Case report

Late diagnosis of classical phenylketonuria in our patient (infant)

The case of a 9.5-month-old girl who was investigated for unexplained psychomotor retardation

History:

- Family history: without interest

- A girl from 4th pregnancy, 2 x spontaneous abortion, healthy brother, oligohydramnion, prenatal ultrasound in pregnancy 2x (12th and 38th week), biochemical screening of M. Down, all in the norm, childbirth in 40th week by caesarean section for non-advancing birth, 3600g/ 51 cm, breastfed 6 months, then mixed baby food, parents observed a difference from older healthy brother – the girl did not smile, did not make contact, family doctor advised to wait

- At 8.5 months – eye examination, finding in the norm

- In 9.5 months was admitted to the hospital, at the Deparment of Neurology – delay of psychomotor development, does not sit, does not climb, she rolls over on the tummy and back, on the tummy is on the elbows, sometimes on the palms, says the syllables

- age-appropriate nutrition, head frontooccipital circumference 41 cm ↓, other anthropometric parameters in the standard

Examination

- Differential diagnosis:
- MRI of the brain: myelinization of white matter corresponds to 6-8 months of age, delayed, further finding in the norm

- metabolic screening was performed to rule out inborn error of metabolism (IEM)

- Phenylalanine (Phe) in the blood was found to be significantly increased and reached **1768µmol/l** (standard up to 120µmol/l), corresponding to classical phenylketonuria (PKU)

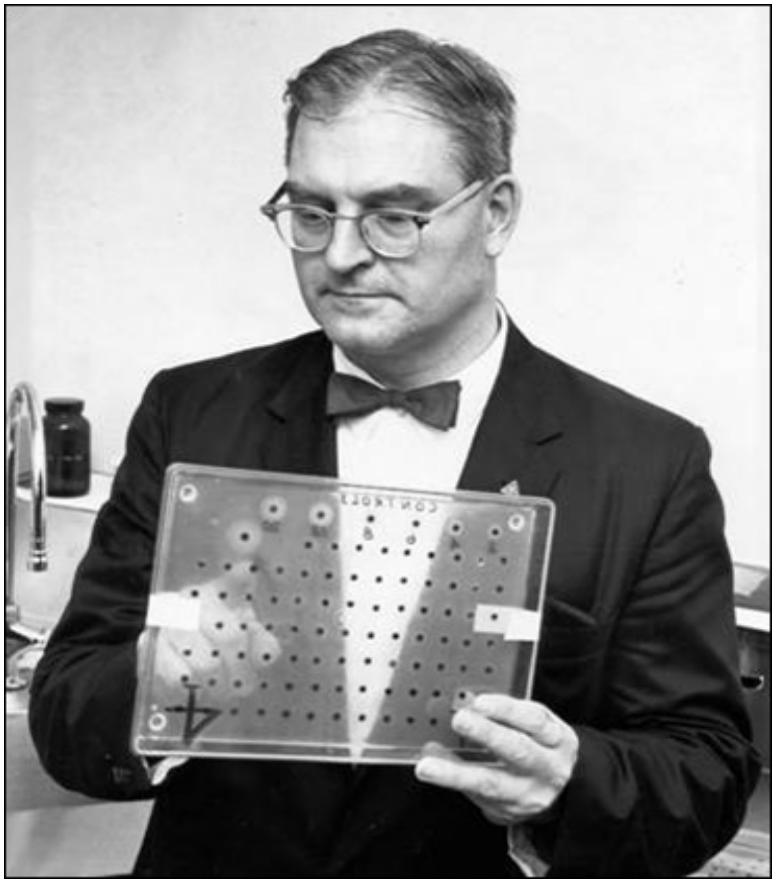
- molecular-genetic examination of *PAH* gene for PKU/HPA: genotype p.(Gly272*)/p.(Thr328Ala),mutations are described causal, listed in the HGMD database (www.hgmd.org)

Phenylketonuria - PKU

- IEM of amino acid Phe caused by deficiency of phenylalanin hydroxylase enzyme (PAH) in the liver (EC 1.14.16.1), *PAH* gen 12q23.2
- Heredity: autosomal recessive, incidence in the Czech Republic 1: 5,250 live birth
- r.1954 - prof. Bickel – therapy: low-protein diet, low in phenylalanine
- Early postnatal, sufficiently intense and long-term low protein diet allows normal or almost normal development of cognitive functions
- The diet is compiled individually according to sex, weight, age, protein, carbohydrate and fat needs and Phe tolerance in the diet
- Other treatment options: GMP-glycomacropeptide, cofactor BH4-Kuvan, enzyme replacement therypy-ERT-Pegvaliasa® (BIOMARINE)

Phenylketonuria-screening

- Introduced by Prof. Robert Guthrie (1916-1995), University of Buffalo, USA, NY
- PKU - bacterial inhibitory test (B. subtilis)
- In 1963 introduced - neonatal screening in the Czech Republic, by law only in 1975
- Since 2009 in the Czech Republic screening is provided using MS/MS (tandem mass spectrometry)



