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LETTER

Cholestasis With ACTH/Cortisol Deficiencies and Hypopituitarism

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To the Editor,

We read with interest the recent review by Li et al. on gastrointestinal (GI) Involvement in hypopituitarism [1]. This comprehensive review included GI manifestations not only due to deficiency of pituitary hormones but also due to overdosing of hormones used for replacement. Liver dysfunction, including jaundice and cholestasis, is a well-known GI manifestation of panhypopituitarism in both children and adults. In this review, jaundice and cholestasis were briefly mentioned but attributed solely to growth hormone (GH) deficiency without noting the important role of ACTH/cortisol deficiencies in the etiology of liver dysfunction, cholestasis, and jaundice. Another recent paper on congenital hypopituitarism mentions cholestasis in relation to GH deficiency only [2].

The literature provides ample evidence supporting liver dysfunction in subjects with ACTH deficiency. Leblanc et al. reported five patients with neonatal cholestasis, two of whom had ACTH deficiency, and three had cortisol deficiency due to primary adrenal insufficiency [3]. In one infant with panhypopituitarism and in infants with adrenal insufficiency, GH stimulation test results were normal. Thus, cortisol deficiency, whether primary or secondary to ACTH deficiency, appears to be an important etiologic factor contributing to liver dysfunction [3]. This study also quoted 13 patients with hypopituitarism and liver disease, nine of whom had cortisol deficiency.

Cholestatic jaundice is a significant initial manifestation of congenital hypopituitarism. Ellaway et al. reported cholestatic jaundice as a presenting symptom in seven of 20 patients with congenital hypopituitarism. In three of them, cholestasis was proven by biopsy [4]. In a case-cohort study including 16 patients with neonatal pituitary stalk interruption syndrome diagnosed before 1 year of age, 5 of 16 patients had cholestasis. All of them had multiple hypothalamic-pituitary hormone deficiencies. Notably, in comparison to 11 patients without cholestasis, the plasma cortisol levels were markedly decreased only in patients with cholestasis [5].

Wada et al. reported a patient with panhypopituitarism who presented with prolonged neonatal jaundice [6]. At 3 months of age, due to rising bilirubin levels and markedly increased transaminases, liver biopsy was performed, confirming intrahepatic cholestasis. Endocrine evaluation revealed ACTH, thyroid, and GH deficiencies. Hydrocortisone therapy resulted in a rapid decrease in direct bilirubin levels before initiation of GH and levothyroxine therapies. A month after treatment, the patient made a remarkable recovery, as evidenced by normal liver biopsy results and laboratory tests.

Cholestasis also appears in isolated ACTH deficiency [7].

Cholestasis has also been reported in adults with panhypopituitarism [8]. A 25-year-old patient presented with jaundice and elevated transaminase levels without evidence of chronic liver disease. She had congenital hypopituitarism due to pituitary ectopia. Diagnosis of central hypothyroidism with ACTH deficiency was established. Therapy with levothyroxine and hydrocortisone resolved all the clinical and laboratory manifestations within a month.

Our experience also clearly shows how, in undiagnosed patients, congenital hypopituitarism with ACTH/cortisol deficiency can be life-threatening. One of our patients, currently aged 19 years, was a full-term baby born after a cesarean section delivery with a weight of 3140 g. The Apgar score was 4/8 (one/5 min). Shortness of breath and hypotonia were successfully treated with respiratory assistance, restoring normal respirations and tonus quickly. He also required IV fluids due to hypoglycemia (39 mg/dl) and indirect hyperbilirubinemia up to 18 mg/dl, necessitating phototherapy. Laboratory evaluation ruled out infectious and metabolic

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causes. Micropenis was overlooked. He was discharged at the age of 10 days. Subsequently, he was hospitalized twice in another hospital at ages 4 and 5 months for recurrent vomiting. During his first hospitalization, pertinent laboratory data revealed elevated direct bilirubin levels at 1.5 mg/dL (normal range: 0–0.3 mg/dL), along with high liver enzyme values (AST = 142 U/L, ALT = 394 U/L, normal ranges, 0–52 U/L and 0–45 U/L, respectively). TSH was normal (2.5 mLU/L). Further laboratory investigation excluded EBV, HIV, CMV, and hepatitis A, B, and C. Abdominal ultrasound did not reveal any hepatic abnormality. In his second hospitalization, he presented with loss of consciousness, hypoglycemia with a glucose value of 44 mg/dl, and hyponatremia, Na=129 mmol/L (normal 135-145 mmol/L), requiring artificial respiration for 24 h. Abnormal liver function tests persisted (direct bilirubin, 0.7, AST = 144 U/L, ALT = 295 U/L). TSH was normal (3 mIU/L) with borderline-low FT4 = 9 pmol/L (normal 8–18.5 pmol/L). He was discharged after 10 days with a recommendation for frequent feeds and referral to the metabolic disease outpatient clinic.

