Teaching Case

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Neurological Symptom in a Case of Adrenal Insufficiency

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ABSTRACT

Around 50% of patients with Addison disease (AD) have other autoimmune disorders. Neuropsychiatric symptoms may be presenting features of an Addisonian crisis or may be presented in patients with adrenoleukodystrophy (ALD) or Hashimoto encephalopathy; that these disorders are associated with primary adrenal insufficiency (AI). Nearly 5% of individuals with autoimmune AD develop pernicious anemia. X-linked ALD (X-ALD) is an inherited neurodegenerative disorder; a frequent but under-recognized cause of primary adrenocortical insufficiency. The classic picture of Vitamin B12 deficiency is subacute combined degeneration of the dorsal (posterior) and lateral spinal columns. The neuropathy is symmetrical, affects the legs more than the arms. It begins with paresthesia and ataxia and can progress to severe weakness, spasticity, paraplegia, even fecal, and urinary incontinence. We report a case of autoimmune AI who had presented with some neurologic symptoms. The challenging point was differentiating between X-ALD and other neurological syndromes that have an association with AI.

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Introduction

The clinical presentation of adrenal insufficiency (AI) is depending on whether the onset of the disease is acute or chronic. A specific sign of chronic AI is hyperpigmentation, especially in under pressure sites. In autoimmune AI, the first zone that affects is zona glomeruza, which cause the first symptoms of low aldosterone concentration (1). Other signs and symptoms are fatigue, weight

loss, hyperkalemia, and hypoglycemia. AI can present with neurologic symptoms in 15% of patients which includes neuropsychiatric symptoms, myopathy, flexion contractures of the legs, and rarely seizures (2).

Moreover, Addison disease (AD) can be a part of other disorders which have neurologic symptoms. Autoimmune AD can present in autoimmune polyendocrine syndrome (APS) Type 1 (13%), APS Type 2 (41%), APS Type 4 (5%), and isolated AD (41%) (3). Type 1 APS is associated with mucocutaneous candidiasis, AD, and hypoparathyroidism, and Type 2 APS is consisted of Type 1 diabetes mellitus, thyroid disease, and AD (4). In APS Type 1 AI appears after mucocutaneous candidiasis, with increasing prevalence with age progression. Neurologic manifestations in these patients could be due to autoantigens (5).

X-linked adrenoleukodystrophy (X-ALD) affects the nervous system white matter and the adrenal cortex which mainly has three phenotypes including childhood vertebral form, adrenomyeloneuropathy (AMN), and AD only (6). Cerebral ALD is associated with AI in at least 50% of cases, however, it may be the only clinical manifestation of X-ALD in up to 10% of cases (7). X-ALD is a genetic disorder with a mutation in Xq28, associated with AI and neurological symptoms due to long chain fatty acid accumulation (8). Diagnosis is mostly by clinical presentation, brain magnetic resonance imaging (MRI) and plasma level of very long chain fatty acids (VLCFA) (6).

Around 50% of patients with AD have other autoimmune disorders such as thyroid disease, Type 1 diabetes mellitus, premature ovarian failure, celiac disease, and autoimmune hepatitis (9). These diseases could have neurologic symptoms too. Moreover, electrolyte disturbances related to AD could cause muscle weakness and neurologic symptoms. Nervousness and lethargy that occurs in AD are related to hyponatremia and acidosis. Moreover, hyperkalemia which seen in AD can cause muscle weakness, however profound muscle weakness is rare (10).

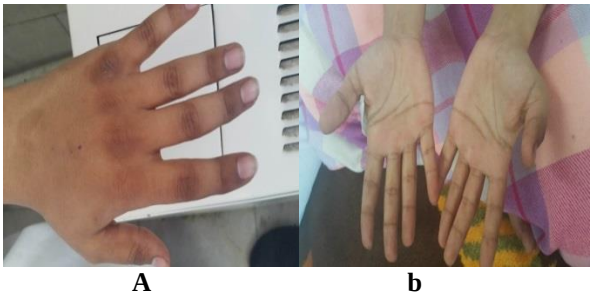
This article presents an interesting case with AD that was presented with neurologic symptoms.

