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Neonatal panhypopituitarism with hypoglycemia, edema, inspiratory stridor and cholestasis

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Introduction

Congenital hypopituitarism is a rare disorder characterized by impairment of pituitary hormone secretion with a variety of non-specific clinical symptoms, including recurrent episodes of hypoglycemia, failure to thrive, temperature instability and prolonged jaundice. Frequently a malformation or underdevelopement of the pituitary gland is found.

Case report

History

First child of healthy, non consanguineous parents.
Family history without distinctive features.
29 year old 1st gravida, 1st para, pregnancy without complications, oGTT within the normal range, maternal HbA1c 5,1%.
Delivery at 42+0 weeks of gestation via caesarean section.
Birthweight 3270 g (P16), length 52 cm (P41) APGAR 10/10/10
Referral to newborn intensive care unit at 21 hours of age because of a hypoglycemia of 12 mg/dl.

Physical examination and early clinical course

Vital female newborn with wide cranial sutures and large anterior fontanel, decreased muscle tone, inspiratory stridor and edema.
Within the first week of life repeated episodes of hypoglycemia, persistent poor muscle tone and inspiratory stridor, hypothermia, failure to gain weight and poor feeding, requiring parenteral nutrition and a gastric tube, and hyperbilirubinemia and cholestasis, requiring therapy with ursodeoxycholic acid.

Diagnostics

Infectious and metabolic diseases were ruled out by clinical and laboratory investigations including normal values for blood count, CRP, blood gases, electrolytes, liver and renal function tests, ketone, ammonia, lactate, amino acids, urine organic acids. Blood cultures and TORCH negative. Newborn screening negative (twice).

Hormonal evaluation revealed subnormal fT3 and fT4 and inappropriately low TSH characteristic of central hypothyrodism (Table1).

Critical sample on day 8 at time of hypoglycemia (Table 1) showed inappropriately low growth hormone (GH) level and inappropriately low cortisol level.

Table 1	Before treatment	Normal range for age	After treatment	Normal range for age
Glucose	33 mg/dl			
fT3	1,69 pg/ml	2,0-5,2	3,97 ng/l	1,61-5,05
fT4	0,28 ng/ml	0,8-3,1	1,31 ng/dl	0,85-1,89
TSH	3,15 µlU/ml	0,43-16,1	0,06 mU/l	0,45-10
Cortisol during hypoglycemia	1,9 ng/ml	7,47-128	214 pmol/l	0-535
Urine Cortisolexcretion	< 2 µg/24 h	2-27		
IGF1	10 ng/ml	28-158	34 ng/ml	28- 272
IGFBP3	< 0,5 µg/ml	0,87-2,52	2,4 µg/ml	0,7-3,6
GH during hypoglycemia	< 0,1 ng/ml	> 7,8		
Prolactin			0,5 µg/l (6 months)	5,3-63,3
FSH			< 1,7 mIU/ml (13 months)	1,7-4,6
Total bilirubin Direct bilirubin	22,3 mg/dl 1,1 mg/dl		1,19 mg/dl 0,24 mg/dl	
γ-GT	748 U/l		150 U/l	16-148

Table 1
Laboratory tests of our patient

Radiologic findings

MRI of the brain (Figure 1)
Empty sella with hypoplastic adenohypophysis and ectopic neurohypophysis

Genetic testing

No mutations in LHX4, HESX1, LHX3, PROP1, POU1F1, OTX2, TSHR, PAX8, NKX2-5, TSHß

Therapy

Hormone replacement therapy was started with Levothyroxine (12µg/kg) on day 9, Hydrocortisone (27 µg/m²BSA) on day 11 and improved muscle tone, stridor and feeding, but the newborn still needed a gastric tube because of poor weight gain. Only after initiation of growth hormone therapy at three weeks of age (0,016 mg/kg/d) weaning of the gastric tube was possible and failure to thrive resolved. The very low dosage of growth hormone was administered via a U100 insulin syringe (Figure 2).

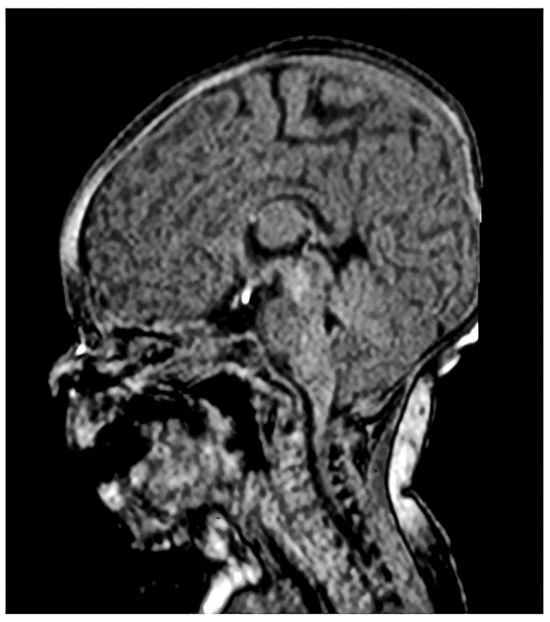

Figure 1
Brain MRI scan of our patient at 3 weeks of age

Figure 2

Discussion

The diagnosis of neonatal panhypopituitarism with deficiency of TSH, ACTH, GH, Prolactin and FSH was established by clinical signs, distinct hormonal values and radiologic findings without the necessity for hormone stimulation tests. In our patient, the early initiation of growth hormone therapy at three weeks of age in addition to levothyroxine and hydrocortisone clearly improved the general condition, feeding and enabled weight gain and growth. Neonatal cholestasis in combined pituitary hormone deficiency (CPHD) is described in the literature[1,2]. Stridor and respiratory distress are not typically seen in neonatal panhypopituitarism. We explained the complete recovery from these symptoms in our patient by improvement of muscle tone, a consequence of hormonal replacement therapy. As in the majority of cases described in the literature, our patient showed no mutation in genes encoding for transcription factors associated with combined pituitary hormone deficiency[3].

Conclusion

Clinical presentation of neonatal hypopituitarism is variable and non-specific and may be mistaken for sepsis or metabolic disease. Recurrent hypoglycemia in combination with hypothermia, poor muscle tone, failure to thrive, edema, cholestasis and respiratory distress should lead to a hormonal evaluation to assure an early diagnosis and management to prevent serious sequelae.

Literature

(1) Choo-Kang et al. Cholestasis and hypoglycemia: manifestations of congenital anterior hypopituitarism J Clin Endocrinol Metab 1996; 81: 2786-2789
(2) Binder et al. The course of neonatal cholestasis in congenital combined pituitary hormone deficiency J Pediatr Endocrinol Metab 2007; 20: 695-701
(3) Giordano M. Genetic causes of isolated and combined pituitary hormone deficiency Best Pract Res Clin Endocrinol Metab 2016 Dec; 30(6) 679-691

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