THE CHILDREN'S MEMORIAL HEALTH INSTITUTE

COMBINED PITUITARY HORMONE DEFICIENCY

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Background: Hipopituitarism may be congenital or acquired disorder, which affects one or more hormonal axes. Congenital hipopituitarism include heterogenic group of disturbances and may be result of mutations in genes for signaling and transcriptional factors responsible for normal sequential pituitary development. The age of appearance and intensity of the first hormone deficiency symptoms may depend on type of mutation. Some symptoms of particular mutations may form syndromes or show characteristic phenotype in neuroimaging.

Objective and hypotheses:

We present group of 24 patients with combined pituitary hormone deficiency (CPHD): 15 boys and 9 girls. In some of the patients the first symptoms were observed at the neonatal period manifested as hypoglycemia or intrahepatic cholestasis, in others later on in childhood as growth or puberty retardation. The symptoms observed in the youngest patients are non characteristic for hipopituitarism what is the cause of delay diagnosis and difficulties in this group.

Methods:

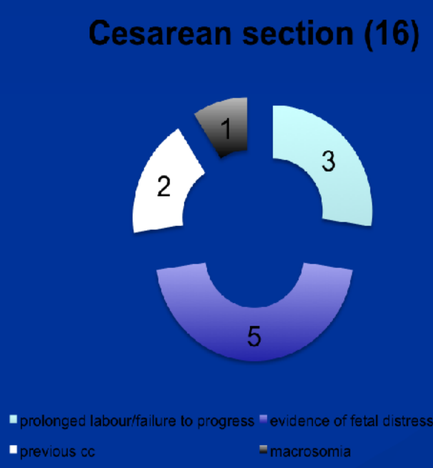
Clinical characteristic of group of patients. Hormonal, imaging tests.
Molecular analysis of genes for transcription factors PROP 1 and OTX 2.

Results:

Mutations in gene encoding PROP 1 were found in 5 of 21 analyzed patients. The analysis of OTX 2 gene was negative in the patient with CPHD and microphthalmia.

Prenatal/neonatal history:

	Average	Minimum	Maximum
Birth weight	3600g	2700g	4600g
Birth lenght	55,5cm	48cm	62cm
Gestational Age	39,5 Hbd	37 Hbd	42 Hbd



Clinical symptoms:

Neonatal period :

Symptomps	Number of cases	Share %
Uneventful	11	45,8%
Hipoglycemia	8	33,3%
Hiperbilirubinemia & cholestasis	8	33,3%
Dysmorphia	8	33,3%
Cryptorhidism/micropenis	5	20%
Generalised infection	4	16,6%
Hipocalcemia, hipomagnesemia	1	4,1%

Infancy :

- Low weight gain
- Psychomotor development delay
- Cholestasis
- Hypoglycemia
- Cryptorhidism, retractile testes
- Micropenis
- Anaemia

Childhood :

- Slow growth velocity
- Short stature
- Anaemia
- Low appetite
- Nausea/vomitus
- Hypoglycemia (ie. during infections)
- Constipation
- Polidypsia, poliuria

Hormonal profile :

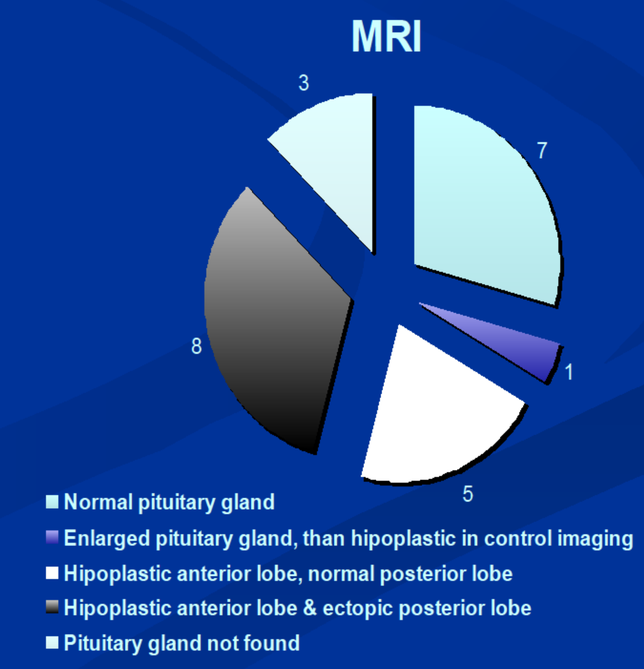
Hormones	Number of patients	Share %
TSH	24	100%
GH	21	87,5%
ACTH	16	66,6%
LH, FSH	12	50%
ADH	1	4,1%

Hormones	Age of diagnosis (year of life)	Minimum	Maximum
TSH	3	1st week	14th year
GH	5	1st month	14th year
ACTH	6	1st week	15th yeat
LH, FSH	13-14		
ADH	5		

Genetic analysis results :

Examined patients	22
PROP 1	21
OTX 2	1
PROP 1 mutation:	5 (23,8%)
296delGA / 296delGA	2
301delAG / 301delAG	2
150delA / 296delGA	1
OTX 2 mutation:	**0**

Molecular analysis by PhD Petra Dusatkova, Prof. Jan Lebl Prague, Czech Republic



Conclusions:

- CPHD should be considered in neonates/infants presenting hypoglycemia, cholestasis, severe distress in course of infection, thermoregulation disturbances.
- The wide variety of symptoms and their different intensity poses serious problem for indication of the one characteristic genetic mutation. Defect in PROP 1 gene constitutes only part of possible genetic causes responsible for CPHD. Determining of specific gene mutations at early diagnostic stage could be helpful to establish proper prognosis and adjust the optimal treatment.

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