Adrenomyeloneuropathy, presenting with sub-acute spastic paraparesis and Addison's disease

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Adrenomyeloneuropathy (AMN) is one of the most frequent phenotypes of X-linked adrenoleukodystrophy (ALD) and its adult variant. Adrenomyeloneuropathy is an X-linked disease, in which there is a deficiency of lignoceryl-CoA ligase, a peroxisomal enzyme, needed for the degradation of very long chain fatty acids (VLCFA).[1] The combined incidence of AMN and Addison's disease, with or without neurological signs, was estimated to be around 1-1.6 per 100,000 population. The disease is caused by a genetic abnormality at the ALD gene, mapped to Xq28. The findings of normal adrenal function in patients with a splice site mutation of the ALD gene, suggest that, besides ALD gene mutation and the increase in VLCFA, additional factors could be responsible for development of endocrinological symptoms in X-linked ALD. Hereditary factors other than the ALD gene, influence the endocrinological phenotype, more than the neurological phenotype. The resultant biochemical defect involves deficiency of a membrane transport protein thought to be responsible for the import of the VLCFA CoA synthetase, into the peroxisome, leading to accumulation of VLCFA particularly C_{24} and C_{26}, in tissues and body fluids.[2] This is responsible for the demyelination of white matter of the spinal cord, causing myelopathy, spasticity, as well as primary demyelination or axonal degeneration causing peripheral neuropathy.

A 24-year-old Indian male, an electrical engineer, developed insidious onset of lower limb weakness with mild spasticity, of 2 weeks duration. He also reported, a 10-month history of loss of appetite and taste for food, craving for salt, progressive lethargy, and easy fatigability. Two weeks prior to admission, he noticed mild weakness, heaviness, and stiffness of both lower limbs. He had normal early developmental history, good secondary school education, attended engineering college, and successfully graduated as an engineer. He did not smoke with no history of drug abuse or risk factors for human immunodeficiency virus (HIV). On physical examination, his blood pressure was 140/90 on lying, and 100/70 on standing position. He has generalized hyper pigmentation of the skin, tongue, mucous membrane of the oral cavity, nipples, and hands. Neurological examination revealed normal fundi, with intact cranial nerves. He has mild symmetrical weakness of upper limbs, with motor power of 4+/5, lower limbs power of 4/5. His deep tendon reflexes were very brisk, with mild spasticity, bilateral ankle clonus and extensor plantar response. There were no sensory or cerebellar deficits. He had spastic gait. Biochemical panel was as follows: serum sodium was 115-130 mmol/L, potassium was 5.62-6.1 mmol/L, and other biochemical parameters were normal. Blood venereal disease research laboratory test, and treponema pallidum hemagglutination assay tests were normal. Anti-human T-lymphotropic virus 1 and 2 screening tests were negative. Serum vitamin B12 and folate levels were normal. The above history, physical findings, and lab results were highly suggestive of the diagnosis of Addison's disease. Computerized tomography scan of abdomen showed the usual shaped adrenal glands, with mild atrophy. Magnetic resonance imaging of the brain and spinal cord were normal. Cerebrospinal (CSF) fluid study was also normal. Nerve conduction velocity study, showed prolongation of the distal latencies and F-waves, motor nerve conduction velocities of examined nerves were low, revealing mild degree of motor and sensory neuropathy. Brain-stem auditory evoked potential study revealed slowing of conduction in the brainstem auditory pathway. An endocrinologist was consulted for further work up to confirm the diagnosis. Basal serum cortisol level at 8 am: 140 nmol/L (reference range: 171-536) and at 8 pm: 138 nmol/L (reference range: 64-340), serum renin activity at rest: 38 mIU (reference range: 5-47), serum testosterone level: 18.2 nmol/L (reference range: 9.9-27.8), serum aldosterone level: 210 pmol/L (reference range: 0-444), serum basal adrenocorticotropic hormone (ACTH): 21 pmol/L (normal <11 pmol/L), ACTH challenge test: no rise in serum cortisol level after injection of ACTH. Injection of ACTH (Synacthen) 0.25mg IV given as bolus, and serum cortisol levels were measured by immunoradiometric assay in the next 30 minutes and 60 minutes: no rise of serum cortisol level after 30 minutes, consistent with the diagnosis. Serum cortisol level after 30 minutes: 161 nmol/L (normal >193nmol/L), and after 60 minutes 148 nmol/L (normal >497 nmol/L). Very long chain fatty acids, particularly C_{24} and C_{26} are elevated (**Table 1**). The findings were consistent with the diagnosis of AMN with Addison's disease.

Table 1 - Serum very long chain fatty acid levels.

Fatty acid chain	Level of fatty acid per liter umol/L	Reference range umol/L
C_{22} acid	75.77	50.78-88.05
C_{24} acid	112.82	40.41-70.95
C_{26} acid	4.978	0.496-0.808
Ratio C_{24}/C_{22}	1.49	0.73-0.89
Ratio C_{26}/C_{22}	0.066	0.008-0.012

The patient was started on replacement therapy with steroids and other supportive treatment. He slowly improved with recovery of his symptoms. He regained his muscle power and the spasticity disappeared. Brisk deep tendon jerks, were still persistent, however the patient was freely ambulant with a maintenance dose of steroids.

Adrenomyeloneuropathy, a rare cause of Addison's disease, is due to accumulation of VLCFA in the adrenal cortex and nervous tissues. Adrenal insufficiency (Addison's disease) is frequently associated with AMN or cerebral ALD.[3] Indeed up to 30% of the young male patients, with idiopathic adrenal insufficiency, may have occult AMN. Overall, in patients with AMN, 70% will have adrenal insufficiency and 80% will show evidence of peripheral neuropathy, mixed type of demyelination, and axonal degeneration.[4] The mean age of onset of AMN is 27.6±8.7 years. Plasma ACTH level is the most sensitive biomedical marker for adrenocortical dysfunction in infantile, adolescent, and adult patients with ALD or AMN. It is not clear if adrenocortical insufficiency in ALD is due to accumulation of VLCFA, as there is no correlation between plasma levels of VLCFA and ACTH. It involves mainly the spinal cord and presents with slowly progressive stiffness, weakness of legs, and sphincter disturbances. Neurogenic bladder dysfunctions, such as urinary urgency, difficulty in voiding urine, with occasional fecal incontinence, have been reported in AMN cases.[1,3] It is often misdiagnosed as multiple sclerosis. Demyelinating lesions of the peripheral nerves and white matter of the spinal cord and cerebrum may be mainly responsible for neurological manifestations, including sphincter disturbances. Abnormalities of somatosensory and motor evoked potential studies are seen in AMN. At the early stage of the disease, neurological dysfunction is localized in the spinal cord, where it is difficult to assess using MRI. Nerve conduction studies and somatosensory evoked potential studies in AMN, demonstrated the frequent, widespread involvement of both peripheral nerves and the central conducting system in men, and predominantly central involvement in women with AMN. Adrenomyeloneuropathy presents with progressive spastic paraparesis and peripheral neuropathy. The prominent pyramidal signs, may make the clinical recognition of peripheral neuropathy, rather difficult in AMN cases. Detailed nerve conduction studies, concluded that the neuropathy in AMN patients, is due to primary axonal degeneration with secondary demyelination.[4] Therefore, the treatment of AMN, has not been fully satisfactory.

Certain mono unsaturated acids such as, glyceryl trioleate (GTO) and the more potent glyceryl trierucate (GTE) combined (GTE:GTO) in a ratio of 4:1, is called Lorenzo's oil. Studies of the use of Lorenzo's oil, in patients with AMN, have failed to demonstrate appreciable benefit. Bone marrow transplantation is considered in children, with the cerebral form of the disease, (CALD). Other new experimental treatment consists of interferon-β and the use of thalidomide, which is considered for the cerebral form of ALD, rather than AMN.[5] Our case is consistent with AMN, and there are no available data support, to treat such patients with either Lorenzo's oil or bone marrow transplantation. Of the listed therapeutic modalities, our patient benefited from the optimal treatment of adrenal failure. No specific neurologic treatment was considered, because he improved over time, with treatment of adrenal insufficiency. He was on maintenance steroid therapy and was doing well with normal motor power, and returned to his home country in good shape. Later, his neurological condition slowly progressed with severe spasticity, and he walks with crutches. At present, he is in his home country, walking aid dependent, and lost to our follow up in Kuwait.

In conclusion, AMN is a rare disorder, however, it is important to recognize it in the differential diagnosis of spastic paraparesis and peripheral neuropathy. Multiple sclerosis is very often, a mistaken diagnosis in such clinical presentation in which the peripheral nerves are not affected. The disorder has variable degrees of presentation and MRI brain can be normal in mild cases and abnormal in the severe variety, as seen in our patient. If diagnosed and treated at an early stage, the neurological manifestations can be reversible to a greater extent. Bone marrow transplantation should be considered as early treatment to prevent morbidity and mortality in such cases.

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