At 6 months of age, he deteriorated, and he was referred to our hospital in Central Israel for diarrhea, vomiting, and hypoactivity (the family moved from Northern Israel). On admission, he was apathetic and hypotonic. Blood glucose level was very low (43 mg/dl). The medical history and micropenis readily suggested the diagnosis of hypopituitarism. Critical blood samples of GH and cortisol drawn during hypoglycemia, just before IV infusion, did not rise and remained very low (GH = 0.7 μg/l, cortisol=0.6 μg/dl), consistent with the diagnosis. Cortisol failed to increase after the ACTH test (basal cortisol at time 0′ = 1, at 30′ = 8 μg/dL). Hydrocortisone and GH were started on Day 1. In addition, very low FT4 (0.46 ng/dl, normal: 0.8–2.1 ng/dL) with normal TSH established the diagnosis of central hypothyroidism, and levothyroxine was started. The patient's response to therapy was impressive. He became responsive and alert within a few hours, with normal blood glucose and electrolyte levels. The liver function tests normalized in a month (Bil. = 0.15, ALT = 38, AST = 38). At the age of 2 years, due to convulsion attacks not associated with hypoglycemia, sodium valproate was started. The brain MRI at 3 years of age showed a hypoplastic pituitary gland, and the stalk was not visible, consistent with the diagnosis of pituitary stalk interruption syndrome. His gonadotropin levels have always been undetectable, consistent with hypogonadotropic hypogonadism. At 19 years of age, the testicular volume is 3 ml, and he is on testosterone enanthate therapy. His final height is 171 cm.

One of the Authors (AH) also treated a similar case during his fellowship decades ago at the University of Maryland, Division of Pediatric Endocrinology. A 5-month-old girl who had recurrent episodes of hypoglycemia, convulsions, jaundice, and nystagmus, underwent extensive metabolic investigation in Johns Hopkins Hospital Division of Neurology (Prof. Ann B Moser) with no definitive diagnosis. She was referred to our division only at the age of 5 months. Her symptoms suggested panhypopituitarism which was confirmed. MRI findings were consistent with the diagnosis of septo-optic dysplasia. Therapy with hydrocortisone, GH, and levothyroxine resolved her symptoms, and the liver function tests normalized.

In conclusion, we believe that the importance of early diagnosis of cholestasis in ACTH/cortisol deficiencies requires a high index of suspicion, especially in the pediatric population, and should not be ignored. Early diagnosis and appropriate therapy prevent life-threatening consequences of ACTH/cortisol deficiencies and may prevent irreversible liver damage due to chronic cholestatic jaundice and allow normal development.

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References

1. M. Li, L. Song, J. Wang, and C. Zhang, "Unveiling Gastrointestinal Involvement in Hypopituitarism: Clinical Features and Treatment Approaches," *Clinical Endocrinology* 103 (2025): 641–650, https://doi.org/10.1111/cen.70021.

2. J. M. Ladd, A. L. Pyle-Eilola, L. Mamilly, M. Chaudhari, and R. K. Henry, "Clinical Presentation of Congenital Hypopituitarism: Lessons From a Large Academic Centre," *Clinical Endocrinology* 102, no. 6 (2025): 649–655, https://doi.org/10.1111/cen.15213.

3. A. Leblanc, M. Odièvre, M. Hadchouel, D. Gendrel, J. L. Chaussain, and R. Rappaport, "Neonatal Cholestasis and Hypoglycemia." Possible Role of Cortisol Deficiency," *Journal of Pediatrics* 99, no. 4 (1981): 577–580.

4. C. J. Ellaway, M. Silink, C. T. Cowell, et al., "Cholestatic Jaundice and Congenital Hypopituitarism," *Journal of Paediatrics and Child Health* 31 (1995): 51–53, https://doi.org/10.1111/j.1440-1754.1995.tb02914.x.

5. F. X. Mauvais, E. Gonzales, A. Davit-spraul, E. Jacquemin, and R. Brauner, "Cholestasis Reveals Severe Cortisol Deficiency in Neonatal Pituitary Stalk Interruption Syndrome," *PLoS One* 11 (2016): e0147750, https://doi.org/10.1371/journal.pone.0147750.

6. K. Wada, H. Kobayashi, A. Moriyama, et al., "A Case of an Infant With Congenital Combined Pituitary Hormone Deficiency and Normalized Liver Histology of Infantile Cholestasis After Hormone Replacement Therapy," *Clinical Pediatric Endocrinology* 26, no. 4 (2017): 251–257.

7. M. Alsaleem, L. Saadeh, A. Misra, and S. Madani, "Neonatal Isolated ACTH Deficiency (IAD): a Potentially Life-Threatening but Treatable Cause of Neonatal Cholestasis," *BMJ Case Reports* (2016): 1–3, https://doi.org/10.1136/bcr-2016-215032.

8. J. Wiese, A. W. El Ghezewi, M. Mohamed, T. Joshi, and W. Frandah, "A Rare Case of Severe Jaundice in a Panhypopituitarism Patient," *Journal of Medical Cases* 14, no. 6 (2023): 204–207, https://doi.org/10.14740/jmc4102.

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