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A case of Congenital Isolated Adrenocorticotropin Deficiency due to TPIT gene mutation

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BACKGROUND

Congenital isolated adrenocorticotrophin deficiency (IAD) is a rare condition that was first reported in 1954 [1]. It is difficult to diagnose because its symptoms are various and unspecific, and its biological expression difficult to interpret particularly in neonates. There are two forms of IAD in childhood. The early onset form appears before the age of one or two years and the late onset form after 3 years [1]. Some authors reported about neonatal cases of IAD having different mutations in TPIT (TBX19) gene [2,3,4,5]. The IAD is characterized by a few clinical/laboratory syndromes: neonatal cholestasis and hepatitis, serious hypoglycemia, hepatic function deficiency. Many researchers support the hypotesis that cortisol deficiency might have a major role in the pathogenesis of cholestasis and hypoglycemia in full-term infants [6,7,8,9]. The replacement therapy with the hydrocortisone leads to normalization of indicators hepatic function and suggest a causal relationship between cortisol deficiency and the development of neonatal cholestasis [6,7,8].

OBJECTIVES

- To describe clinical /laboratory features at the child and steps before the diagnosis

- To analyze markers of hepatitis and cholestasis and blood glucose level during symptomatic treatment and further replacement treatment

- To define a mutation of the causal gene and association with the onset and the gravity of the disease

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Materials and methods

- The history of our patient, including origin, consanguinity, familial diseases or unexplained death, pre- and perinatal features was recorded. Newborn screening for Congenital Hypothyroidism, Cystic Fibrosis, Congenital Adrenal Hyperplasia, Phenylketonuria, Galactosemia was reviewed
- Clinical and anthropometric data
- Biochemical liver function parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin total/ bilirubin direct (BiT/BiD), Gamma-glutamil transferase (GGT)
- Blood glucose (BG)
- Serum hormone analyses: Thyrotropin (TSH), Free Thyroxin (FT_4), Growth Hormone (GH), Cortisol, Adrenocorticotropin (ACTH), Insulin-like growth factor-1(IGF-1), Insulin, C-peptide
- Enzyme Immunoassay for Toxoplasma, Herpes simplex 1,2, Mycoplasma hominis/pneumoniae, Chlamydia trahomatis/pneumoniae, HBsAg, HCV ,HIV
- Polymerase Chain Reaction (PCR) for EBV, CMV, HHV -6
- The urine succinylacetone level for Tyrosinemia 1 type
- Tandem Mass Spectrometry (TMS) for metabolic disorders
- Molecular Genetic Analyses (by Sanger sequencing) for mutations POMC, TPIT(TBX19) genes
- Ultrasonography of the abdomen
- Liver Elastography (with assessment by Metavir scale)
- Magnetic Resonance Imaging (MRI) of the brain

RESULTS. Past history

- The girl was carried full term and born a healthy weight and height
- The parents are cousins
- Jaundice had started during the first week and had prolonged course.
- Short tonic seizures started when the girl was 5.5 months old
- When she was 7 months old her condition worsened and became severe and she fell into a coma. The girl had been admitted to an intensive care unit. (laboratory data see table 1)

Results.

Tab.1 Indicators of the blood glucose and liver enzymes

parameters (normal range)	Results
BG,mmol/L (3,0-6,1)	0,6
ALT, U/L (5-30)	400
AST,U/L (8-40)	180
BiT/BiD, μmol/L (<20,5/<5,3)	200/142

Results.On examination

- Impaired consciousness (coma)
- Muscle hypotonia
- Jaundice is increased, prolonged
- Bradycardia. Pulse rate 110/min
- Depression of respiration frequency. Respiration rate 10/min
- Severe hypotension with a BP 65/40 mmHg
- Hepatosplenomegaly
- Dark urine
- Clay-colored bowel movements

Results. Symptomatic treatment

- The symptomatic therapy was begun by the continuous intravenous introduction of glucose solutions with the rate 10-15-20 mg/kg/min and Ursodeoxycholic acid 25 mg 2 times a day orally, Ademetionine 200 mg/daily by intravenous injection
- General condition improved with termination of seizures and coma elimination. Jaundice was decreased but without elimination completely.
- BG was increased to 2,8 mmol/L (3,0-6,1 mmol/L), ALT, BiT/BiD were reduced but remained out of normal range.

