

Adrenoleukodystrophy: Two Case Reports and a Review of the Literature

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X-linked adren oleukodystrophy (ALD) is an inherited disease characterized by progressive neurologic dysfunction, occasionally associated with adrenal insufficiency. Widely varying phenotypes of the disorder range from the rapidly progressive childhood cerebral form to the slowly progressive adult onset ALD. We present two cases of adult onset ALD and the clinical presentation, the diagnostic and therapeutic options for the disorder.

Key words : Adrenoleukodystrophy, adrenal insufficiency

Introduction

X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder characterized by the accumulation of saturated very long chain fatty acids (VLCFA) in plasma, and various tissues, central nervous system demyelination, and adrenocortical insufficiency (1). The adult onset form of ALD shows a wide range of phenotypic variability, ranging from pure adrenomyeloneuropathy (AMN), with neurologic signs that are confined to the spinal cord and peripheral nerves, to forms with variable cerebral involvement (2). Herein we describe two patients with adult onset ALD with atypical clinical and laboratory features to illustrate the wide clinical variability of this condition.

Case report 1

A 30-year-old man presented with a two year history of gradually progressive trouble walking, unsteady gait, generalized weakness and fatigue.

Over the last few months, his gait had deteriorated further and he needed assistance in walking. He

had progressive slurred speech and problems with erection. He had no hearing, urinary, bowel or sensory symptoms. There was no history of seizures, alcohol or substance abuse, meningitis or head trauma. He was divorced a year ago and socially he interacted aggressively. Family history revealed that his mother also had trouble walking. His medications comprised fluoxetine, thioridazine and alprazolam.

On examination, the height was 187 cm, the weight was 70 kg, the pulse was 80/min, and the blood pressure was 100/70 mmHg. He was alert and fully oriented. His speech was dysarthric. His skin was normal without any pigmentation, he couldnot walk unaided. The cranial nerves' examination and muscle strength in the upper extremity were normal. Sensation to pinprick, light touch and proprioception were intact. He had moderate spastic paraparesis. Lower extremity deep tendon reflexes were increased with ankle clonus and bilateral babinsky signs.

Complete blood count, electrolytes, liver and renal function tests, urine analysis, chest X-ray and electrocardiogram were normal. Spine and brain MRI were normal. ACTH was 200 pg/ml (N: 10-60 pg/ml), basal cortisol was 4.3 ug/dl (N: 6-30 ug/dl), DHEAS was 240 ug/dl (N: 80-560 ug/dl), free testosterone was 3.27 pg/ml (N: 8.69-54.69 pg/ml) After 250 ug intravenous synacthen stimulation test, first hour cortisol was 3.2 ug/dl. Because the

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patient did not give consent, LHRH test could not be performed.

Fasting plasma VLCFA assay revealed the following: C22: 63.3 $\mu\text{mol/l}$ (N: <34.3 $\mu\text{mol/l}$), C24: 90.2 $\mu\text{mol/l}$ (N: <61.4 $\mu\text{mol/l}$), C26: 2.87 $\mu\text{mol/l}$ (N: <0.83 $\mu\text{mol/l}$) (Table 1).

Table 1. Laboratory data of the patients.

	Patient 1	Patient 2
ACTH (N: 10-60 pg/ml)	200	75
Basal cortisol (N: 6-30 $\mu\text{g/ml}$)	4.3	14.1
Synacthen stimulation	3.2*	13.7**
Free testosterone (N: 8.69-54.69 pg/ml)	3.27	14.3
VLCFA		
C22 (N: <34.3 $\mu\text{mol/l}$)	63.3	46.3
C24 (N: <61.4 $\mu\text{mol/l}$)	90.2	81.9
C26 (N: <0.83 $\mu\text{mol/l}$)	2.87	2.77

* First hour cortisol value after 250 μg intravenous synacthen

** Fourth hour cortisol value after 1 mg intramuscular synacthen

Case Report 2

A 27-year-old man first experienced trouble walking four years ago. His gait deteriorated last year and since then he has needed assistance in walking. He had no hearing, urinary, bowel or sensory symptoms. He had no erectile dysfunction. He was a nonsmoker and there was no history of alcohol or substance abuse. Family history revealed that he had a healthy mother, father, two sisters and two brothers but his elder sister's 6-year-old son had a diagnosis of adrenoleukodystrophy.

