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Liver dysfunction and hypoglycaemia as presentations of hypopituitarism in a child

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In the presence of hypoglycaemia and liver dysfunction in the neonatal period and/or during the first months of life, a myriad aetiologies should be considered. We report herein the case of a child with refractory hypoglycaemia and severe liver dysfunction, highlighting the importance of a multidisciplinary and rapid investigation to obtain the final diagnosis.

A girl was born by emergent caesarean delivery at 37 weeks, due to a non-reassuring foetal state and maternal fever after a pregnancy complicated by insulin-treated gestational diabetes, de novo maternal hyperthyroidism without detectable thyrotropin (TSH) receptor antibody (TRAb), and intrauterine growth restriction. She was admitted to the Neonatal Intensive Care Unit because of feeding difficulties and hypoglycaemia, needing enteric nutrition by gavage for 48 h. Newborn screening was normal. After discharge, preterm formula was continued with weight evolution in the 3–10th percentile. At 2 months of life, she presented vomiting, jaundice, pale stools, and refusal to feed and was admitted to the local hospital. On physical examination, she presented jaundice and peculiar facies (Fig. 1). Laboratory results were as follows: total bilirubin (TB) — 8.28 mg/dL, direct bilirubin (DB) — 6.76 mg/dL, aspartate aminotransferase (AST) — 194 U/L, alanine aminotransferase (ALT) — 93 U/L, gamma-glutamyl transferase (GGT) — 52 U/L, alkaline phosphatase (ALP) — 671 U/L, and glucose — 59 mg/dL. In the first 48 h, she started with fever, repeated episodes of hypoglycaemia (min. 35 mg/dL, nonketotic), vomiting, worsening clinical status, and persistent abnormal results: AST — 883 U/L, ALT — 266 U/L, TB — 11.5 mg/dL, DB — 6.7 mg/dL, ALP — 678 U/L, GGT — 31 U/L, albumin — 31.7 g/L; activated partial thromboplastin time (APTT) — 66.8 s, partial thromboplastin time (PT) — 26.6 s; C-reactive protein (CRP) — 82.6 mg/L; no electrolyte abnormalities; and alpha-1 antitrypsin normal. She was admitted to the Intensive Care Unit, requiring high doses of glucose (glucose infusion rate max. 11 g/kg/min); fresh frozen plasma was also administered. Abdominal ultrasound showed normal liver, gallbladder without bile duct dilatation, and moderate ascites. Transfontanellar ultrasound revealed hyperechogenicity of basal ganglia/thalamus bilaterally. Due to the severity of the clinical presentation a simultaneous investigation for infectious, metabolic, genetic, and endocrinological causes was started. We observed: decreased insulin-like growth factor (IGF-1) (< 15 ng/mL) and growth hormone (GH) (0.56 ng/mL); adrenocorticotrophic hormone (ACTH) within reference values (15.2 ng/L, N: < 63.3) and low cortisol (4.5 µg/dL, N: 6.2–19.4), both inappropriately normal in

hypoglycaemia; decreased insulin ($< 0.2 \mu\text{U/mL}$, N: 2.6–24.9) and C-peptide (0.28 ng/mL, N: 1.1–4.4); TSH normal (4.23 $\mu\text{UI/ml}$, N: 3.5 ± 2.6), free-T4 low (0.57 ng/dL, N: 1.5 ± 0.47). Rhinovirus was detected in bronchial secretions; the study for hepatotropic virus was negative. Ammonia, lactate, amino acids, acylcarnitines, organics acid, and succinyl acetone were normal or unremarkable. Brain MRI revealed ectopic neurohypophysis and sella turcica without definition, reduced to a thin lamina, with suspected pituitary stalk interruption (Fig. 2). Panhypopituitarism was confirmed; levothyroxine, hydrocortisone, and somatropin were started. No recurrence of hypoglycaemia and progressive normalization of liver function was verified.

Hypoglycaemia and cholestatic jaundice may be the first signs of pituitary hormone deficiency, but the diagnosis of hypopituitarism may be challenging. Clinical presentation is variable, from asymptomatic to a broad spectrum of symptoms, including failure to thrive, hypoglycaemia, jaundice, dysmorphic features, such as midline defects, nystagmus, optic atrophy, and micropenis, or later with short stature and delayed puberty [1, 3]. These symptoms are often assigned in a suspected hepatic or metabolic disease, and the endocrinological study is frequently delayed, with severe consequences including death.¹

In a previous experience with another case referred to our Gastroenterology Unit, severe hypoglycaemia and the signs on transfontanelar ultrasound contributed to the suspicion of an endocrine aetiology. The association between non-infectious hepatitis, hyperbilirubinaemia, cholestasis, and hypopituitarism has been described [3, 4].