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Results.

- Serum hormone analyses showed the following:
- Insulin =0,2 IU/L (2,3-26 IU/L), C-peptide=0,1 ng/ml (0,36-3,6 ng/ml). The results of Insulin and C-peptide which were taken during severe hypoglycemia excluded hyperinsulinism
- TSH=3,52 mIU/L (0,62-8,0 mIU/L)
- FT4=12,9 pmol/L (10-26 pmol/L)
- GH=3,5 ng/ml (1,3-9,1 ng/ml)
- IGF-1=29,2 ng/ml (28-131 ng/ml)
- **ACTH - under 1,1 IU/ml (1,8-10,2 IU/ml)**
- **Cortisol=15,9 nmol/L (138-635 nmol/L)**

On the basis of the above findings the case was diagnosed as isolated ACTH deficiency.

The hormone replacement therapy by hydrocortisone (5 mg/kg/daily) was prescribed for the girl (third day of survey).The hydrocortisone dose was corrected due to blood cortisol control.The blood glucose level was normalized and remained within the normal range without intravenous glucose infusion (Fig.1). Cholestatic syndrome and especially hepatitis disappeared slowly (Fig.2)

Results. The hormone replacement therapy

Fig.1 Blood glucose monitoring during the replacement treatment

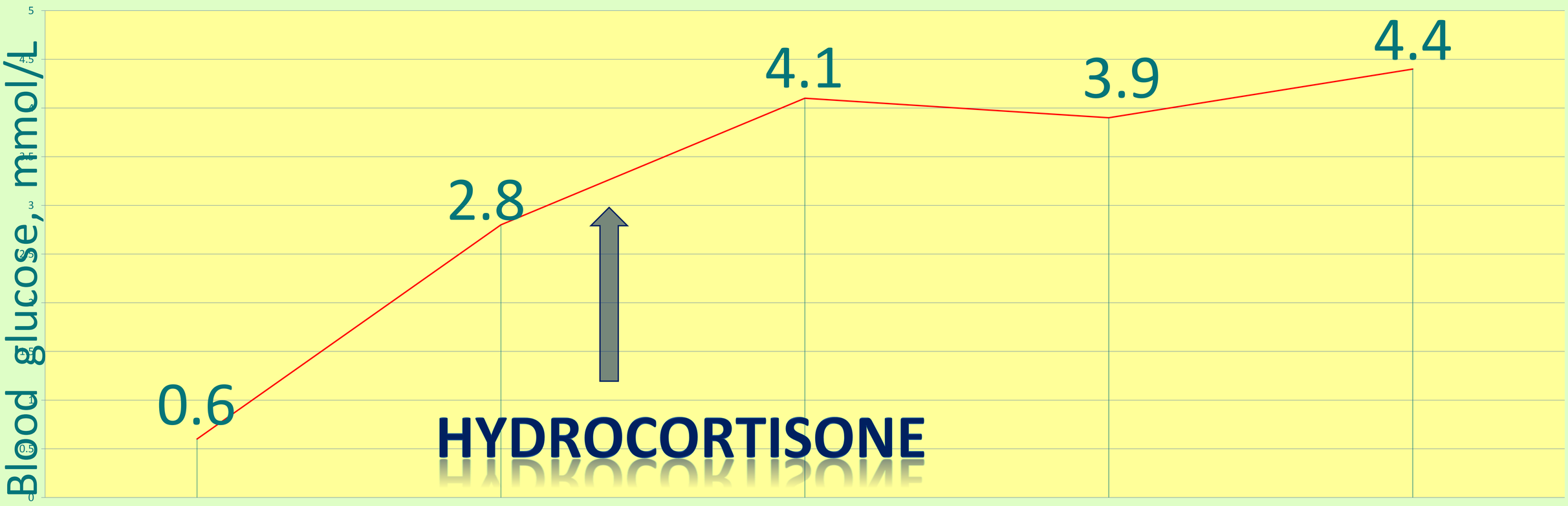
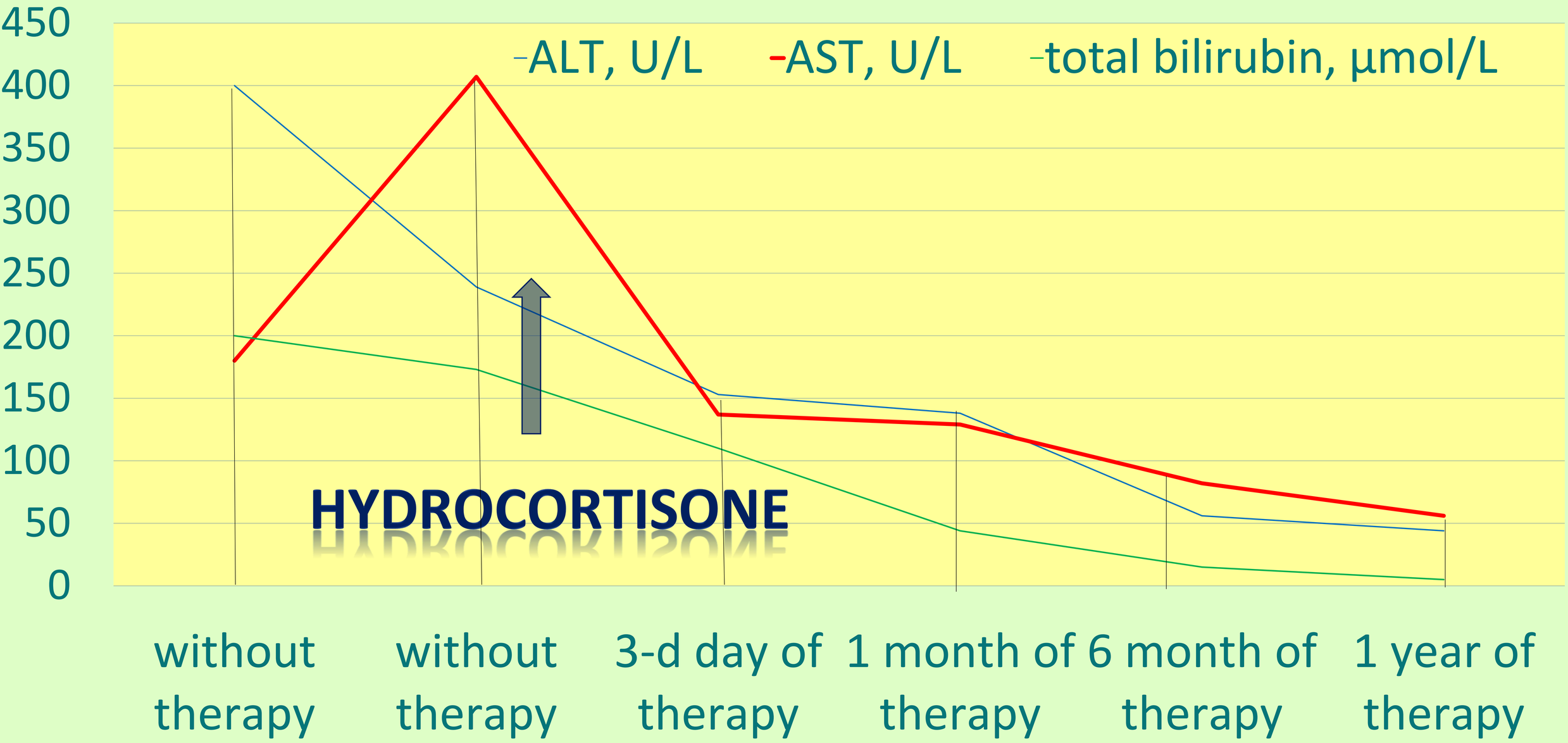


Fig.2 Liver enzymes, total bilirubin monitoring during the replacement treatment



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Results.

