

Cholestatic hepatopathy and hypoglycaemic seizures as primary manifestation of hypocortisolism in infancy

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Introduction

Cholestatic hepatopathy is a rare but serious threat to neonates and young infants, predisposing for severe and rapidly progressive hepatic injury.

Although there are numerous studies, little is known about the susceptibility of the newborn's liver metabolism and the etiology is thought to be multifactorial.

An immediate and accurate diagnosis is essential for optimal therapeutic management, but often difficult to make because of the limitations of diagnostic procedures in neonates and the wide range of possible etiologies. These include anatomic abnormalities, obstructive cholestasis, viral or bacterial infections, metabolic and genetic disorders, toxicity, total parenteral nutrition or endocrine disorders.

One rare endocrinological cause is hypocortisolism, which may be of primary / adrenal (e.g. agenesis, adrenogenital syndrome) or secondary / tertiary origin (e.g. panhypopituitarism).

Patient 1

- Seven-week-old term-born female infant, consanguineous Turkish parents
- **Elevated liver enzymes, fatigue and history of hypoglycaemic seizures led to referral from a Turkish hospital to our centre**
- Adrenal glands were small and rudimentary in sonographic evaluation
- **For initial lab evaluation see table 1**
- Genetic testing showed a **homozygous mutation in Melanocortin 2 receptor-associated protein (MRAP)**, causing familial glucocorticoid deficiency (FGD) by congenital ACTH resistance because of defective receptor signalling.
- **Under hydrocortisone replacement therapy liver enzymes and bilirubin normalized completely within 4 months.**

Patient 2

- A two-day-old female full-term newborn, non-consanguineous German parents
- **Presentation in our emergency room due to hypoglycaemic seizures, treated with intravenous glucose**
- **Labwork and screening for metabolic diseases were normal. At this time only GGT was elevated to 300 U/l (< 181).**
- She was discharged 13 days later with stable blood sugar levels and the diagnosis "transient hypoglycaemia"
- **Two weeks later she presented again: Labwork see table 1**
- **Liver biopsy showed giant cell hepatitis with distinct cholestasis, confluent hepato cellular necrosis, portal and septal fibrosis and siderosis of stellate macrophages and hepatocytes.**
- **Cranial magnetic resonance imaging (MRI) showed septo-optic pituitary dysplasia as cause for central hypocortisolism.**
- **Hydrocortisone replacement therapy was started. Bilirubin and liver enzymes normalized within 5 months following that.**
- Later she showed signs of growth hormone deficiency and was started with growth hormone therapy at 18 months of age.

Table 1	Patient 1	Patient 2
Total bilirubin	11.34 mg / dl (< 1)	12.92 mg/dl (< 1)
Conjugated bilirubin	9.6 mg / dl (< 0.4)	5.35 mg / dl (< 0.4)
Aspartate transaminase (AST / GOT)	884 U / l (< 79)	797 U / l (< 79)
Alanine transaminase (ALT / GPT)	215 U / l (< 48)	278 U / l (< 48)
Alkaline phosphatase (AP)	1043 U / l (< 412)	604 (< 412)
Ferritin	5365 µg / l (< 327)	8131µg / l (< 327)
Gamma-glutamyl transferase (GGT)	norm.	norm.
Electrolytes	Norm.	norm.
Adrenocorticotrophic hormone (ACTH)	2000 pg / ml (< 63)	CRH-Stimulation: basal: 6.3 pg / ml 30 min: 10.3 pg / ml
Cortisol basal	not detectable	0.3 µg/dl (6 - 19)

Discussion

In our presented cases the low levels of cortisol were the underlying cause of liver insufficiency and hypoglycaemia. The initiation of hydrocortisone replacement therapy resolved in decreasing liver enzymes. At least in one case where a liver biopsy was performed histology showed a severe hepatitis which explained the cholestasis and high levels of liver enzymes. Highly elevated ferritin can be misleading.

Finding and confirming the diagnosis of septo-optic pituitary dysplasia respectively adrenal insufficiency helped us managing the condition, which led to complete normalization of liver disease in our patients.

Therefore, we strongly emphasize to analyse cortisol and ACTH levels early in the work-up of cholestasis in newborns and infants in particular in association with severe hypoglycaemia.

For this purpose we propose following algorithm for general evaluation which does not meet full accuracy:

