CASE REPORT

A Case Report of Adrenomyeloneuropathy- A variant of X linked Adrenoleukodystrophy

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ABSTRACT

We, hereby, report a case of 33 years old menwith 10 years history of progressive spastic paraparesis with bladder involvement. His MRI dorsal spine was suggestive of dorsal cord atrophy & on nerve conduction velocity he had sensorimotor axonal polyneuropathy affecting both lower limbs. His very long-chain fatty acids (VLCFA) levels were raised. His cortisol level was reduced. He is currently being treated with oral steroids & physiotherapy. Adrenomyeloneuropathy is a rare X-linked inherited disorder of peroxisomes. It is caused bymutations in the ABCD1 gene that encodes the peroxisomal membrane protein ALDP which is involved in the transmembrane transport of VLCFA ($\geqslant$ C22). A defect in ALDP results in elevated levels of VLCFA in plasma and tissues. X linked Adrenoleukodystrophy (ALD) has three main phenotypes: Addison-only, adrenomyeloneuropathy, and cerebral ALD. Cerebral ALD is further divided into childhood and adolescent/adult onset.

INTRODUCTION

X-ALD is the most common peroxisomaldisorder.The adult neurologic variants of ALD affect approximately 30% of the males and 15% to 20% of female heterozygotes.[2] Adrenomye-loneuropathy (AMN) is the most common form.[3] Patients develop gradually progressive spastic paraparesis, sensory ataxia, sphincter dysfunction, pain in the legs and impotence. Neuroimaging of brain is normal or may show moderately increased signal intensities of the pyramidal tracts in brainstemand internal capsules on FLAIR and T2 sequencesanddorsal cord atrophy.[1]

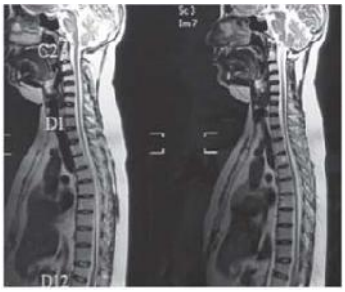
CASE PRESENTATION

A 33 years old gentleman presented to our hospital with insidious onset gradually progressive both lower limb weakness with tightness (proximal followed by distal)& urinary urge incontinence since 10 years. He didn't have upper limb weakness, sensory complains, back or neck pain. There was no seizure, loss of consciousness, memory impairment, abnormal behavior, decreased or double vision, dysphagia, dysarthria or nasal regurgitation of food. He didn't have blood transfusion or indescent sexual exposure.At present, he is on crutch support.In past, he had history of generalized hyperpigmentation of skin. Patient was put on oral steroids with which he improved over time. Family history was unremarkable.

On general examination, he had cushingoid face.He had normal higher mental and cranial nerve function.On motor examination, both lower limbs were spastic. Motor power was 3-/5 in both lower limbs proximally & 2/5 distally. Upper limb strength was normal. On Sensory examination, there was impaired joint position & vibration sense upto both metatarsophalangeal joints. All deep tendon reflexes were 3+ except bilateral ankle hyporeflexia (1+) with bilateral extensor plantar response. Cerebellum, skull, back & spine were normal.

Routine lab investigations including hematological, biochemical parameters were within normal limits. CSF examination was also normal. HIV, HBsAg, HCV, RPR, ANA were nonreactive. B12 & Thyroid profile were within normal limits. MRI spine (figure 1) showed dorsal cord atrophy & Brain imaging (figure 2,3) was suggestive of T2 & FLAIRhyperintensity in pons, splenium of corpus callosum, bilateral peritrigonalwhite matter & left cerebellum.NCV study showed sensorimotor axonal polyneuropathy affecting lower limbs. Considering

Figure 1 (MRI spine: Dorsal cord atrophy)



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presenting symptoms and past history of hyperpigmentation, further investigations were planned. Serum cortisol was low (2.32 ug/dl) while ACTH level was normal. CT abdomen with contrast showed bilateral renal calculi with normal suprarenal glands. Based on clinical & typical MRI findings along with laboratory parameters, diagnostic possibility of adrenomyeloneuropathy was considered & VLCFA level was sent and it was suggestive of elevated levels of C26:0 & increased C26/C22 ratio. At present he is being treated with oral glucocorticoids as well as mineralocorticoids, antispasticity drugs & physiotherapy.

Figure 2 (MRI Brain T2 hyperintensity along internal capsule)

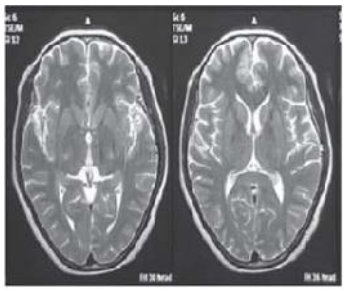
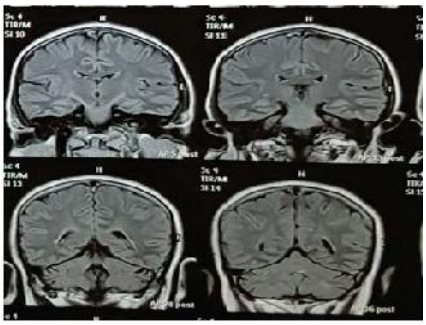


Figure 3 (MRI Brain; FLAIR hyeprintensity in bilateral corticospinal tract)



DISCUSSION

In 1976, an X-linked adult onset progressive myelopathy that was often associated with Addison's disease was reported.4,5 A year later, the term adrenomyeloneuropathy (AMN) was proposed. The phenotypes of X-linked ALD are childhood cerebral ALD, adolescent or adult cerebral ALD, adrenomyeloneuropathy, Addison's – only phenotype, atypical ALD and asymptomatic ALD.It is an X-linked peroxisomal disorder in which VLCFA, accumulate within cells (especially those in adrenal cortex, Leydig cells in testes and myelin producing cells) as a result of defective beta-oxidation within the peroxisome.6The disease is caused by mutations in the ABCD1 gene that encodes the peroxisomal membrane protein ALDP, involved in the transmembrane transport of VLCFA. This defect results in elevatedVLCFA in plasma and tissues.The neurologic syndrome is one of slowly progressive spastic paraparesis, hyperreflexia with a symmetric distal neuropathy beginning in the 3rd or 4th decade of life. Sphincter disturbances (+/- sexual dysfunction), cerebellar ataxia and intellectual deterioration may occur as later manifestations.Adrenal function is normal in up to 30% of AMN patients.

Brain MRI is normal or show T2 & FLAIR hyperintensitiesof the pyramidal tracts in brainstem and internal capsules.MRI of the spinal cord shows dorsal cord atrophy. The definitive diagnostic test for ALD is the serum VLCFA particularly absolute concentration of C26:0 as well as the C24:0/C22:0 and C26:0/C22:0 ratios.6Other tests include serum ACTH and baseline cortisol levels. The diagnosis is confirmed by ABCD1 mutation analysis. For AMN there is no effective disease modifying therapy available yet. Although Lorenzo's oil (LO) had great promise, the disease progresses even when plasma VLCFA are normalized by LO treatment. Other treatment options for AMN in research include lovastatin & antioxidants.

CONCLUSION

High index of clinical suspiction should be kept in any young male with long standing spastic paraparesis with bladder involvement with or without history of adrenal insufficiency. Typical clinical picture along with MRI findings helps in early diagnosis which is confirmed by elevated serum VLCFA levels & ABCD1 genetic analysis. Our case went undiagnosed for almost ten years until the evolution of neurological symptoms, which reveals the unawareness of this entity in developing countries.

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