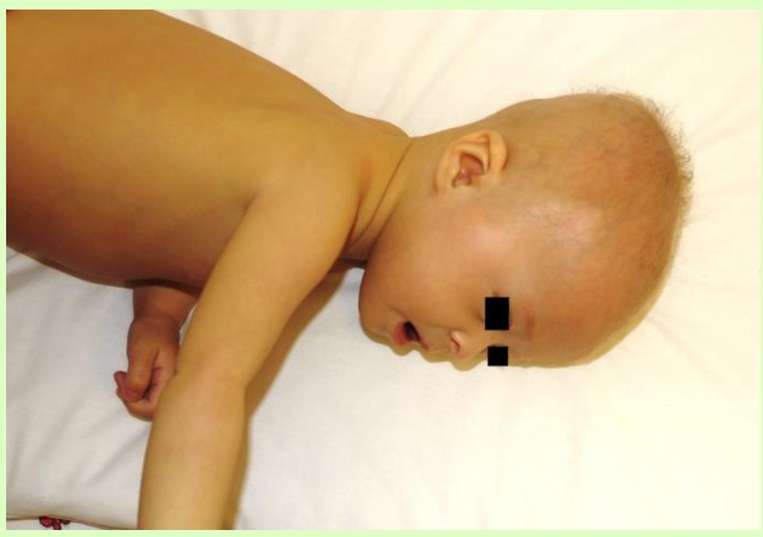
Genetic analyses:

- Molecular analyses for mutations POMC, TPIT(TBX19) genes were investigated
- Genetic analyses were negative for any mutation in the POMC gene
- Homozygous mutation Q28X TPIT gene was found in the child
- Heterozygous mutation Q28X TPIT gene was found in the girl`s mother

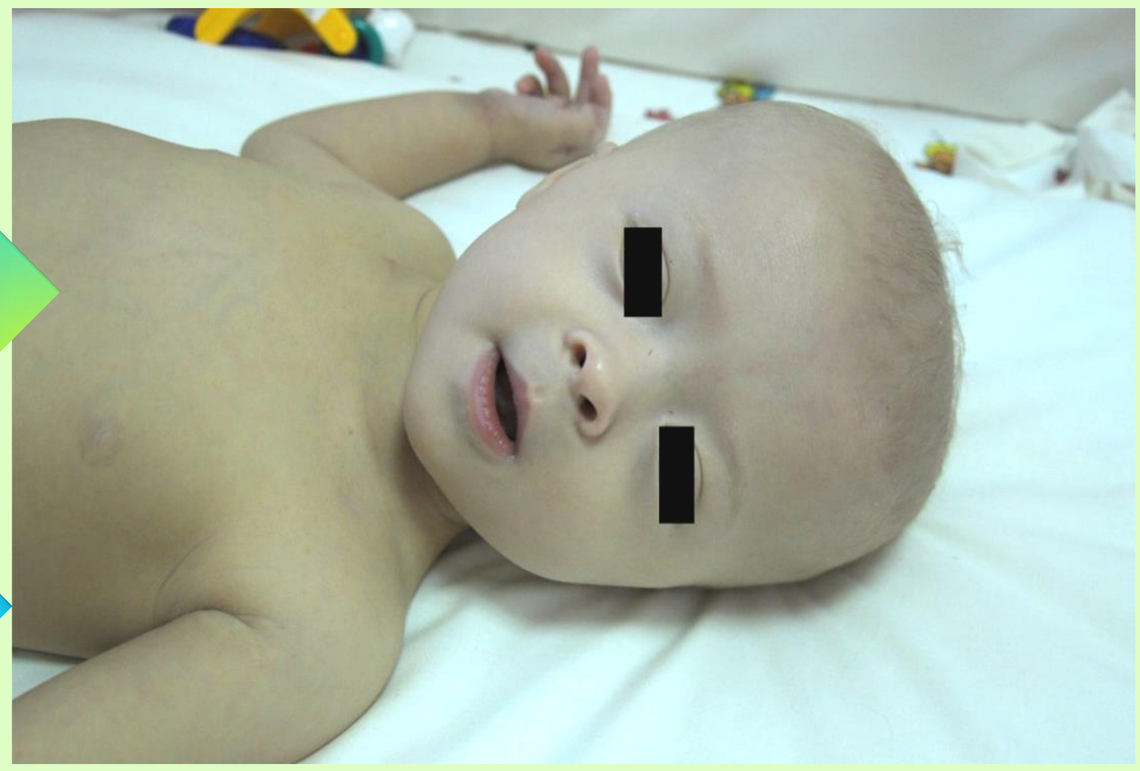
Dysmorphic features:

