

Uncommon Cause of Acute Adrenal Failure

Akut Sürrenal Yetersizliğinin Seyrek Rastlanan Bir Nedeni

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Abstract

Adrenomyeloneuropathy is a rare X-linked inherited disorder of peroxisomes characterized by accumulation of very-long-chain fatty acids (VLCFA) in the central and peripheral nervous system, adrenal glands and testes, leading to dysfunction of these organs and systems (1). Here, we report a case of adrenomyeloneuropathy presenting initially as acute adrenal crisis, which progressed rapidly within one year to variant neurological manifestations, dementia, sensory, motor and psycho-intellectual dysfunction, and generalized spasticity. *Türk Jem 2010; 14: 103-5*

Key words: Adrenomyeloneuropathy, acute adrenal failure, long-chain fatty acids, VLCFA

Özet

Adrenomyelonöropati santral ve periferik sinir sistemi, adrenal korteks ve testislerde çok uzun zincirli yağ asitlerinin (VLCFA) birikimi ile karakterize ve bu organların işlev bozukluğuna yol açan, X e bağlı geçiş gösteren genetik bir hastalıktır (1). Bu çalışmada, başlangıçta akut adrenal yetmezlik şeklinde ortaya çıkan, bir yıl zarfında çeşitli nörolojik belirtiler, demans, motor, sensoryal ve entelektüel fonksiyonlarda bozukluk ve genel spastisite şeklindeki semptomlarla çok hızlı bir gelişim gösteren bir adrenomyelonöropati olgusu sunulmuştur. *Türk Jem 2010; 14: 103-5*

Anahtar kelimeler: Adrenomyelonöropati, akut sürrenal yetersizliği, uzun zincirli yağ asitleri, VLCFA

Introduction

The common causes of adrenal failure in adult patients in Saudi Arabia are either autoimmune destruction of the adrenal glands or tuberculosis. However, other causes are occasionally seen. This case report describes an adult onset of adrenomyeloneuropathy (AMN) due to a single gene mutation. The patient presented with acute adrenal crisis and subsequently developed neurological disease. The purpose of this report is to highlight the difficulties in diagnosing adult-onset adrenomyeloneuropathy (1).

Case Report

A previously asymptomatic 29-year-old Saudi male patient, a product of non-consanguineous marriage, presented to the emergency room with a history of dizziness for four days, and abdominal pain and diarrhea for three days. He was acutely unwell with a Glasgow Coma Score of 7/15, central cyanosis and

unrecordable blood pressure. Routine laboratory investigations including hemogram, blood sugar, liver and renal function tests were normal. His morning 800 hr serum cortisol was 6.4 µg/dl (normal: 5-25 µg/dl); plasma adrenocorticotrophic hormone (ACTH) was 7579 pg/ml (normal: <46.00). The diagnosis of acute adrenal crisis secondary to upper respiratory tract infection was made and later, confirmed by a defective rise in the cortisol level with ACTH stimulation test. Testosterone was 3.4 (normal: 0.28-11.1 ng/mL), luteinizing hormone (LH)-17.7 (normal: 1.7-8.6 mIU/mL), and follicle-stimulating hormone (FSH) was 27.7 (NR 1.5-12.4 mIU/mL). An autoimmune origin of Addison's disease was excluded by negative adrenal antibodies. Tuberculosis as a cause of adrenal failure was excluded due to the presence of atrophic adrenal glands and absent adrenal calcification on abdominal computed tomography (CT) and negative tuberculin skin test. The patient was admitted to the intensive care unit (ICU) at King Abdulaziz Medical City in Jeddah, and made a full recovery within 24 hours.

Fluids, hydrocortisone and antibiotics are used in the management of acute adrenal crisis. Our patient was also treated with replacement therapy with hydrocortisone and fludrocortisone.

