A Rare Case of Autoimmune Polyglandular Syndrome Type 2 in a Child With Persistent Fatigue

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Abstract

Adrenal insufficiency is a rare, potentially life-threatening condition whose diagnosis requires a high index of suspicion. Adrenal insufficiency may be primary, secondary, or tertiary with varied etiologies. Primary insufficiency may be part of a cluster of autoimmune diseases, referred to as autoimmune polyglandular syndrome(s) (APS). We describe a case of a 15-year-old male who presents to a local emergency department complaining of fatigue, fever, abdominal pain, nausea, and vomiting for a few days with a preceding viral illness. The patient was hyponatremic and hyperkalemic with skin hyperpigmentation, raising concern for adrenal insufficiency. Laboratory workup confirmed autoimmune primary adrenal insufficiency, with subsequent laboratory studies revealing autoimmune thyroiditis and celiac disease. Concomitant Addison’s and Hashimoto’s diseases led to a diagnosis of APS type 2. The patient was started on steroid replacement with rapid clinical improvement.

Keywords

autoimmune polyglandular syndrome, schmidt’s syndrome, addison’s disease, hashimoto’s disease, adrenal insufficiency

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APS type 1, or autoimmune polyglandular, candidiasis, ectodermal dystrophy (APECED), is an autosomal recessive disorder related to mutations in the autoimmune regulator (AIRE) gene. Often seen in groups of people indigenous to Finland and Sardinia, APS type 1 is notable by adrenocortical insufficiency, hypoparathyroidism, candidiasis, dental enamel hypoplasia, and nail dystrophy.\(^1,6\) Diabetes, pernicious anemia, hypothyroidism, and hypogonadism are examples of other autoimmune disorders that may be associated with APS type 1.\(^1,7\) APS type 1 generally manifests in infancy, between ages 3 and 5 years, or in early adolescence; as such, APS type 1 is also known as juvenile autoimmune poly-endocrinopathy.\(^5\) APS type 1 is considered very rare, with an incidence of less than 1:100 000/year.\(^5\)

APS type 2, also known as Schmidt’s or Carpenter’s syndrome, is a cluster of autoimmune diseases characterized by autoimmune adrenal insufficiency and thyroid disease with or without type 1 diabetes.\(^1,5,7\) Autoimmune diseases that may be associated include hypogonadism, hypopituitarism, immunoglobulin A deficiency, myasthenia gravis, celiac disease, and vitiligo.\(^1,5,7\) APS type 2 is more prevalent than APS type 1, often associated with multiple autoimmune conditions, and is more common in women than men.\(^1,3\) There is a peak incidence between 20 and 60 years of life, with the third or fourth decades being the most common.\(^3,5,6\) In contrast to APS type 1, which has an association with a defect in the AIRE gene, APS type 2 is associated with genetic abnormalities of class II HLA alleles.\(^3,6,7\) APS type 2 has a male-to-female ratio of 1:3 and is relatively common with an incidence of 1-2:10 000/year.\(^5\) Given predilection to concomitant diseases, regular surveillance is crucial to screen for other conditions.\(^7\)

Clinical signs of adrenal insufficiency include hypoglycemia, hyperpigmentation, hyponatremia, hyperkalemia, and hypotension.\(^3\) Symptoms are nonspecific, including fatigue, weakness, nausea, vomiting, abdominal pain, anorexia, myalgias, and salt craving.\(^3\) As such, diagnosis begins with a high index of suspicion. Laboratory studies consistent with primary insufficiency include elevated early morning ACTH, elevated plasma renin activity, low aldosterone, hypernatremia, and hyperkalemia.\(^1\) Whereas ACTH is elevated in primary insufficiency, ACTH is low or normal in secondary and tertiary insufficiency.\(^1\) An early morning cortisol level with a level <3 µg/dL is suggestive of adrenal insufficiency.\(^3\) The “gold standard” cosyntropin (synthetic ACTH) stimulation test is often used for diagnosis, wherein synthetic ACTH is administered intravenously, with cortisol level checked 30 and 60 minutes after administration.\(^1,3\) Cortisol levels <14 µg/dL are positive.\(^1,3\) Diagnosis of specific APS syndromes is achieved by screening for each individual disease process suspected.\(^5\)

Ethical Approval and Informed Consent
This is a case report requiring only chart review and literature review, without any direct intervention or harm to the patient referred to in this case, and as such, informed consent and ethical approval was not needed.

