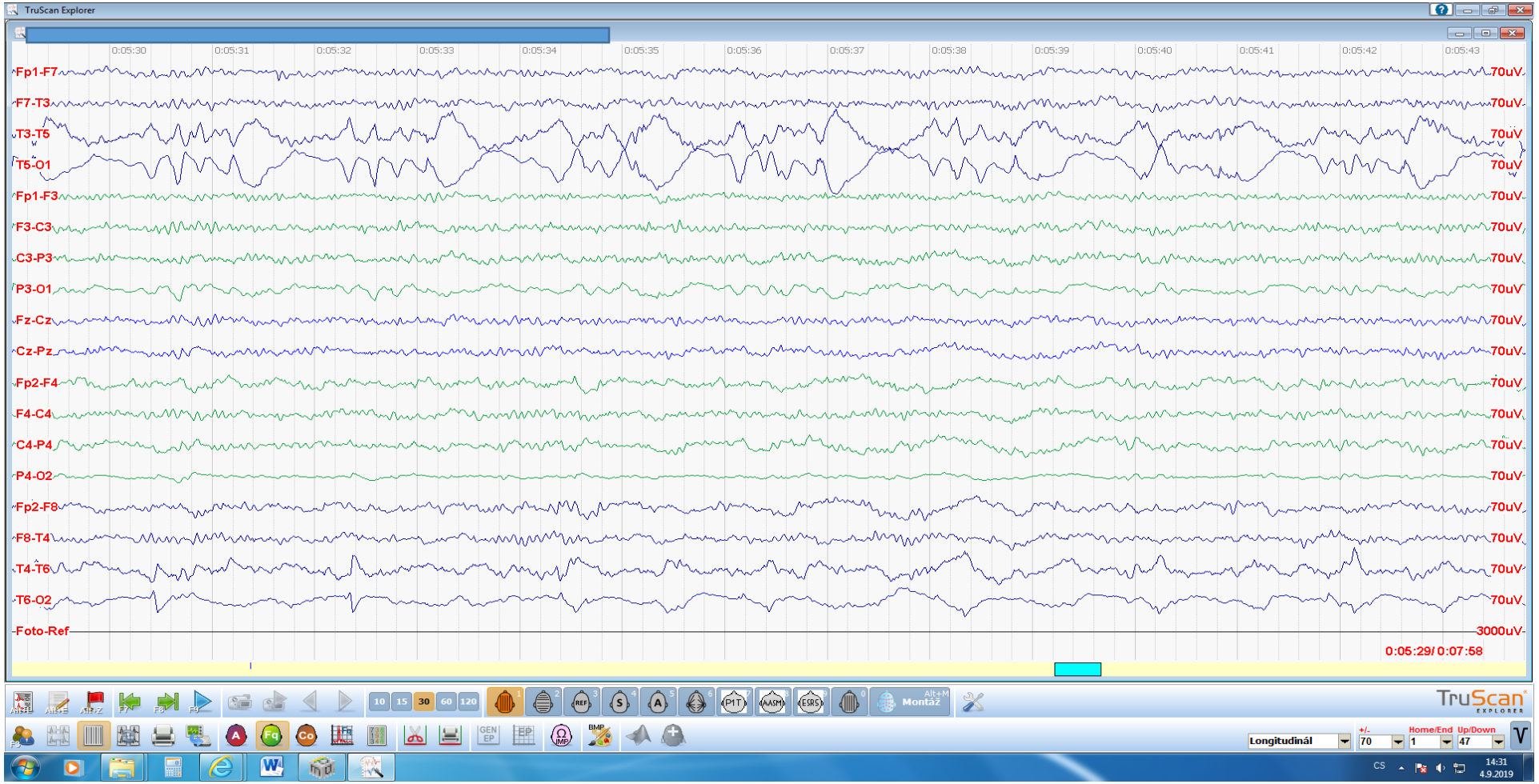
vascular, structural epilepsy, continuous epiactivity over the right hemisphere



treatment with parenteral benzodiazepines - i.v.



Therapy of pharmacoresistant epilepsy, (Kuba, 2012)

- 25% of patients cannot be fully compensated pharmacologically
- **PHARMACORESISTENT** ≈ failure to fully compensate with two appropriately selected antiepileptic drugs at adequate therapeutic doses, monotherapy or combination therapy
- „**Pseudopharmacoresistance**“
  Wrong dg.
  Incorrect syndromological diagnosis
  Inadequate pharmacotherapy
- Pharmacoresistant - tutorials in epileptology center

Procedures for pharmacoresistant epilepsy

Epilepsy surgery resection x stimulation

Resection procedures - removal of the part of the brain responsible for focal seizures

any brain lobe

Preoperative examination - determines the extent of resection (risk of damage to speech, memory, movement) temporal lobe epilepsy 50-80% full cure

Hemisferectomy - catastrophic epilepsy of childhood
diffuse hemispheric epilepsy (functional or structural impairment) hemispheres)
perinatal lesions, hemimegalencephaly, hemispheral dysplasia, Rasmussen encephalitis
hemisferotomy (discontinuation of hemisphere)

Calosotomy - intersection of corpus callosum
Anterior calosotomy (truncus and corporis calosi gene)
generalized atonic or tonic seizures

Procedures for pharmacoresistant epilepsy

- Nervus vagus stimulation (VNS)

  palliative surgery

  an implanted generator stimulates the wandering nerve on the left side of the neck

  is not an alternative to resection operations (resection operation cannot be performed, seizures persist after surgery)
- Deep Brain Stimulation (DBS)

  palliative epileptochirgic method

  long - term stimulation of anterior thalamus by intracerebral electrodes

Prognosis

- **Long-term / lifelong disease**
- If the cause is removed, epilepsy can be cured
- Sometimes healing epilepsy, usually after many years of treatment, ??? treatment ??, ?? spontaneous process ???
- **Often inferior to the patient's quality of life**, restricting him in a number of activities, modifying career choices, patient personality, and partner relationships
  the patient may be at risk of accidents (falls - stairs, water)
- **The life-threatening condition is the convulsive status of epilepticus**
  sudden unexpected death in epilepsy (SUDEP) is rare, more common in uncompensated generalized seizures, possibly due to cardiac or respiratory causes, and the incidence of SUDEP in children is lower than in adulthood
- The probability of achieving complete suppression of seizures with monotherapy with the first drug is approximately 48%
- Surgical treatment is successful in indicated cases in about 60-80% of cases