Title

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Journal

Endocrinology, diabetes & metabolism case reports, 2023(2)

ISSN

2052-0573

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Publication Date

2023-05-01

DOI

10.1530/edm-23-0021

Endocrinology, Diabetes & Metabolism CASE REPORTS

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ID: 23-0021; May 2023
DOI: 10.1530/EDM-23-0021

Abnormal thyroid function: an unusual presentation of pituitary stalk interruption syndrome

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Summary

An 11-year-old girl with past medical history of septic shock and multi-organ failure at age 5 presented to her primary care doctor with concern for pallor of the lips. Laboratory studies demonstrated low free thyroxine (T4) and normal thyroid-stimulating hormone (TSH). A referral to endocrinology was made where the patient was evaluated, and laboratory evaluation was repeated. The patient was asymptomatic and clinically euthyroid with a height consistent with her mid-parental height and was in mid- to late-puberty. The repeated laboratory evaluation demonstrated a pattern suggestive of primary hypothyroidism with low free T4 and an elevated TSH. However, the magnitude of elevation of TSH was less than expected, given the degree of lowering of free T4; therefore, central hypothyroidism was considered. Workup was initiated, and laboratory studies and MRI imaging confirmed an underlying diagnosis of panhypopituitarism in the setting of pituitary stalk interruption syndrome.

Learning points

- Pituitary stalk interruption syndrome is a rare but important cause of panhypopituitarism.
- Central hypothyroidism should be suspected in patients with low free thyroxine with an inappropriate degree of elevation of thyroid-stimulating hormone.
- Workup of central hypothyroidism should include multi-pituitary hormone assessment, and, if evident, MRI imaging should be done.
- Adrenal insufficiency should be suspected in a hypotensive, critically ill patient who is failing to improve on standard-of-care therapy.

Background

Here, we report a unique case of pituitary stalk interruption syndrome (PSIS) initially presenting with hypothyroidism. Initial abnormal thyroid tests were unclear regarding the nature of the dysfunction. Follow-up testing demonstrated elevated thyroid-stimulating hormone (TSH) and low free thyroxine (T4), a pattern suggestive of primary hypothyroidism. Past medical history was significant for a prolonged pediatric intensive care unit (PICU) stay with poor response to intervention, suggesting possible adrenal insufficiency. Hypothyroidism occurring in the context of adrenal insufficiency is suggestive of panhypopituitarism, which was confirmed by subsequent laboratory studies. MRI of the brain with pituitary cuts showed an interrupted stalk and a diminutive anterior pituitary, findings consistent with PSIS.

PSIS is a common cause of panhypopituitarism but more typically presents with either hypoglycemia in

ID: 23-0021; May 2023
DOI: 10.1530/EDM-23-0021

infancy or growth failure in childhood. Hypothyroidism is a rare but not unreported presentation of this condition.

The challenge in making a diagnosis of panhypopituitarism in this patient was the lack of signs of other pituitary hormone deficiencies. In retrospect, however, her history of a prolonged PICU stay with poor response to medical intervention is suggestive of unremittent adrenal crisis.

Case presentation

An 11-year-old girl presented to her primary care physician with concern for pallor of the lips. Regarding this complaint, the episodes were of variable duration (minutes to days) and were not associated with an obvious trigger, fever, illness, dizziness, or fatigue. Laboratory studies were obtained by her primary care physician and demonstrated low free T4 (0.63 ng/dL (normal range (NR): 0.71–1.85 ng/dL)) and normal TSH (3.47 uIU/mL (NR: 0.35–5.00 μIU/mL)). A referral was placed to endocrinology.

Review of the patient's birth history demonstrated an uncomplicated full-term gestation with delivery by emergency cesarean section secondary to fetal distress and maternal fever of 104°F. Delivery was followed by a 2-week neonatal intensive care unit stay to rule out sepsis. She received phototherapy for hyperbilirubinemia. Family history is negative for sudden death. Her developmental history is unremarkable. Her past medical history is notable for several urinary tract infections (UTIs) prior to 1 year of age and a prolonged hospitalization at age 5 for septic shock and multi-organ dysfunction.

At age 5, she presented to an emergency department with nausea, vomiting, diarrhea, fever, and abdominal pain. Initial vitals demonstrated hypotension, tachycardia, tachypnea, and fever. She was admitted for presumed gastroenteritis and intravenous fluid resuscitation and to rule out sepsis. Cultures were drawn, and empiric ceftriaxone (Rocephin) was provided. In the emergency department, she became unresponsive and was intubated. Laboratory studies demonstrated hypoglycemia. She received multiple dextrose 25% boluses without significant improvement and was transferred to another facility for a higher level of care. Over her subsequent 5-week PICU stay, she received broad-spectrum antibiotics, intravenous fluids, and pressor support. Despite intensive inotropic and fluid support, hypotension persisted. She developed acute renal failure requiring dialysis over the subsequent 3 weeks. High-dose intravenous glucocorticoids were initiated to address a general worsening in her clinical course despite maximal supportive care. Following initiation of glucocorticoids, clinical findings improved.

