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Acute mental status change as the presenting feature of adrenal insufficiency in a patient with autoimmune polyglandular syndrome type II and stroke

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Abstract

Primary adrenal insufficiency (AI) in children usually presents with non-specific symptoms such as fatigue, nausea, vomiting, and anorexia. Here, we report an unusual case of a 15 year old girl who presented with acute mental status change and was ultimately diagnosed with AI due to autoimmune polyglandular syndrome type II (APS2). Central nervous system imaging revealed a cerebral infarction. To our knowledge, the constellation of APS2, stroke and acute mental status change has not been previously reported. We review the literature with regard to the presentation of AI as well as the association between vasculitis and APS2.

Keywords

acute mental status change; adrenal insufficiency stroke; autoimmune polyglandular syndrome type 2

Background

Autoimmune polyglandular syndrome type II (APS2) is the occurrence of primary adrenal insufficiency (AI) in association with autoimmune thyroid disease and/or type 1 diabetes mellitus. Autoimmune thyroid disease occurs in 70%–90% of patients while type 1 diabetes

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mellitus occurs in 20%–50% (1). These patients are also more likely to develop other autoimmune diseases, both of an endocrine and non-endocrine origin.

AI is usually the first manifestation of APS2 and the diagnosis is most often made in adulthood. Presenting features are typically non-specific and include anorexia and fatigue. Rarely, autoimmune vasculitis has been reported in association with autoimmune endocrinopathies.

Here, we describe a 15 year old girl who presented with acute mental status change and was diagnosed with AI due to APS2 as well as stroke. This unusual case expands the spectrum of presentation of AI in children as well as potential co-morbid conditions in the setting of APS2.

Case presentation

Our patient is a 15 year old female who presented to her primary care physician with dizziness and vomiting that rapidly progressed to urinary incontinence, inability to walk, and increasing confusion and combativeness. She was brought by paramedics to the hospital. She was initially very bellicose, requiring ziprasidone. She was admitted to the pediatric intensive care unit due to acute mental status change. Her blood pressure was noted to be consistently low and sodium on routine chemistry was 129 mmol/L (normal 135–145) with a potassium of 4.1 mmol/L (normal 3.5–5.5). Toxicology was consulted for possible ingestion and recommended a random cortisol which was $<0.4 \mu\text{g/dL}$ (normal 4–20 $\mu\text{g/dL}$). The endocrinology service was then consulted, and an adrenocorticotrophic hormone (ACTH) stimulation test with 250 μg of cosyntropin was performed. This revealed a peak cortisol of 0.3 $\mu\text{g/dL}$ (normal 20) consistent with a diagnosis of primary AI.

Recent past medical history included a diagnosis of primary hypothyroidism one month prior to presentation as well as depression diagnosed two days earlier for which she was prescribed fluoxetine. She had no other known medical problems. Family history was significant for hypothyroidism in her mother. A review of symptoms included being withdrawn, a decreased appetite, a thirty pound weight loss, suicidal thoughts, a two month history of fatigue, alopecia, irregular menses, frequent early morning headaches, and early morning vomiting. On exam, she was obtunded, was without goiter, and had skin hyperpigmentation. Neurologic examination revealed mild facial asymmetry with right hemiparesis of her arm, face, and leg.

The patient was started on stress doses of hydrocortisone with significant improvement in her mental status over the next few days. A magnetic resonance imaging study showed areas of restricted diffusion consistent with acute to subacute infarction involving branches of the left middle cerebral artery (Figure 1). Computed tomography angiography of the head and neck were normal. An electroencephalogram (EEG) showed normal sleep architecture that was displaced to the right, likely indicative of the left hemispheric abnormalities, but no seizure activity. Due to lack of wakefulness during the EEG, encephalopathy was not able to be graded. A spinal tap was considered to rule out encephalitis; however, this was not performed due to the rapidity of her clinical improvement. An echocardiogram was also