Newborn screening in the Czech Republic - IEM

- Disturbances of amino acid metabolism:
- Phenylketonuria – PKU
- Maple sirup urine disease – MSUD
- urea cycle defects: Argininemia, Citrullinemia
- Homocystinuria from CBS deficiency, pyridoxine non-responsive
- Homocystinuria from MTHFR deficiency

- Organic acidurias
- Glutaric aciduria type 1, Isovaleric aciduria (IVA)

- Disorders of fatty acid oxidation
- Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
- Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
- Very long-chain acyl-CoA dehydrogenase (VLCHAD) deficiency
- Carnitine palmitoytransferase I (CPT1) deficiency
- Carnitine palmitoytransferase II (CPT2) deficiency
- Carnitin acylcarnitine translocase (CACT) deficiency

- biotinidase deficiency

- How could that happen?


Surin Islands
Richelieu Rock
N
Ko Tachai
Thailand
Ko Bon
Tap Lamu
Similan Islands
Phang Nga
Phang Nga Bay
Krabi
Phuket Island
Patong Beach
Chalong Bay
Kata & Karon Beach
Racha Yai
Racha Noi
Phi Phi Islands
Ko Lanta
Shark Point
Anemone Reef
King Cruiser Wreck
Ko Ha
Ko Rok Nok
Hin Daeng
Hin Muang
Andaman Sea

- The child was born in Thailand, his parents worked here in tourism
- Parents had health insurance
- Screening was conducted: 2nd day after birth, blood Phe level 3.4 mg/ dl, i.e. 204µmol/l, standard up to 2 mg/dl or 120µmol/l
- Parents were communicated that the blood Phe up to 4 mg/ dl, i.e. 240µmol/l, is normal in Thailand, within this range, no further control was performed !!!!!!!!!!???????

Thailand and inborn errors of metabolism (IEM)

- Incidence of IEM in Europe and North America 29-40/100,000, in Asia 16-26/100,000 live births

- In Thailand provided PKU screening since 1996, incidence of PKU 2.22/ 100,000 live births (180,000 newborns examined in 2012 at Siriraj Hospital Bangkok)

- Method: Guthrie test for low price and simple examination

- In 2015, a pilot study on selected IEM using MS/MS – a highly costly method for Thailand, yet the introductions recommend for PKU, IVA, MSUD, MCD (Thiboonboon K et al.: An Economic Evaluation of Neonatal Screening fo Inborn Errors of Metabolism Using Tandem Mass Spectrometers in Thailand, Plos One, August 2015)

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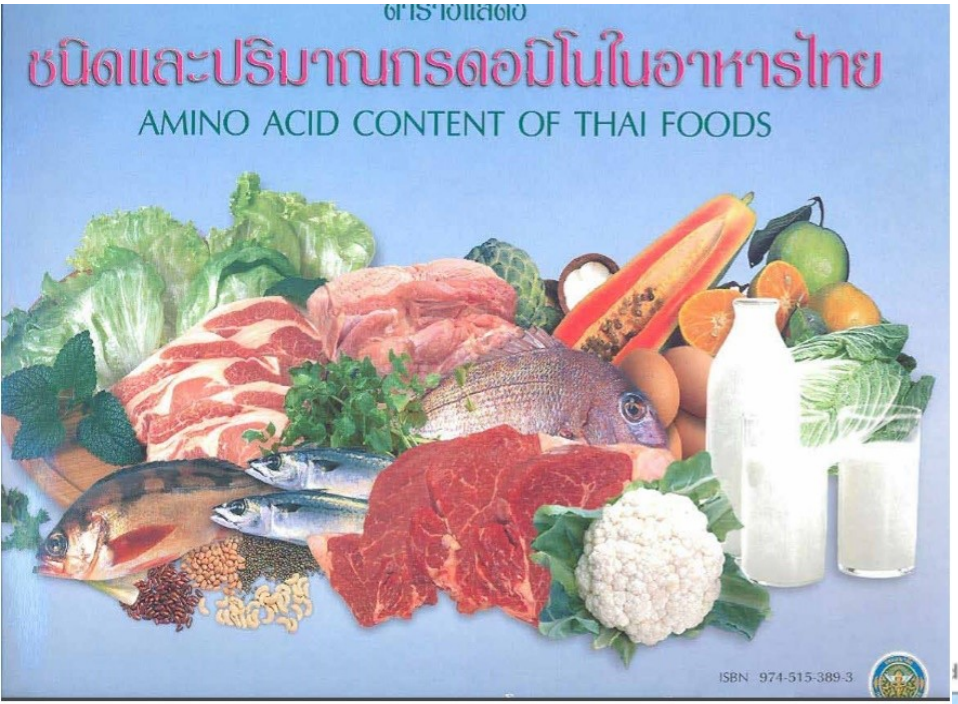