Case Report
A 15-year-old male presented to a local hospital with fatigue, fever, abdominal pain, nausea, and vomiting for a few days prior to presentation. He reported a severe viral illness roughly 6 weeks prior to his presentation. Laboratory studies in the emergency department were significant for hyponatremia and an elevated thyroid-stimulating hormone (TSH). The remaining results, including complete blood count, hepatic panel, lactic acid, lipase, infectious mono screen, and creatine kinase level, were all normal. A chest radiograph and abdominal ultrasound were both unremarkable, and he was admitted.

Further history revealed recent gait instability as well as a change in skin color for a few weeks preceding presentation. Physical examination was significant for generalized pallor and a dusky gray appearance, generalized abdominal tenderness, and right-sided CVA tenderness. Because hyponatremia in the context of nausea, vomiting, fatigue, and skin color changes raised suspicion for Addison’s disease, a comprehensive metabolic panel and early morning cortisol were ordered.

The next day he had documented pigmentation of the lower lip and both nipples. Further laboratory evaluation revealed positive thyroid peroxidase antibody, elevated ACTH, cortisol levels nonresponsive to cosyntropin, and persistent hyponatremia and hyperkalemia (see the Appendix for pertinent laboratory values.). Laboratory data were consistent with primary adrenal insufficiency and Hashimoto’s thyroiditis. Hydrocortisone and fludrocortisone were initiated for glucocorticoid and mineralocorticoid replacement, respectively. Because adrenal dysfunction and acute illness can elevate the TSH, the putative Hashimoto’s disease was not treated. Thyroid hormone replacement was also held to prevent adrenal crisis from stimulation of the patient’s metabolism with thyroid hormone. A respiratory virus panel was positive for coronavirus, which might have precipitated the acute illness. Direct renin level was elevated, and the aldosterone level was low. By day 3, his electrolyte abnormalities and clinical status improved significantly, so he was discharged.
At outpatient follow-up, very long chain fatty acids were normal, eliminating adrenoleukodystrophy as a possible etiology for the adrenal insufficiency. The diabetes autoimmune test group was normal, but the TSH remained elevated with a normal T4, confirming autoimmune hypothyroidism. Follicle-stimulating hormone and luteinizing hormone were normal, eliminating concomitant hypogonadism, but tissue transglutaminase immunoglobulin A was elevated, raising suspicion for celiac disease. Levothyroxine was started and he was referred for intestinal biopsy to confirm celiac disease.

**Discussion**

The diagnosis of adrenal insufficiency requires a high index of suspicion. In our case, a 15-year-old male presented with nonspecific gastrointestinal complaints, fatigue, and skin color changes with hyponatremia and hyperkalemia. Our investigation confirmed adrenal insufficiency and ultimately led to a diagnosis of APS type 2. Adrenal insufficiency and APS type 2 are rare diagnoses in the pediatric and adolescent population, although both disorders have been described in children.4,8-11

Other investigators have emphasized the wide ranging clinical and laboratory findings associated with adrenal insufficiency, the importance of screening for adrenoleukodystrophy, the importance of alterations in glucose levels, and insulin requirements in type 1 diabetes as it relates to surveillance, and determining etiology and screening for concomitant disorders.4,8-11

Although APS type 2 has been reported,12-15 there are few reports of pediatric patients.14,15 There is a need for continued surveillance over a lifetime, as there is potential for development of other autoimmune disorders even decades after the initial diagnosis.

In a study of 18 pediatric patients with primary adrenal insufficiency, hypotension was the presenting sign in 13, hyperpigmentation in 12, hyponatremia in 16, and hyperkalemia in 9. Of 15 who underwent a cosyntropin stimulation test, all failed.16 Our patient did not have hypotension, yet he had hyperpigmentation, hyponatremia, hyperkalemia, and failed a cosyntropin stimulation test.