Six months post-treatment, the patient presented with complaints of calf muscle pain and weakness, exacerbated by exercise. These symptoms progressively worsened and neurological assessment revealed a spastic diplegia associated with reduced sensation to vibration, light touch and pinprick. The neuropathic pain increased and the patient developed myoclonus. He became wheelchair-bound with an indwelling urinary catheter and subsequently developed features of a dementia of frontal lobe type. There was no history of any similar disease in the family.

Vitamin B12 and folate levels were normal. The Venereal Disease Research Laboratory (VDRL) test for syphilis was negative.

Electrocardiogram and chest X-ray were normal. Cerebrospinal fluid examination showed no oligoclonal bands and magnetic resonance imaging of the spine was normal. Nerve conduction studies revealed a demyelinating motor neuropathy.

Transverse FLAIR MRI series (progression of white-matter hyperintensity within one year) showed incipient demyelination predominantly in the left hemisphere with relative sparing of the U fibers Fig (1).

The diagnosis of AMN was confirmed by raised circulating concentrations of very-long-chain fatty acids (VLCFA) detected by mass spectroscopy at the National Guard laboratory hospital. Molecular genetic analysis was performed. Leukocyte DNA was

extracted by standard methods. SSCP analysis of each of the exons of the adrenoleukodystrophy (ALD) gene suggested the presence of a gene mutation at Xq28 in our patient.

The treatment of our patient included a comprehensive physiotherapy program for the neurological disturbances and hormone replacement therapy for the adrenal insufficiency. Dietary restriction of VLCFA and Lorenzo's oil were not applied in our patient because of noncompliance from his family.

Discussion

The findings of primary adrenocortical failure together with mild spastic paraparesis, ataxia, and an elevated plasma level of VLCFA established the diagnosis of AMN. AMN is a rare X-linked recessive disorder. A variant, adrenoleukodystrophy (ALD), was first described in 1923, and both forms may occur in one family (2). AMN is a disorder due to a deficiency of peroxisomal VLCFA Co-A synthesis and results in accumulation of VLCFAs in the brain and adrenal glands leading to their dysfunction. AMN usually presents in the third and fourth decades and is characterized primarily by involvement of long ascending and descending tracts of the spinal cord and peripheral neuropathy due to demyelination, which leads to spastic quadri- or paraparesis and urinary dysfunction (3). Several studies have shown that up to 35% of patients with presumed idiopathic adrenal insufficiency have elevated VLCFA levels and experience AMN (3,4,5). Early identification may allow the opportunity for prompt interventions to delay the subsequent onset of neurological symptoms. Males with primary adrenal insufficiency should be evaluated for underlying ALD or AMN. In addition, males and females presenting with an unknown progressive neurological disorder involving the brain or the spinal cord should be examined for ALD. Measurement of plasma VLCFA levels is the initial screening test of choice. The abnormal gene is located in the Xq28 region. It consists of approximately 26 kilobases of DNA and encodes an mRNA of 4.3 kb and a protein of 745 amino acids. Over 500 mutations have been identified. Of these, 59% are missense mutations, 23%-frame shifts, 10%-nonsense mutations, 5%-in-frame deletions-insertions, and 4% are large deletions (2). The hypoadrenalism in AMN can be sufficiently treated with corticosteroids as in Addison's disease; however, the correction of the hypoadrenal state does not change the progressive course of neurological symptoms.

This case had some classical features: male gender, age at presentation- third decade, brain demyelination, and peripheral neuropathy due to demyelination, leading to spastic quadri- or paraparesis. However, rare features included no spinal cord involvement and no family history of males with spinal cord disease or AMN (since this disease is X-linked disorder), though 5% may occur by de novo mutation (7).