Trigonocephalia,

skull shape beveled



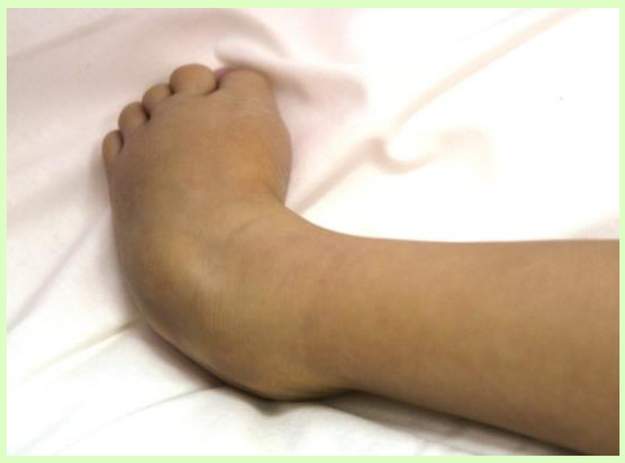
Flattening of the bridge of the nose, epicanthus



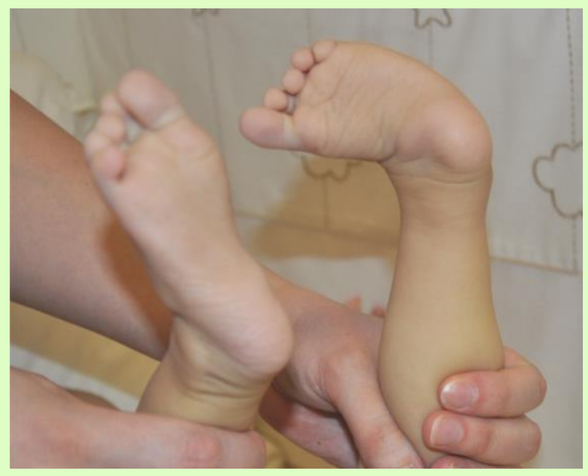
Arched palate

Narrowing of the oral cavity

Flat pointed ears with a low position



Left-side clubfoot



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Follow-up results.

Age	Height (cm)	BMI (kg/m²)	THERAPY		Cortisol level (nmol/L)
			Replacement, hydrocortisone (mg/m²/daily)	Symptomatic	
1 year	78 (+ 1 SDS)	17 (P=50%)	10	Ursodeoxy-cholic acid (courses)	634,2
2 year	90 (+ 1,2 SDS)	16,6 (50<P<75%)	9,2	Without any drugs	378,9

Summary.

The time before identification the diagnosis IAD lasted 7 months for our patient. Hyperbilirubinemia began progressively to resolve a month after replacement therapy introduction. It is corresponded with the data of other researchers [6]. We have shown that elevated liver enzymes take longer to normalize than cholestasis itself, although the time of normalization may be quite variable [8,9]. The transaminase level in our patient was decreased to normal range only after 1 year of adequate dosage of hydrocortisone. The presenting symptom in neonates is frequently hypoglycemia [7,8,9,10]. We registered severe hypoglycemia with the hypoglycemic coma development in our patient. The permanent glucose infusion wasn't effective before the hydrocortisone therapy hadn't been given. We diagnosed Q28X mutation of TPIT gene, which was described earlier as a nonsens mutation resulting in a stop codon [2,3]. In our case the mutation Q28X TPIT gene associated with early and severe onset of the disease [2,3,4].

We suggest in the case of severe hypoglycemia associated with the neonatal liver dysfunction the diagnosis of IAD should be considered.

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