The Endocrine Society recently published a clinical practice guideline that details recommendations for both diagnosis and treatment of primary adrenal insufficiency.2 The cosyntropin stimulation test is recommended for establishing the diagnosis of adrenal insufficiency, together with measurement of plasma ACTH, renin, and aldosterone levels.2 Treatment includes replacement of both glucocorticoid and mineralocorticoid hormones with hydrocortisone and fludrocortisone, respectively.2

Numerous are the etiologies of primary adrenal insufficiency, including autoimmune (isolated or part of APS), adrenal injury, infectious, congenital adrenal hyperplasia, drug-induced, or metabolic disorders such as mitochondrial diseases or adrenoleukodystrophy.2 Thus, effective treatment must be directed toward the underlying cause.

When initiating hormone therapy for treatment of an APS with both adrenal insufficiency and thyroid disease, it is important to be aware that thyroid hormone therapy can initially cause an adrenal crisis with stimulation of increased metabolism of corticosteroids by the hepatic system. Thus, thyroid hormone replacement is usually postponed until appropriate adrenal hormone replacement has occurred.3

**Conclusion**

Adrenal insufficiency is a rare diagnosis in pediatric patients and timely diagnosis is crucial to prevent life-threatening complications. Clinicians must maintain a high index of suspicion when there are any signs, symptoms, or laboratory findings suggesting adrenal pathology. Once the diagnosis is made, it is imperative to determine etiology. The presence of adrenal antibodies confirms an autoimmune cause. Autoimmune adrenal disease may be isolated or associated with a cluster of other autoimmune diseases referred to as APS. It is important to screen for other autoimmune diseases in patients with confirmed autoimmune adrenal insufficiency to adequately treat these patients and avoid complications and sequela.
Appendix

Laboratory Values.

|                      | Day 1 | Day 2 AM | Day 2 PM | Day 3 | Follow-up | Reference Range               |
|----------------------|-------|----------|----------|-------|-----------|-------------------------------|
| Sodium               | 127   | 130      | 125      | 135   | 142       | 135-145 mmol/L                |
| Potassium            | 4.9   | 5.6      | 5.4      | 5.8   | 4.8       | 3.5-5.2 mmol/L                |
| Glucose              | 92    | 96       | 100      | 144   | 89        | 60-99 mg/dL                   |
| TSH                  | 8.54  |          |          |       | 6.13      | 0.40-4.50 μIU/mL              |
| FT4                  | 1.3   |          |          |       | 1.1       | 0.8-1.80 ng/dL                |
| Cortisol             |       | 1.9      |          |       |           | 4.0-27.0 μg/dL                |
| Adrenal antibodies   |       |          | 1:4 titer|       |           | <1:2 titer                    |
| ACTH                 |       |          | >1250    |       |           | 5-46 pg/mL                    |
| Aldosterone          |       |          | <3.0     |       |           | <23.3 ng/dL                   |
| Direct renin         |       |          | 1944     |       | 12.4      | 3.1-57.1 pg/mL                |
| Cosyntropin test: cortisol at 30 minutes |       |          | 2.1      |       |           | 4.0-27.0 μg/dL                |
| Cosyntropin test: cortisol at 60 minutes |       |          | 2        |       |           | 4.0-27.0 μg/dL                |
| Thyroglobulin antibody |     |          | <20      |       |           | 0.0-20.0 IU/mL                |
| Thyroid peroxidase antibody |       |          | 64       |       |           | 0.0-35 IU/mL                  |
| FSH                  |       |          |          |       | 3.2       | 1.6-11.0 mIU/mL               |
| LH                   |       |          |          |       | 3.8       | 1.3-7.2 mIU/mL                |

Abbreviations: TSH, thyroid-stimulating hormone; FT4, free thyroxine; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Author Contributions

Ryan Kenneth Smith, D.O., was involved in the initial evaluation, diagnosis and management of the patient referenced in this case report at Beaumont Children’s Hospital in Royal Oak, MI, USA, after which time Ryan performed an extensive literature review on pediatric autoimmune polyglandular syndrome prior to the composition of this case report. Once the literature review was complete, Ryan incorporated the key information into this article, ultimately composing the entire case report itself. Peter M. Gerrits served as a mentor and expert reviewer for this case report, offering his expertise as a pediatric endocrinologist in accurate diagnosis of this patient as well as ensuring all pertinent information regarding the patient’s case and background information on APS were included.

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