At age 6, she was hospitalized for observation in the setting of a febrile illness associated with a sore throat and a dry cough. Temperature was 102.5°F (39.2°C). Blood pressure was 114/69 mm Hg. During the hospitalization, her temperature spiked to 105°F (40.6°C). Blood, urine, throat, and stool cultures were obtained, and she was started on empiric antibiotic therapy. Over the next 5 years, there were no hospitalizations or health concerns until the onset of episodic lip pallor.

On initial endocrinology evaluation, she reports dry skin but denies cold intolerance, constipation, fatigue, weakness, or recent change in weight. On examinaton, she was well appearing. Her weight was at the 70th percentile, and her height was at the 60th percentile, with growth records showing a plateau over the previous 6 months suggesting she was at final height. Mid-parental height is at the 10th percentile. Examination was remarkable for mildly delayed deep tendon reflexes and a Tanner stage of B3PH1. The thyroid gland was not enlarged, and no proximal muscle weakness was evident on examination.

Laboratory studies were obtained and again showed a low free T4, but TSH, previously normal, was now mildly elevated (Table 1).

Investigation

Upon initial presentation to endocrinology, laboratory studies displayed low free T4 and slightly elevated TSH, a pattern suggestive of primary hypothyroidism. However, the magnitude of the elevation of TSH was less than expected for the degree of free T4 lowering, making central hypothyroidism an important consideration in the

Table 1 Pituitary laboratory evaluations upon presentation to endocrinology.

Laboratory study	Reference range	Patient's values
Free T4 (ng/dL)	0.71–1.85	0.49
TSH (μIU/mL)	0.35–5.00	9.38
IGF-binding protein-3 (mg/L)	2.4–8.4	2.2
IGF-1 ECL (ng/mL)	152–593	33
Estradiol (pg/mL)	≤65	<2
Cortisol (μg/dL)		
8:00 h	3.7–19.4	<1.0
30 min post ACTH (1 μg)	>18	1.3
Prolactin serum (ng/dL)	2.6–18.0	24.7

ACTH, adrenocorticotropic hormone; ECL, electrochemiluminescence; IGF, insulin-like growth factor; T4, thyroxine; TSH, thyroid-stimulating hormone.

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differential diagnosis (1). The findings of her earlier episode of septic shock suggested a possible manifestation of adrenal insufficiency. The occurrence of these two deficiencies raise suspicion for possible panhypopituitarism. Thyroid autoantibodies and pituitary laboratory studies were requested.

Results demonstrated non-elevated titers of thyroid peroxidase and thyroglobulin antibodies. Pituitary laboratory studies were abnormal (Table 1). Early morning cortisol was undetectable, and ultrasensitive estradiol and insulin-like growth factor-1 (IGF-1) were also low. Bone age was not skeletally mature (12–13 years at a chronologic age of 11.5/12 years (S.D. ±11.94)) with a predicted adult height of 62.8 inches. Adrenocorticotropic hormone (ACTH) simulation testing was completed. Following 1 µg intravenous cosyntropin, serum cortisol was 1.3 µg/dL at 30 min. A brain MRI with pituitary cuts was performed, demonstrating an ectopic posterior pituitary gland and a severely hypoplastic and anteriorly displaced pituitary stalk (Fig. 1). A diagnosis of central hypothyroidism in the setting of panhypopituitarism due to PSIS was made.

Treatment

In the patient presented in this case, hydrocortisone was started with a total dose of 9.25 mg/m²/day (7.5 mg in the morning and 5.0 mg at bedtime). Twenty-four hours later, thyroid hormone replacement was initiated (50 mcg). Other pituitary insufficiencies were addressed according to standard of care (estrogen provided via oral contraceptive and growth hormone).

Outcome and follow-up

The patient in this case has since had no significant illnesses or emergency visits. She responded well to growth hormone treatment with an initial annualized growth velocity of 7.2 cm/year in the first 3 months of treatment and a first-year height gain of 6.8 cm. Her final height is 5'7". Of interest, she subsequently developed hypertension, likely due to acute tubular injury in the setting of her history of hypotensive crisis, which is now well-managed with low-dose lisinopril.

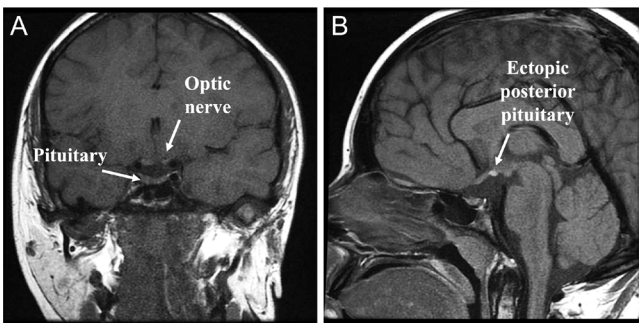

Figure 1
Brain MRI with pituitary cuts.