Case Report

A 19-year-old boy, known case of AI from the age of 10; came to our hospital with lower limb spastic paraparesis. Moreover, he was unable to walk. The patient had a history of hospital admission because of severe fatigue and loss of consciousness 2 months before his admission in our hospital. That time he had paresthesia in his lower limbs and slight memorial loss. But his brain MRI and electromyography were normal there, cerebral spinal fluid (CSF) examination was a normal and oligoclonal band of CSF was negative; also acetylcholine receptor antibody was negative, so Guillain-Barre disease had been ruled out.

In our hospital at 1st day of his admission he was a little lethargic, he had slurred speech, his pupils were normal size and isocoric and reactive to the light. He had bilateral partial ptosis. His gag reflex was normal with no tongue deviation. Fundoscopic examination was normal. He had no nystagmus. The upper extremity forces were 5/5, but lower extremity forces was 3/5 and symmetrical. Upper limbs deep tendon reflex (DTR) were 2+ and lower limbs DTR were 3+. Plantar reflex was upward and Babinski presented. In the sensorial examination, he had impaired vibration and position sensations, and he had spastic paraparesis.

In general examination he had hyperpigmentation of axillary, nipples, knuckles, and his extensors (Figure 1).



A **b**

Figure 1. (a and b) Our patient's hands

He had no Kayser-Fleischer ring in an eye examination.

The lab tests summarized in tables 1 and 2.

Table 1. Lab tests

Na	138 meq/l
K	3.9 meq/l
FBS	107 mg/dl
Urea	32 mg/dl
Cr	0.9 mg/dl
Ca	9.3 mg/dl
Mg	2 meq/l
Ph	4.9 meq/l
AST	20 U/l
ALT	11 U/l
ALP	250 U/l
Bil	0.8 mg/dl
PT	14 seconds
PTT	25 seconds
INR	1.21
Albumin	4.7 g/dl
LDH	1114 U/l
WBC	2.89 /µl
Hg	9.8 g/dl
MCV	93 fl
Retic count	0.5%
Fe	117 µg/dl
Ferritin	183 ng/ml

WBC: White blood cell, FBS: Fasting blood sugar, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, PTT: Partial thromboplastin time, LDH: Layered double hydroxide

Brain and spinal cord MRI showed an abnormal signal in dorsal cord in thoracic level suggestive of subacute combined degeneration of spinal cord (Figure 2).

With these findings, we considered reversible leukoencephalopathy due to B12 deficiency and treatment with folic acid 5 mg daily and Vitamin B12 1 mg IM daily had begun. And after 2 weeks his white blood cell (WBC) was 65700/µl, his hemoglobin was 11.2, and platelet count was 263,000/µl. After 2 months his WBC becomes 5500/µl, Hg becomes 15.4 g/dl and platelet 225,000/µl.

VLCFA, phytanic and pristanic acids were in normal range.no evidence of a peroxisomal disease was detected in lab tests.

Discussion

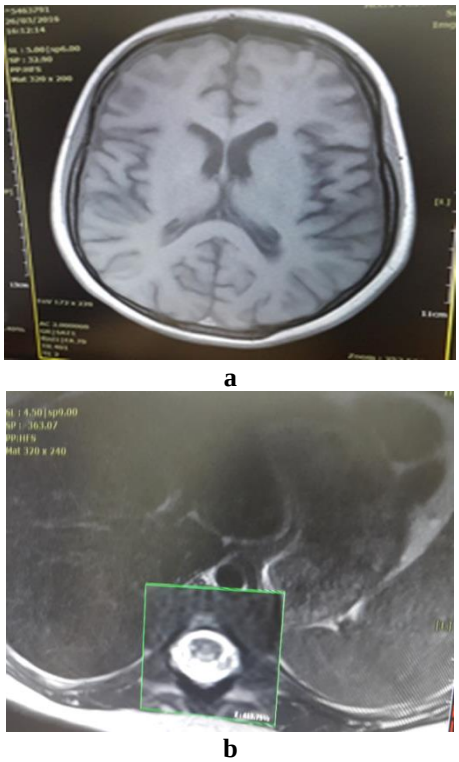
AD can have neurologic symptoms in 15% of cases.

