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Case Report

Adrenomyeloneuropathy in a subacute combined degeneration suspect: a diagnostic dilemma

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ABSTRACT

Adrenomyeloneuropathy (AMN) is a variant of adrenoleukodystrophy (ALD) which is a peroxisomal disorder of beta-oxidation that results in accumulation of very long-chain fatty acids (VLCFAs) in plasma, central and peripheral nervous systems, adrenal glands and testes leading to their dysfunction. These conditions are known as the ALD/AMN complex. In this article we discuss a case of AMN with respect to clinical presentation, diagnosis and treatment.

Keywords: Adrenomyeloneuropathy, Paraparesis, Subacute combined degeneration

INTRODUCTION

Adrenoleukodystrophy (ALD)/adrenomyeloneuropathy (AMN) is an X-linked disorder. It is caused by mutations in the adenosine triphosphate (ATP)-binding cassette (ABC), subfamily D, member 1 gene (ABCD1), located at Xq28, that encodes an ABC transporter. This transporter helps form the channel through which very long-chain fatty acids (VLCFAs) move into the peroxisome, probably as coenzyme A (CoA) esters.[1-3] ABCD1 mutations may prevent normal transport of VLCFAs into peroxisomes, thereby preventing their beta-oxidation and breakdown. People with ALD or AMN do not produce fatty acylcoenzyme A (acyl-CoA) synthetase, which breaks down VLCFAs in first step in their oxidation. VLCFAs therefore accumulate and form cytoplasmic inclusions, leading to progressive dysfunction in the nervous system, adrenal glands and testes, all of which are sites of VLCFA metabolism. Accumulation of abnormal VLCFAs in affected organs is presumed to underlie the pathologic process of ALD/AMN. However, plasma VLCFA levels do not predict phenotype and cell-specific functions of ABCD1 may play a role in the pathogenesis independent of VLCFA.[4]

In vitro studies suggest that the VLCFA accumulation that occurs in the absence of ABDC1 function promotes inflammation. In AMN, both inflammatory and non-inflammatory demyelination lesions occur. Affected individuals also develop a degenerative axonopathy that involves the ascending and descending tracts of the spinal cord, especially in fasciculus gracilis and the lateral corticospinal tracts. The histologic pattern is Wallerian degeneration. Mitochondrial pathology and oxidative stress also contribute to pathogenesis. When peripheral nerves are affected in ALD/AMN, characteristic lamellar and lamellar-lipid inclusions are seen in Schwann cell cytoplasm or within endoneurial macrophages. Central nervous system macrophages, but not oligodendrocytes, may also have inclusions. Spicular or trilaminar inclusions may also occur in the central nervous system.[5,6]

AMN typically presents in adult males between 20-40 years of age (average 28 years) comprising approximately

40-45% of ALD/AMN complex. Primary manifestation is spinal cord dysfunction with progressive stiffness and weakness of legs (spastic paraparesis), abnormal sphincter control, neurogenic bladder, and sexual dysfunction. Numbness, pain from polyneuropathy is also common in males with AMN. Gonadal dysfunction may precede motor abnormalities. They may also have adrenal insufficiency.

There may be presence of sensorimotor abnormalities in the dorsal columns extending into the brainstem, correlated with overall severity in AMN. Auditory brainstem evoked responses correlate more with AMN than ALD, while auditory function is generally normal.[7,8]

Possibility of ALD/AMN may be raised by the above clinical signs or symptoms, family history of ALD/AMN, or positive new-born screen.

Diagnostic approach includes VLCFA levels, adrenal function testing, genetic testing and neuroimaging to determine the extent of cerebral involvement. Prenatal testing involves determination of VLCFA level or DNA test.

CASE REPORT

A 27-year-old male patient occasional smoker with mixed diet and no past history, presented with history of progressive difficulty in walking and weakness of bilateral lower limbs for past one and a half years. Initially patient could walk without support with short steps slowly but it progressed to walking with support within 1 year. Patient also complained of bladder urgency for the last 6 months without incontinence. Family history suggested similar complaint in a maternal uncle several years back. On examination, all the cranial nerve's function was intact. Upper limb examination, tone was increased, bulk was normal and power was unremarkable in all joints in all movements and hand grip. On lower limb examination, tone was increased, bulk was normal and power was found to be reduced bilaterally. 3/5 in hip flexion and adduction, 2/5 in hip extension and abduction. 4/5 in knee flexion and 5/5 in knee extension. In ankle, dorsiflexion power was 3/5 and 5/5 on plantar flexion. Deep tendon reflexes were 3+ bilaterally in upper and lower limb. Plantar reflex was extensor bilaterally. Meningeal signs were absent.

On sensory examination, pain, touch, temperature sense was present in all dermatomes. Joint position and vibration sense was impaired distally in bilateral lower limbs.

No abnormal cerebellar signs were found. Gait was spastic.