obtained and was normal. Further evaluation included an ACTH of 1995 pg/mL (normal 10–60), anti-thyroid peroxidase level of 5475 IU/mL (normal 0–9), thyroglobulin antibody titer of 263 IU/mL (normal <116), and 21-hydroxylase antibody titer of 269 units/mL (normal <1). The patient was diagnosed with autoimmune polyglandular syndrome type II (APS2). Additional results included anti-neutrophil cytoplasmic antibodies (ANCA) of <1:20 (normal), an antiphospholipid antibody panel, angiotensin-converting enzyme, double-stranded deoxyribonucleic acid antibody and Smith antibody, all of which were also normal. The patient spent seven days in rehabilitation prior to discharge. At the time of discharge, she was on prednisone 12 mg/m²/day hydrocortisone equivalent, and levothyroxine 75 µg by mouth once daily.

Discussion

The primary manifestations of APS2 are AI, primary hypothyroidism, diabetes mellitus and primary hypogonadism, with 100% of affected individuals developing AI. Although cognitive symptoms have rarely been reported in association with AI (2, 3), to our knowledge the constellation of APS2, stroke, and acute mental status change has not previously been described.

There is limited information about the presentation of primary AI in childhood. One review of 18 pediatric patients found that hyponatremia was the most frequent presenting sign, occurring in 89%, followed by hypotension in 72%, hyperpigmentation in 67% and hyperkalemia in 50% (4). Another series of 16 cases of primary AI in childhood reported a wide variation in presenting complaints that included weakness, hyperpigmentation, poor school performance, recurrent abdominal pain and nausea (5). Notably, mental status change was not reported in any of these patients.

Given the multiple autoimmune diseases in our patient, an autoimmune origin for the stroke was sought. Associations between autoimmune vasculitis and both isolated Hashimoto thyroiditis and APS have rarely been reported (6–8). Evaluation for diseases known to be associated with vasculitis, such as Sjogrens syndrome, sarcoidosis and systemic lupus erythematosus, was negative in our patient. While this does not exclude vasculitis, it makes it less likely. Another potential autoimmune origin for her stroke is the presence of endothelial cell inhibitory autoantibodies, although there is no commercially available way to test for them at this time. Interestingly, there is a described association between autoimmune diabetes mellitus and recurrent small-vessel stroke in a patient found to be positive for endothelial cell inhibitory autoantibodies (9). These immunoglobulin G autoantibodies have been shown to cause stress fibre formation and endothelial cell apoptosis in mice.

The only previously reported combination of APS2 and stroke was in a patient with a mitochondrial gene mutation (10). The mutation in the linker region of DNA polymerase gamma 1 gene (POLG1) was found in twin sisters. Both have a diagnosis of APS 2 and progressed to neurologic sequelae with twin A having seizures and choreiform movements while twin B had multiple infarctions. In both of these patients, the neurologic symptoms manifested several years after their diagnosis with APS2. While our patient is different as

she presented with neurologic symptoms at the time of diagnosis with APS2, a mitochondrial gene mutation has not been ruled out.

The exact temporal relationship between our patient's cerebral infarction and her symptomatology are unknown, and her clinical course was not typical for the acute neurological abnormalities seen following an ischemic stroke. However, the recent diagnosis and treatment of hypothyroidism was likely a precipitating factor since initiation of levothyroxine in the setting of untreated AI is known to precipitate an adrenal crisis (11, 12). The proposed mechanism for this is the higher clearance rate of cortisol and an increased cortisol requirement due to the increased metabolic rate caused by the restoration of euthyroidism (12).

Conclusion

In summary, this unique case expands the spectrum of presenting features of AI to include acute mental status change. However, whether our patient's entire presentation can be attributed to APS2 is unclear. Given the time course between cerebral infarctions and MRI findings, it is highly unlikely that our patient's stroke caused her cognitive deterioration. Although the relationship between her stroke and APS2 is speculative, the reported association between autoimmune disease and vasculitis suggests autoimmunity as a common theme. Additional studies elucidating the immune dysfunction in patients with APS2 would be helpful.

Consent

Written informed consent was obtained from the guardian and assent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Figure 1.
T2 (A) and diffusion weighted (B) imaging showing areas of infarction in the left hemisphere.