

# Congenital Hypopituitarism and Giant Cell Hepatitis in a Two-Months-Old Boy

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## Background:

Congenital hypopituitarism (CH) in the neonate that manifests as the deficiency of one or more pituitary hormones can be presented by a highly variable phenotype, either as isolated hypopituitarism or with associated developmental defects such as ocular, midline and genital abnormalities. Mutations in genes encoding for a number of transcription factors have been described in a minority of patients with CH. Genetic damage isn't always possible to detect. Japanese scientists examined 91 patient with CH, and they identified 2 heterozygous mutations in LHX4 and 1 mutation in POU1F1 (1). In the Netherlands researchers examined 78 patients with CH, and they found 1 mutation in POU1F1 (2). In some children with CH, unique non-infectious forms of hepatitis were found, manifested by hepatomegaly, cholestasis, impaired liver function, and its giant cell transformation hepatocytes confirmed by biopsy. Remission occurs during the first few months of life (3). The study of 62 cases of neonatal giant cell hepatitis (73%) showed that the disease is most often associated with CH (16%) (4).

## Objective:

- To describe clinical /laboratory features of a child and stages of a differential diagnosis.
- Analysis of hepatitis and cholestasis markers, blood glucose levels during the symptomatic treatment and further replacement therapy
- To define gene mutation and to detect a causal relationship with the onset and severity of disease

## Method:

- The anamnesis of life and disease (history of our patient, including origin, consanguinity, family illness or unexplained death, pre - and perinatal characteristics, neonatal screening for congenital hypothyroidism, cystic fibrosis, congenital adrenal hyperplasia, phenylketonuria, galactosemia)
- Clinical and anthropometric data were obtained.
- Biochemical liver function: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Bilirubin Total/ Direct Bilirubin (BiT/BiD), Alkaline Phosphatase (ALP), LDH, Blood Glucose (BG)
- Serum hormone analyses: Thyrotropin (TSH), Free Thyroxine (FT4), Growth Hormone (GH), Cortisol, Adrenocorticotropin (ACTH), Insulin-like Growth Factor-1 (IGF-1), Insulin.
- Enzyme immunoassay for Toxoplasma, Herpes simplex 1,2, Mycoplasma hominis/pneumoniae, Chlamydia trachomatis/pneumonia, HBsAg, HCV, HIV.
- Polymerase chain reaction (PCR) for EBV, CMV, HHV -6
- Tandem mass Spectrometry (TMS) for metabolic disorders. The urine succinylacetone levels for Tyrosinemia type 1
- PROP1, GH1, GHRH, GHRHR, BTK, GHSP, POU1F1, HESX1, LHX3, LHX4, SOX3, SOX2, OTX2, GLI2, ARNT2, ARPC5L, DLK1, DRD2, PAX6, RNPC3, SHH, SPCS2, SPCS3 gene mutations were investigated by direct sequencing.
- Magnetic resonance imaging (MRI) of the brain. Ophthalmoscopy
- Laparoscopic liver biopsy and cholecystocholangiography were carried out

## Results:

The boy was carried full term and born with healthy weight and height. Jaundice started during the first week and had a prolonged course. In addition, the boy had repeated episodes of severe hypoglycemia. At the age of 2 months, the non-specific giant cell hepatitis was revealed. Physical examination: the patient had craniofacial dysmorphism and genital abnormality, symptoms of cholestasis (Picture 2). Results of liver function tests were abnormal (Table 1). The symptomatic therapy was initiated immediately (Tab.1). The biopsy results: giant-cell hepatitis with symptoms of pronounced cholestasis (primarily intracellular), with the initial signs of fibrosis. The blood hormone levels are presented in Table 2. The results of the pituitary gland MRI scan were normal. Genetic analyses were negative for mutation in the all gene what we investigated. The diagnosis of congenital hypopituitarism was completed with confirmation of FT4, Cortisol, ACTH, GH deficiencies. The hormone replacement therapy with Levothyroxine, Hydrocortisone and later with Somatropin was prescribed to the boy. Now the boy is 3.5 years old and he's in a good physical condition, biochemical liver function parameters and blood glucose level are within the age norm. He takes Hydrocortisone 9 mg/m<sup>2</sup>/daily, Levothyroxine 100 mkg/m<sup>2</sup>/daily, Somatropin 0.033 mg/kg/daily.

Picture 2. physical examination.

Lethargy, scleral icterus, dry and pale skin, bradycardia, hepatomegaly, white stool, dark urine.

craniofacial dysmorphism

hydrocephalic head shape, protruding forehead,

sunken nasal bridge,

hypoplasia of the facial skull in the midline



micropenis; in the right half of the scrotum - testis 1 sm<sup>3</sup>, in the left - hydrocele 1\*0.6 sm