Patient was investigated thoroughly. Routine investigations were done and found to be normal. Morning cortisol levels were normal. Vitamin B12 levels was 95 pg/ml. Patient was kept as a suspected case of subacute combined degeneration (SACD) and started on injection methylcobalamine 1000 ug daily for 5 days then weekly. On follow up after 6 months patient's B12 levels had increased to >2000 pg/ml but complaints were not resolved and had progressed. Patient underwent cerebrospinal fluid (CSF) analysis and contrast magnetic resonance imaging (MRI) of brain with whole spine. CSF analysis was found to be normal. MRI showed bilateral symmetrical subtle T2 hyperintensity along B/L corticospinal tract (demyelination/autoimmune etiology). VEP was done which showed moderate degree of demyelinating involvement with mild to moderate degree of secondary axonal involvement of visual pathways bilaterally. Patient was kept as a suspected case of multiple sclerosis, following this patient was started on pulse corticosteroid therapy methylprednisolone for 5 days but no improvement was noted.

On suspicion of clinical features and family history, whole exome sequencing was done which showed hemizygous ABCD1 (+) (ENST00000218104.6) mutation variant c.1017G>A(p.Trp339Ter) on exon 2 of chromosome X along with heterozygous deletion on chromosome 15 of variant chr15:g.(?_22184710)_(23133534_?)del.

Patient was diagnosed as a case of AMN with spastic paraparesis.

The patient was enrolled in a program of physiotherapy and rehabilitation. No specific treatment of the underlying AMN was initiated. Screening of the patient's family members was also recommended. On a recent follow-up visit, the patient had stable neurological findings.

DISCUSSION

AMN, the most common phenotype of ALD, usually manifests in male patients between 20 and 30 years of age and has an insidious progression. Weakness and spasticity of the lower extremities, sphincter dysfunction, and impotence are common symptoms. Neurologic dysfunction usually develops slowly over years, with only moderate increases in brain MRI signals of the white matter in the centrum ovale, internal capsule, or brainstem on FLAIR sequences without gadolinium enhancement; these disease characteristics suggest an intact blood–brain barrier and the absence of an active inflammatory process.[9]

In the patient, the clinical presentation, examination and initial investigations lead to a strong suspected diagnosis of severe B12 deficiency related SACD which is relatively less uncommon and for which treatment was initiated but in vain. Further investigations pointed towards demyelinating lesions and hence patient was treated on the lines of multiple sclerosis but still to no avail. Due to a family history of paraparesis and no improvement on previous lines of treatment, a very rare diagnosis of AMN was considered and genetic testing was done which showed ABCD1 mutation and confirmed the rare diagnosis in a relatively less uncommon presentation. Although patients with AMN may present with various

symptoms at various age groups, they are relatively common in young age males with peripheral nervous system involvement.

Despite the practice of using low VLCFA diet with glycerol or Lorenzo's oil, no specific treatment is yet found to be effective. A study involving patients with ALD using the combination of dietary restriction and supplementation with glyceryl trioleate and glyceryl trierucate (Lorenzo's oil) produced significant reductions in plasma VLCFA levels but failed to convincingly change the neurological status of the patients.[10]

Most important aspect in these patients is the correct diagnosis and physical rehabilitation to prevent wrong long-term treatment.

CONCLUSION

Although AMN being a disorder found rarely in clinical practice, the clinical features of progressive weakness and spasticity are found overlapping with various spectrums of disorders, SACD being one of them. In developing nations where nutritional deficiencies are common the diagnosis of a rare disorder may be commonly overlooked and attributed to nutritional deficiency and long-term treatment to correct these deficiencies may be initiated in vain hence resulting in mental trauma and dissatisfaction to the patient and clinician both. In such cases where no improvement is seen even on multiple lines of treatment for a long duration, a strong suspicion and prompt genetic testing may help in making the correct diagnosis.

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REFERENCES

1. Berger J, Gärtner J. X-linked adrenoleukodystrophy: clinical, biochemical and pathogenetic aspects. Biochim Biophys Acta. 2006;1763:1721.
2. Mosser J, Douar AM, Sarde CO, Kioschis P, Feil R, Moser H, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. Nature. 1993;361:726.
3. Holzinger A, Kammerer S, Berger J, Roscher AA. cDNA cloning and mRNA expression of the human adrenoleukodystrophy related protein (ALDRP), a peroxisomal ABC transporter. Biochem Biophys Res Comm. 1997;239:261.
4. Kemp S, Wanders R. Biochemical aspects of X-linked adrenoleukodystrophy. Brain Pathol. 2010;20:831.
5. Powers JM. Adreno-leukodystrophy (adreno-testiculo-leukomyelo-neuropathic-complex). Clin Neuropathol. 1985;4:181.
6. Powers JM, DeCiero DP, Ito M, Moser AB, Moser HW. Adrenomyeloneuropathy: a neuropathologic review featuring its noninflammatory myelopathy. J Neuropathol Exp Neurol. 2000;59:89.
7. Percy AK, Rutledge SL. Adrenoleukodystrophy and related disorders. Ment Retard Dev Disabil Res Rev. 2001;7:179.
8. Pillion JP, Kharkar S, Mahmood A, Moser H, Shimizu H. Auditory brainstem response findings and peripheral auditory sensitivity in adrenoleukodystrophy. J Neurol Sci. 2006;247:130.
9. Teriitehau C, Adamsbaum C, Merzoug V, Kalifa G, Tourbah A, Aubourg P. Subtle brain abnormalities in adrenomyeloneuropathy. J Radiol. 2007;88:957-61.
10. Aubourg PK, Adamsbaum C, Lavallard-Rousseau MC, Rocchiccioli F, Cartier N, Jambaque I, et al. A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. New Engl J Med. 1993;329.

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