Clinical or subclinical hypogonadism is rarely associated with ALD and it has been reported that testicular deficiency occurs more often in association with long-standing neurological abnormalities in pubertal boys. In our patient, testosterone level was normal, while LH and FSH concentrations were slightly elevated, indicating subclinical primary hypogonadism (8). Treatment of a patient with X-ALD poses a great challenge to both the physician and the patient's family. The management program needs cooperation

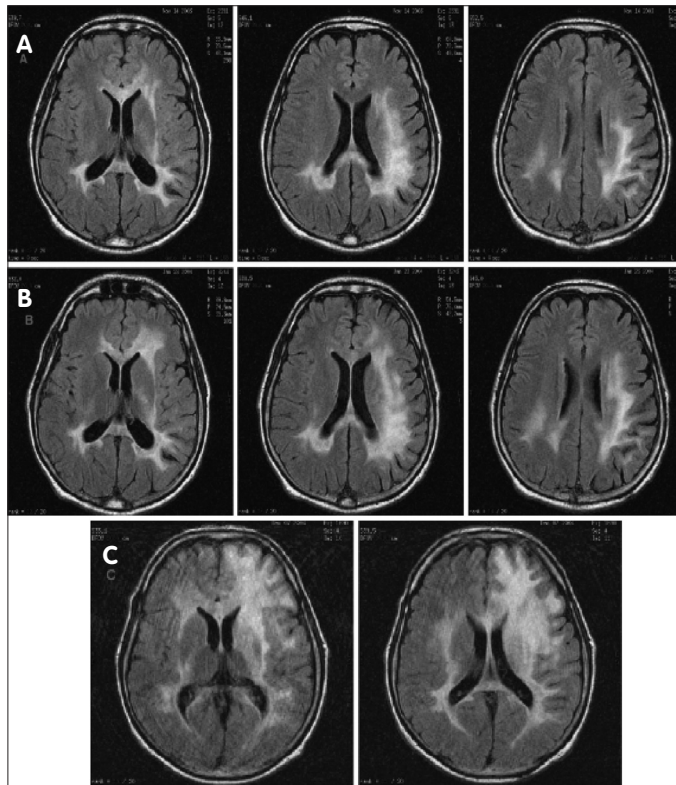


Figure 1. A. Transverse FLAIR MRI series (progression of white-matter hyperintensity within one year) showed incipient demyelination predominantly in the left hemisphere with relative sparing of the U fibers. B. 6 months later. C. 12 months later confluent hyperintensive lesion representing severe demyelination including the U fibers

between the family, physician, visiting nurses, dietitian, school authorities, and counselors. In a study (9), a diet with Lorenzo's oil, a mixture of 4:1 of GTO/GTE-glyceryl trioleate (GTO) and glyceryl trierucate (GTE), normalized or at least reduced to 50% the baseline plasma C26 level in more than 70% of patients. However, it did not alter the rate of the progression of the disease once overt neurological symptoms developed. The dietary restriction of VLCFA and Lorenzo's oil were not applied in our patient because of non-cooperative caregivers.

Bone marrow transplantation (BMT) causes a substantial reduction of plasma VLCFAs level. In spite of these encouraging results, the neurological problems continue to progress.

Since inflammatory/immune changes appear to be of central importance in the pathogenesis of the demyelinating process, several therapeutic approaches have been tried to modify this mechanism (10).

Intravenous immunoglobulin was reported to be helpful in some patients, but without clear benefit in others (11). Pentoxifylline, a methylxanthine inhibiting the activity of tumor necrosis factor α (TNF α), an important component in the X-ALD inflammatory response, has been recently used in the treatment of X-ALD. Diet low in VLCFAs and Lorenzo's oil were tried in our patient.

The recent isolation of the X-ALD gene raises the hope of gene therapy in the future. At present, genetic counseling for the immediate and extended family members who may be at risk is a fundamental part of the management plan and its importance cannot be overemphasized (12).

Several reports have described this disease originating from Saudi Arabia. The centre for Arab Genomic Studies documented the occurrence of X-ALD in Saudi Arabia (13). Al-Essa et al. (2000) conducted a retrospective study to evaluate the data of 10 patients from Saudi Arabia with X-linked ALD regarding the clinical, biochemical, neuroradiological, and neurophysiological findings (14).

Conclusions

AMN should be considered in the differential diagnosis in male patients who present with adrenal failure and particularly in those of Saudi Arabian descent.

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