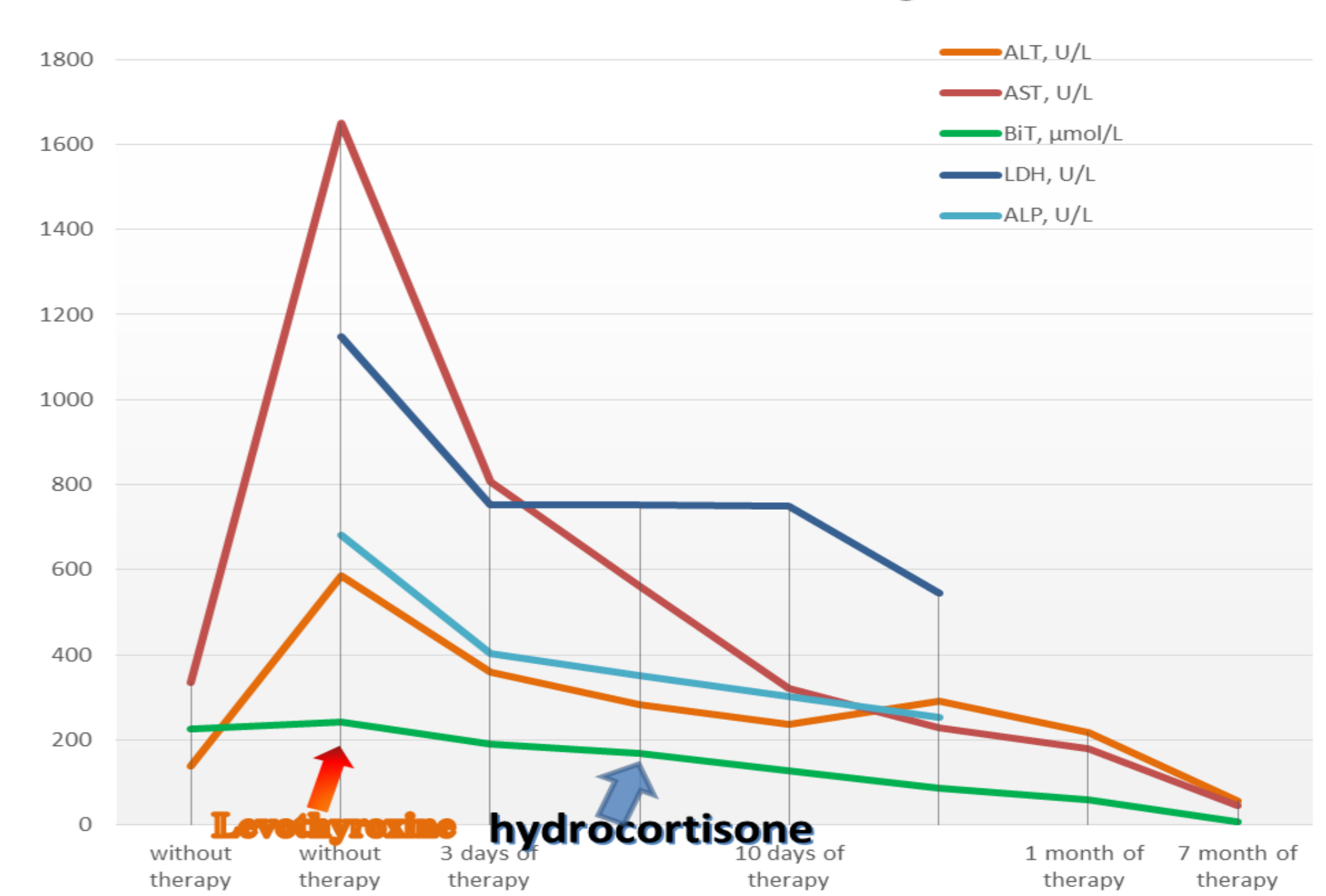
Table 2. The levels of hormones and glucose in the blood before and on replacement therapy.

Date of collection	FT4 pmol/L (10-26)	TSH mIU/L (0,62-8,0)	Cortisol nmol/L (138-635)	ACTH pmol/L (1,8-10,2)	IGF-1 ng/ml (28-131) GH ng/ml (1,3-9,1)	BG mmol/L (3,0-6,1)	Insulin IU/L (2,3-26)
01.11.12	7,7	9,6	-	-	-	2,1	0,2
08.11.12	6,8	9,4	14,6	-	-	1,5	0,3
<b>+ Levothyroxine</b>							
12.11.12	-	-	-	-	-	3,5	0,2
14.11.12	8,6	-	5,9	1,7	<25 0,9	3,8	-
15.11.12	-	-	8,9	-	-	4,0	-
<b>+ Hydrocortisone</b>							
19.11.12	13,3	4,0	350,4	-	-	4,5	5,9
22.11.12	-	-	459,8	-	-	-	-

Table 1. Biochemical liver function parameters

Date of collection	Results				
	ALT, U/L (5-30)	AST, U/L (8-40)	BiT/BiD μmol/L (<20,5/<5,3)	LDH U/L (< 580)	ALP, U/L (< 420)
<b>Continuous intravenous introduction of glucose solutions with the rate 10-15-20 mg/kg/min. Ursodeoxycholic acid 25 mg 2 times a day orally</b>					
24.10.12	94	217	164/100	1743	-
25.10.12	103	234	174/110	-	-
29.10.12	138	335	225/150	-	-
<b>+Ademetionine 200 mg/daily by intravenous injection</b>					
08.11.12	587	1650	241/180	1148	680

Fig.1 The hormone replacement therapy. Liver enzymes, BiT/BiD monitoring



## Conclusion:

The patient presented with early and persistent direct hyperbilirubinaemia and hypoglycemia. A constant infusion of glucose was not effective until he was given replacement therapy (Tab.2). On hormone therapy, BG level was normalized and remained within the normal range without intravenous glucose infusion. Hyperbilirubinemia began to resolve progressively a month after initiation of replacement therapy (Fig.1). An extensive evaluation excluded infectious, metabolic, and anatomic causes of neonatal cholestasis. Some researchers believe that a deficiency of pituitary hormones may be responsible for delay of the hepatic transport mechanisms development or inhibit bile acid synthesis, which lead to cholestasis. We suggest that in the case of neonatal liver dysfunction associated with hypoglycemia the diagnosis of CH should be excluded.

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