Table 2. Lab tests

Folic acid	16.1 ng/ml
Vitamin B 12	< 125 pg/ml
Urine cu/24 hours	154 µg/24 hours
HBS Ag	Negative
Wright test	Negative
Ceruloplasmine	33 mg/dl
ANA	2.6 u/ml
Anti-ds DNA	24.9 IU/ml
HCV Ab	Negative
Coombs wright test	Negative
Anti TPO	12.8 IU/ml
Testosterone	4.6 ng/ml
LH	3.8 Miu/ml
HIV Ab	Negative
2ME wright test	Negative
FSH	14 MIU/ml
Anti TTG Ab IgA	< 3
Anti TTG Ab IgG	< 3
HTLV1, 2 Ab	Negative

HBS: Hepatitis B virus surface, HTLV1: Human T-lymphotropic virus, TTG: Tissue transglutaminase, IgA: Immunoglobulin A, IgG: immunoglobulin G, TPO: Thyroid peroxidase, ANA: Anti-nuclear antibody, FSH: Follicle stimulating hormone

Moreover, neurologic symptoms in these patients could be due to other coexisted diseases including ALD especially in young men with AI.



a

b

Figure 2. (a and b) Brain and spinal cord magnetic resonance imaging

ALD is a peroxisomal X-linked disorder which has three major phenotypes including classic ALD, AMN, and AD (11). Fluid-attenuated inversion recovery MRI in X-ALD shows symmetric confluent hyperintense white matter lesion in the posterior cerebral hemisphere, and in T1, symmetric linear enhancement (12), however, MRI is normal in AMN (11). Neurologic manifestations of X-ALD range from leukoencephalopathy in the first decade to spastic paraparesis or psychiatric symptoms in later life. However, the delay between sign and symptoms of AI to neurologic symptoms could be as long as 3 decades (13). AMN usually manifests at the late twenties with spastic paraparesis and attention deficit disorders. In our patient, because of being a young male with AD, X-ALD definitely should be ruled out, especially because of his neurological symptoms. However, his brain MRI and VLCFA levels were inconsistent with this diagnosis.

Due to patient's neurologic symptoms which were started from lower extremities, the Guillain-Barre syndrome was one of the differential diagnoses. However, brisk DTR and normal CSF ruled out this diagnosis (14). Another diagnosis of neurologic symptoms in a patient with autoimmune disease is Wilson syndrome. Wilson disease has some neurologic symptoms, classically flapping tremor and dysarthria. Some features of Parkinson disease, brisk DTR and abnormal behavior could also be present. However, paresthesia and paralysis are unlikely (15). Our patient's liver function tests were normal, and he did not have any abnormal behavior or Parkinsonism. 24 hours urine copper and ceruloplasmin were in normal range.

As we mentioned earlier, AD could be associated with other autoimmune disorders in 50% of cases. One of the most prominent related autoimmune diseases is pernicious anemia. Pernicious anemia is an autoimmune disorder with atrophy of gastric body and fundus with destroying gastric parietal cells. Pernicious anemia may be presented with paresthesia of lower and upper extremity, which could progress to distal weakness specially in lower extremity as in our case (16), mostly due to involvement of dorsal column, lateral corticospinal and spinothalamic tract (17). Psychosis and memory loss could also be evident in pernicious anemia due to corpus callosum involvement, which may cause encephalopathic signs (16, 18). MRI findings of patients with Vitamin B12 deficiency showed linear T2 hyperintensity in posterior column of cervical cord (inverted V sign appearance) and bilateral nodular T2 hyperintensity in thoracic cord region (16, 19). In this case, MRI revealed abnormal signal in dorsal thoracic root, consistent with Vitamin B12 deficiency, which also rapidly responded to the treatment. Moreover, as mentioned in a single previous article, in coexisting of AD and pernicious anemia, normal mean corpuscular volume may be due to the chronic disease anemia (4).

Conflict of Interests

Authors have no conflict of interests.

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