Ataxia with Vitamin E Deficiency: A Never to be Missed Treatable Ataxia

Ataxia with Vitamin E deficiency (AVED) is an autosomal recessive disorder that presents with progressive ataxia, mimicking Friedreich's ataxia. It is caused by mutations in the α-tocopherol transfer protein (*TTPA*) gene. Vitamin E replacement therapy not only stabilizes disease progression but also may lead to symptom reversal in most cases. It is rare but should always be considered in "mutation negative" cases with a phenotype akin to Friedreich ataxia.[1] We report the second case of AVED from India. One previous case was reported in 2005.[2]

A 25-years old female presented with complaints of progressive unsteadiness while walking with recurrent falls for the past 10 years. These complaints worsened in the dark and on uneven surfaces. She had become wheelchair-bound for the past 3 years. She had no complaints of tremulousness of limbs, dysarthria, foul-smelling sticky stool, decreased night vision, cognitive impairment, or self-mutilatory behavior. She was born to non-consanguineous parentage and had no similar complaints in the family. Birth and developmental history were normal. Her past history was non-contributory.

Examination revealed the presence of head titubation, dysmetria involving both upper and lower limbs, with worsening on the removal of visual perception. She had a loss of joint position and vibration sense up to the ankles with a loss of ankle reflexes. Her fundus and extra-ocular movements were normal. The remaining neurological examination was non-revealing. Romberg's test and gait examination could not be done due to her wheelchair-bound state. She had no ichthyosis, telangiectasias, tendon xanthomas, or cataracts.

Routine investigations (hemogram, renal and liver function tests, lipid profile, glycosylated hemoglobin, and thyroid profile) were normal. Her antinuclear antibodies, extractable nuclear antigen (ENA) panel, and viral markers for human immunodeficiency virus (HIV), hepatitis B and C were negative. A nerve conduction study (NCS) revealed non-recordable sensory nerve action potentials (SNAPs) in bilateral sural and superficial nerves with normal SNAPs in the bilateral median and ulnar nerves. Motor conductions were within normal limits. Magnetic resonance imaging of the brain was normal. Molecular testing for GAA repeats on the frataxin gene was normal. A presumptive diagnosis of combined sensory and cerebellar ataxia was made and further investigated. Serum vitamin E (alpha-tocopherol) levels were found to be <0.4mg/L (normal: 5–18 mg/L). Clinical exome sequencing revealed a homozygous pathogenic (predicted to be damaging both by SIFT and PolyPhen2) mutation in the exon 4 of *TTPA* gene (c. 661C >T), enabling a diagnosis of AVED. Her 2D-echocardiography was normal, and she was treated with oral vitamin E supplementation (Tab Vitamin E 400mg thrice daily) with good functional recovery. She started ambulating with support six months into treatment and independently one year later [Video 1]. Repeat NCS after 6 months of treatment revealed the normal study.

AVED was first described in 1981 as patients with neurological manifestations (most commonly ataxia) associated with isolated vitamin E deficiency[3] and the genetic basis of it was elucidated by Ouahchi *et al*.[4] in 1995. They identified mutations in the *TTPA* gene on chromosome 8 in these patients. AVED patients absorb dietary alpha-tocopherol normally and incorporate it into chylomicrons. However, abnormal TTPA function prevents the transfer of alpha-tocopherol to very low-density lipoproteins (VLDL) secreted by the liver, preventing peripheral delivery to tissues.[1] AVED patients

typically present in the 1st or 2nd decade of life with progressive ataxia and sensory loss but lack gastrointestinal symptoms.[5] Pathologically, vitamin E deficiency leads to axonal dystrophy and spinal cord posterior column, spinocerebellar tract degeneration, gracile and cuneate nuclear loss, and peripheral nerve demyelination.[6] They may have concomitant pyramidal signs, scoliosis or cardiomyopathy and commonly masquerade as Friedreich's ataxia (FA).[5] The clinical differences between the two include: the presence of pigmentary retinopathy and normal/mildly abnormal SNAPs in some patients of AVED. In contrast, retinitis pigmentosa is not seen in FA, and SNAPs are grossly abnormal in these patients.[5] The presence of dystonia also points toward AVED and may uncommonly be a presenting feature. Head tremor or titubation are prominently seen in patients with AVED. In a large study among 132 Tunisian patients, head tremor may be seen in up to 40% of patients.[7] The other prominent features in this study were sensory disturbances, pyramidal symptoms, and skeletal abnormalities. The most frequent mutation worldwide is 744delA.[7] Other clinical differentials include abetalipoproteinemia and Niemann-Pick's type C [NPC]. Gastrointestinal features, especially steatorrhea, anemia, and acanthocytosis are seen in abetalipoproteinemia. In NPC, differentiating features include the presence of prominent vertical gaze palsy and cognitive deficits, and absence of titubation, skeletal abnormalities, and neuropathy in NPC. Finally, the use of AVED in such genetically associated causes is now discouraged and FIVED (familial isolated vitamin E deficiency) is considered a better alternative to prevent confusion (because other causes of vitamin E deficiency can also lead to ataxia).[8]

A diagnosis of AVED/FIVED should be considered in all patients with a sensory ataxia phenotype with low vitamin E levels, and genetic testing ordered. These patients respond well to 800-1200 mg/day supplementation of oral vitamin E. Most AVED patients show some response to therapy, with better response with earlier treatment initiation.[9] However, discontinuation of replacement therapy even after prolonged administration can lead to a symptom recurrence within 3 days. Therefore, supplementation needs to be given lifelong.[1] There is some evidence to suggest that molecular variants may influence treatment and contribute to resistance to vitamin E in some cases with exon skipping of all transcripts.[10] Hence, making a genetic diagnosis is imperative.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Ayush Agarwal, Divyani Garg, Achal K. Srivastava

Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Dr. Divyani Garg, Assistant Professor, Department of Neurology, All India Institute of Medical Sciences, New Delhi, India.
E-mail: divyanig@gmail.com

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