On examination, the height was 170 cm, the weight was 70 kg, the pulse was 90/min, the blood pressure was 130/85 mmHg. He was alert and fully oriented. His skin was normal, there was a fairly general increase in mucous membrane and palmar creases pigmentation. Muscle strength was normal and deep tendon reflexes were intact in the upper extremity. Sensation to pinprick, light touch and proprioception were intact. He had moderate spastic paraparesis. Lower extremity deep tendon reflexes were increased with ankle clonus and bilateral babinsky signs.

Complete blood count, electrolytes, liver and renal function tests, urine analysis, chest X-ray and electrocardiogram were normal. Spine and brain MRI were normal. Electroneuromyogram (EMG) showed segmental demyelination. Muscle and sural nerve

biopsies were normal. ACTH was 75 pg/ml (N: 10-60 pg/ml), basal cortisol was 14.1 $\mu\text{g/dl}$ (N: 6-30 $\mu\text{g/dl}$), free testosterone was 14.3 pg/ml (N: 8.69-54.69 pg/ml). After 1 mg intramuscular synacthen stimulation test, 4th hour cortisol was 13.7 $\mu\text{g/dl}$. Basal LH was 3.79 mIU/ml and basal FSH was 5.09 mIU/ml, and LHRH test results were all in normal limits.

Fasting plasma VLCFA assay revealed the following: C22: 46.3 $\mu\text{mol/l}$ (N: <34.3 $\mu\text{mol/l}$), C24: 81.9 $\mu\text{mol/l}$ (N: <61.4 $\mu\text{mol/l}$), C26: 2.77 $\mu\text{mol/l}$ (N: <0.83 $\mu\text{mol/l}$), C24/C22: 1.77 (N: <1.39), C26/C22: 0.06 (N: <0.023) (Table 1).

Discussion

The clinical presentation and physical examination of the patients were supportive for adult onset ALD, and the diagnosis of the disorder was confirmed by the abnormally high levels of VLCFA in the plasma. While raised plasma VLCFA levels can be seen in Zellweger syndrome or childhood X-ALD, the history and examination did not support this. Because of the raised plasma concentrations of ACTH and inadequate cortisol increases after ACTH stimulation, prednisolone 7.5 mg p.o. daily in two divided doses were started for both of the patients.

X-linked ALD, the most common inherited peroxisomal disorder is characterized by abnormal accumulation of saturated VLCFAs in plasma, brain white matter, testis, adrenal cortex and cultured skin fibroblasts (2). The first case, a seven year old boy with a bronzed skin, behavioural abnormalities and spasticity of the lower limbs was reported by Siemerling and Creutzfeldt in 1923 (3). Adrenomyeloneuropathy (AMN), a more indolent phenotypic variant that has its onset in adulthood, was first reported in 1976 (4). The X-ALD locus was mapped to Xq28 (5), and the gene predisposing for X-ALD was identified in 1993 (6).

Elevated VLCFA levels in X-ALD cells are associated with reduced ability to degrade these fatty acids by peroxisomal α -oxidation (7). This, in turn, is caused by decreased activity of peroxisomal very long chain acyl-coenzyme A synthetase (VLCs), the enzyme that activates VLCFA to their coenzyme A (coA) derivatives (8). The defective gene product in X-ALD, referred to as ALD pro

tein (ALDP), is a peroxisomal membrane protein that seems to be a member of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter family. It is not homologous to VLCS, which until then had been considered the most likely candidate (9). The role of ALDP in the α -oxidation of VLCFA is under intense investigation.

Pathologic characteristics are the lamellar cytoplasmic inclusions consisting of cholesterol esterified with VLCFA in brain macrophages, Schwann cells, Leydig cells, and adrenocortical cells (10). In AMN, mainly the spinal cord and, to a lesser extent, peripheral nerves are affected.