- the diet of our patients with PKU is vegetarian and vegan

ducts)

Food ID	Food and Description		Protein (g/100 g)	Isoleucine	Leucine	Lysine	Methionine	Cystine	Total S-cont. amino acids	Phenylalanine	Tyrosine	Total Aromatic amino acids	Threonine	Tryptophan	Valine	Arginine	Histidine	Alanine	Aspartic acid	Glutamic acid	Glycine	Proline	Serine	Total essential amino acids	Total amino acids	Chemical Score		
	Thai	English																								A/E	A/T	Limited amino acid
01001	ก๋วยเตี๋ยจันท์ แห้ง	Noodle, rice, small size, dried	6.3	222	463	214	69	133	202	226	83	309	226	62	312	377	223	272	458	1007	219	318	264	2030	5168	69	62	Lys
01002	ก๋วยเตี๋ยว เส้นเล็ก	Noodle, rice, small size	3.6	143	262	138	47	91	138	146	40	186	138	66	181	224	116	192	299	644	150	155	162	1252	3194	72	69	Lys
01003	ก๋วยเตี๋ยว เส้นใหญ่ สด	Noodle, rice, big size, fresh	2.4	94	173	94	39	54	93	96	42	138	92	43	115	153	70	114	194	423	90	101	104	842	2091	73	71	Lys
01004	ข้าวเจ้า 5%	Rice, polished, 5%	6.6	178	487	242	95	176	271	260	76	336	221	108	286	383	193	325	513	1130	260	230	289	2129	5452	74	67	Lys
01005	ข้าวเจ้า 10%	Rice, polished, 10%	6.5	188	423	243	95	148	243	229	104	333	215	101	222	338	152	290	439	853	238	314	265	1968	4857	81	68	Lys
01006	ข้าวเจ้า กข 1	Rice, polished	7.8	380	718	331	174	146	320	380	166	546	340	108	459	658	243	432	688	1599	344	341	390	3202	7897	67	76	Lys
01007	ข้าวเจ้า กข 5	Rice, polished	7.3	222	437	244	94	158	252	298	127	425	249	101	316	466	169	310	481	1029	234	311	290	2243	5533	70	71	Lys
01008	ข้าวเจ้า กข 7	Rice, polished	6.7	265	471	272	88	142	230	273	109	382	246	104	389	386	206	302	466	943	235	230	286	2279	5327	78	75	Lys
01009	ข้าวเจ้า กข 21	Rice, polished	8.7	276	660	238	124	254	378	446	109	555	332	134	362	464	226	425	691	1442	324	337	407	2985	7301	63	60	Lys
01010	ข้าวเจ้า กข 21 ข้าวกล้อง	Rice, unpolished	9.1	287	673	299	152	251	404	377	88	465	346	129	381	494	255	400	638	1405	334	382	406	2984	7298	66	60	Lys
01011	ข้าวเจ้า กข 23	Rice, polished	8.4	318	705	295	104	258	362	381	124	505	350	140	412	539	255	468	672	1568	376	432	418	3087	7815	62	64	Lys
01012	ข้าวเจ้า กข 23 ข้าวกล้อง	Rice, unpolished	9.6	354	782	336	149	261	410	432	141	573	402	140	440	645	290	495	740	1485	418	483	483	3437	8476	64	64	Lys
01013	ข้าวสาร กข 25	Rice, polished	8.9	315	697	291	139	242	381	387	105	492	361	148	414	568	237	473	698	1562	367	400	425	3099	7829	61	59	Lys
01014	ข้าวเจ้า กข 25 ข้าวกล้อง	Rice, unpolished	9.6	373	765	328	154	267	421	428	130	556	405	148	452	677	276	495	747	1597	404	462	441	3448	8545	62	62	Lys
01015	ข้าวเจ้า กข 27	Rice, polished	8.5	289	632	288	228	235	463	447	143	590	343	137	422	829	378	481	784	1730	399	494	475	3224	8794	58	61	Lys

Our patient at the age of 24 months:

- Anthropometric parameters: weight 12.1 kg, length 86.5 cm, head frontooccipital circumference 46.7 cm

- Laboratory tests: Phe in the blood 60-150μmol/l (60-360); Zn in the blood 10.5μmol/l (11.5-15.3); Se in the blood 0.67μmol/l (0.7-1.24); other laboratory parameters in the standard

- Neurological examination: pathological EEG in the sense of epilepsy, but the finding improved, clinically free of seizures, antiepileptics is not used

- NMR of the brain now not done due to progress in psychomotor development and improved EEG

- psychological examination: the level of motor functions ranged from 12 months, the overall level of mental functions corresponded to about 10 months of age. Prediction for the future: **IQ 44**, **impairment of neurocognostic functions is irreversible**