Discussion

Pituitary stalk interruption is a rare pituitary malformation and well-recognized cause of hypopituitarism (2). It is generally characterized by the classic triad on MRI of thin or absent pituitary stalk, anterior pituitary hypoplasia, and ectopic posterior pituitary (2). Genetically heterogenous, its clinical presentation is highly variable in time of onset as well as number and severity of deficiencies (3). The underlying mechanism involved in PSIS ontogenesis has yet to be elucidated. Although perinatal injury was initially suspected, the majority of patients with PSIS have no history of perinatal trauma, rendering this hypothesis unlikely (2). In about 5% of patients with PSIS, mutations in genes encoding transcription factors involved in early pituitary development (*HESX1, LHX4, OTX2, SOX3*, and *PROKR2*) have been identified (2, 3). Syndromic causes of PSIS, including septo-optic dysplasia, are more often implicated in this group, highlighting the importance of distinguishing isolated forms of PSIS from more complex disease (4, 5). Patients with PSIS are typically initially referred either for hypoglycemia during the neonatal period or more commonly for growth retardation during childhood. Out of a group of 67 patients with PSIS, 10 (15%) were referred for neonatal hypoglycemia, while 47 (70%) were referred for growth retardation (2).

Combined anterior pituitary hormone deficiency is the hallmark of PSIS, with deficiencies in posterior pituitary hormones very rarely identified (3). Typically, PSIS is not initially identified as the cause of hormone deficiency. Screening is important to complete for any patient diagnosed with a hypothalamic pituitary hormone deficiency. Because these deficiencies frequently develop over the life span of the patient, lifelong screening is necessary. Although our patient's findings of thyroid, adrenal, gonadotropin, and growth hormone deficiencies are typical for this condition, her presentation is not. Central hypothyroidism is a rare, though not unreported, initial manifestation of PSIS (6). Most often, it is identified following the initial laboratory evaluation. For example, in one study of 89 patients with PSIS, 71 (80%) demonstrated central hypothyroidism on comprehensive laboratory assessment (7). It is important to note that TSH levels can be

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low, normal, or high in PSIS patients (7). Mechanistically, this may be attributed to alterations in post-translational modifications that alter both the biological activity and serum half-life of the TSH molecule (8).

The undetectable morning cortisol in this patient was suggestive of adrenal deficiency. In the context of central hypothyroidism, this finding was suggestive of central adrenal insufficiency. A low peak cortisol (1.3 mcg/dL) on 1 µg ACTH stimulation testing confirmed this diagnosis. Growth hormone stimulation testing was not performed prior to replacement; low IGF-1 and growth arrest in the context of two other central hypothalamic pituitary deficiencies and an interrupted stalk confirmed the diagnosis of GH deficiency in this case.

Atypically, our patient had an appropriate height for her genetic potential; thus, GH deficiency was not initially suspected. Likewise, her appropriate pubertal development for age was not suggestive of gonadotropin deficiency. Laboratory studies, however, demonstrated both growth hormone and gonadotropin deficiencies. On careful review of her growth record, a slowing in growth velocity from 5 cm/year to 3.6 cm/year was evident over the 6 months prior to her presentation to endocrinology, suggesting a relatively recent onset of her growth disturbance. We therefore suspect that both growth hormone and gonadotropin deficiencies became clinically evident during this time. The lack of bone age advancement lends further support to a more recent development of gonadotropin deficiency.

Of interest, it is possible that the first manifestation of hypopituitarism was septic shock due to adrenal crisis at age 5. Although a formal diagnosis of adrenal insufficiency was not made, her findings of hypotension, hemodynamic instability despite aggressive fluid resuscitation, and subsequent response to high-dose glucocorticoids favor a diagnosis of adrenal insufficiency. The diagnosis of adrenal insufficiency is challenging in the setting of critical illness, as features suggestive of corticosteroid insufficiency such as nausea, vomiting, diarrhea, abdominal pain, and delirium are non-specific (9). A diagnosis of adrenal insufficiency should be considered in a critically ill patient with hemodynamic instability and clinical deterioration despite aggressive fluid resuscitation and empirical treatment (9).

Lastly, we note that the patient in this case had at least one significant febrile illness following the severe sepsis event at age 5; however, it was not associated with clinical decompensation. Although the reason for the lack of decompensation is unclear, she was aggressively hydrated and did not became hypotensive. Symptomatic adrenal insufficiency, which typically manifests in the setting of hypovolemia, may not have been provoked in this second febrile event.

Treatment of central hypopituitarism comprises hormonal replacement. During initial treatment, cortisol should be replaced prior to thyroid hormone replacement. Induction of cortisol metabolism by thyroid hormone is a recognized cause of acute adrenal insufficiency in those at risk (10). Stress dosing for hydrocortisone should be reviewed with patients and families, and Solu-Cortef (hydrocortisone) should be provided for emergencies (11).

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Author contribution statement
EAS and SAP wrote the manuscript. MEP and MRV reviewed and edited the manuscript. SAP was the physician responsible for the care of this patient.

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Received 5 February 2023
Accepted 24 April 2023
Version of Record Published 15 May 2023