The estimated incidence of the disease is 1-5/100000. The classification of the different phenotypes of X-ALD is somewhat arbitrary. At present, at least six variants can be distinguished (11). These are childhood cerebral ALD, adolescent cerebral ALD, adult cerebral ALD, AMN, the "Addison" only and asymptomatic phenotype. Surprisingly, a variation in phenotypic expression has even been found in monozygotic twins suggesting that non-genetic factors may also be involved in the varying phenotypic expression (12). Not only men are affected: in the early 1980s it was shown that female carriers are at risk for developing neurological deficits as well (13). Our first patient's mother also had trouble walking. Adrenomyeloneuropathy is the most common phenotype with an incidence of 25-46 %. The onset of neurological symptoms in this phenotype usually occurs in the third and fourth decade (14) as in our patients. Neurological deficits are primarily due to myelopathy, and to a lesser extent to neuropathy. Patients gradually develop a spastic paraparesis, often in combination with voiding disturbances (1,13,14). Similarly both of our patients have progressive spastic paraparesis. Interestingly although our patients have neurological symptoms, their spinal and cranial MRI did not reveal the white matter changes characteristic of AMN. Kumar et al pointed out that about 50 % of men with AMN show mild to moderate involvement on MRI (15). Nerve conduction studies and EMG are compatible with a predominantly axonal, sensorimotor polyneuropathy (16). We also have detected polyneuropathy by EMG in our second patient. Differential diagnosis includes progressive multiple sclerosis and hereditary spastic paraparesis (14).

Asymptomatic patients are identified by family screening, they may have neither neurological nor endocrinological abnormalities, even in the presence of mild cerebral involvement on MRI. The risk of asymptomatic patients developing neurological symptoms is high (17). Some patients have isolated adrenocortical dysfunction (Addison only phenotype). The risk of developing neurological involvement is very high in these patients. Several studies have disclosed that 4-63 % of patients with Addison's disease in fact may have the Addison only phenotype of X-ALD (18,19).

About two thirds of male patients with neurological dysfunction also have overt or subclinical adrenocortical insufficiency (Addison's disease) as in our patients. This may precede, accompany, or follow the onset of neurological symptoms. Overt adrenal insufficiency or an impaired cortisol response to synacthen is present in 61 % of patients with AMN at the time of diagnosis. Adrenal insufficiency is present before the onset of neurological symptoms in 39 % of patients. Affected men may have manifest or subclinical testicular insufficiency (20). Our first patient had low free testosterone levels but LHRH test could not be performed.

The raised plasma concentrations of VLCFAs (C22:0 docosanoic acid, C24:0 tetracosanoic acid, C26:0 hexacosanoic acid) are reliable and relatively simple biochemical diagnostic tests for ALD. Most laboratories also measure the C24:0/C22:0 and C26:0/C22:0 ratios (21). The delay between onset and diagnosis may be long, particularly in probands. In a study by van Geel et al, in 16 patients from 14 different families with X-ALD, total delay (interval between onset of symptoms and diagnosis) and specialist (neurologist, internist/endocrinologist, or pediatrician) delay (interval between referral to a specialist and diagnosis) were determined. Mean total delay was 9.9 (range 1-33) years, and mean specialist delay was 8.4 (range 0-33) years. Three patients who presented with adrenocortical insufficiency had mean total and specialist delays of 17.3 (range 9-33) years (22).

After the discovery of increased concentrations of VLCFAs in blood and other tissues of patients with X-ALD, several dietary treatments were developed. Bone marrow transplantation and immunosuppressive therapies are currently being investigated. Oleic acid (C18:1), a monounsaturated fatty acid, was shown to competitively inhibit the

fatty acid elongation system, thus interfering with the biosynthesis of VLCFAs. With the combination of fat restriction and oral supplementation with glycerol trioleate (GTO) it was possible to reduce plasma VLCFA concentrations by about 50 %. After glycerol trierucate (erucic acid C22:1 in triglyceride form GTE) was added, a dramatic lowering of the plasma concentration of C26:0 was noted. The 4:1 combination of the GTO and GTE oils became known as “Lorenzo’s oil” as a tribute to Lorenzo Odone, a boy with childhood cerebral ALD, whose parents helped to develop the dietary treatment (23). So many patients are still treated with Lorenzo’s oil worldwide. Lorenzo’s oil has no effect in patients with neurologic symptoms but it may postpone the onset of neurological symptoms in asymptomatic males (24).

X-linked adrenoleukodystrophy is probably underdiagnosed as not everyone is aware of the relatively high incidence and the clinical presentations of the different phenotypes of X-ALD, in particular those variants with only mild or no neurologic symptoms. From an endocrinological point of view, adrenoleukodystrophy should be kept in mind and actively excluded in patients with Addison’s disease. The most important issue is that the adrenocortical insufficiency, found in most patients with X-ALD, if left untreated, may be lethal. Therefore, the adrenocortical function, either measured by plasma ACTH and cortisol concentrations, or by the rise in cortisol after ACTH stimulation, should be tested in all affected ALD patients at regular intervals, unless they are already on steroid hormone substitution therapy.

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