Hypoglycaemia, generally serious, can occur in the first days, but less severe episodes may not manifest until a stressful situation occurs [2]. In our case, the possible relationship with rhinovirus infection and fever as a situation that triggered imbalance can be questioned. Hypoglycaemia usually resolves with the replacement of GH and/or cortisol, although it may occur during stressful periods when it is adequate to double the dose of corticosteroid [5].

Hypopituitarism is confirmed by determination of cortisol, ACTH, and GH in hypoglycaemia and other hormones (TSH, T4, prolactin, gonadotropins) under baseline conditions and/or by functional tests; brain MRI is the choice of method for definitive diagnosis. In our case, the normal newborn screening could be a confounding factor, but we must bear in mind that screening for congenital hypothyroidism in Portugal is established by measuring the elevation of TSH in newborns, which does not exist in this situation.

Early treatment is crucial to reduce morbidity and prevent progressive hepatic disease and neurological complications. It is essential to maintain follow-up in a Paediatric Endocrinology consultation.

We emphasize the importance of a high suspicion index for this condition when an infant presents cholestasis, unexplained hepatitis, hypoglycaemia, and other manifestations of pituitary malfunction.

References

1. Cavarzere P, Biban P, Gaudino R, et al. Diagnostic pitfalls in the assessment of congenital hypopituitarism. *J Endocrinol Invest*. 2014; 37(12): 1201–1209, doi: [10.1007/s40618-014-0139-9](https://doi.org/10.1007/s40618-014-0139-9), indexed in Pubmed: [25080869](https://pubmed.ncbi.nlm.nih.gov/25080869/).
2. Braslavsky D, Keselman A, Chiesa A, et al. Diagnóstico de endocrinopatía congénita en neonatos con ictericia prolongada e hipoglucemia. *An Pediatría*. 2012; 76(3): 120–126, doi: [10.1016/j.anpedi.2011.08.011](https://doi.org/10.1016/j.anpedi.2011.08.011).
3. Karnsakul W, Sawathiparnich P, Nimkarn S, et al. Anterior pituitary hormone effects on hepatic functions in infants with congenital hypopituitarism. *Ann Hepatol*. 2007; 6(2): 97–103, indexed in Pubmed: [17519832](https://pubmed.ncbi.nlm.nih.gov/17519832/).
4. Binder G, Martin DD, Kanther I, et al. The course of neonatal cholestasis in congenital combined pituitary hormone deficiency. *J Pediatr Endocrinol Metab*. 2007; 20(6): 695–702, doi: [10.1515/jpem.2007.20.6.695](https://doi.org/10.1515/jpem.2007.20.6.695), indexed in Pubmed: [17663294](https://pubmed.ncbi.nlm.nih.gov/17663294/).
5. Geffner ME. Hypopituitarism in childhood. *Cancer Control*. 2002; 9(3): 212–222, doi: [10.1177/107327480200900304](https://doi.org/10.1177/107327480200900304), indexed in Pubmed: [12060819](https://pubmed.ncbi.nlm.nih.gov/12060819/).

Figure 1. Peculiar facies — high forehead, low-set ears that are slightly rotated, broad nasal bridge, and retrognathism



Figure 1: Peculiar facies - high forehead, low-set ears that are slightly rotated, broad nasal bridge, and retrognathism.

Figure 2. Brain MRI. The arrows point to the sella turcica, reduced to a thin lamina without definition, and suspected pituitary stalk interruption

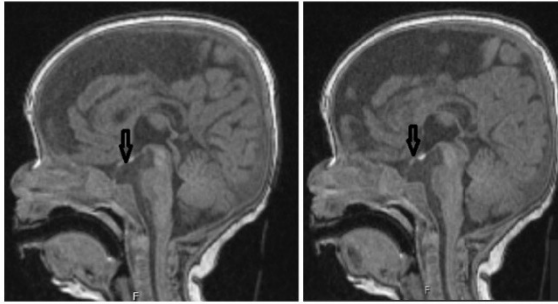


Figure 2: Brain MRI. The arrows point to the sella turcica, reduced to a thin lamina without definition, and suspected pituitary stalk interruption.