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Tremor and Other Hyperkinetic Movements

Case Reports

Ataxia with Vitamin E Deficiency May Present with Cervical Dystonia

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Abstract

Background: Ataxia with vitamin E deficiency (AVED) is an autosomal recessive disorder that usually presents with ataxia, areflexia, and proprioceptive and vibratory sensory loss. Dystonia has been reported rarely.

Case Report: An 11-year-old female presented with dystonic head tremor and cervical and bilateral arm dystonia. Her 14-year-old older brother had dystonic head tremor and generalized dystonia. One year later, the brother developed dysarthria, limb dysmetria, and gait ataxia. Compound heterozygous mutations in *TTPA* were detected, confirming the diagnosis of AVED.

Discussion: AVED may present with dystonia rather than ataxia, and should be considered in the differential diagnosis of progressive dystonia.

Keywords: Tremor, myoclonus, AVED, TTPA, myoclonus–dystonia

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Introduction

Ataxia with vitamin E deficiency (AVED) is a rare, autosomal recessive neurodegenerative disorder, with approximately 225 reported cases in over 100 families. Mutations in the gene encoding the α-tocopherol transfer protein (*TTPA*/α*TTP*) result in normal intestinal absorption of vitamin E but defective transportation out of the liver, resulting in systemic vitamin E deficiency.[1] The disease typically presents in childhood with progressive ataxia, areflexia, and loss of proprioceptive and vibratory sense, resembling Friedreich's ataxia.[2,3] Early diagnosis is imperative, as treatment can halt or even reverse disease progression.[3,4]

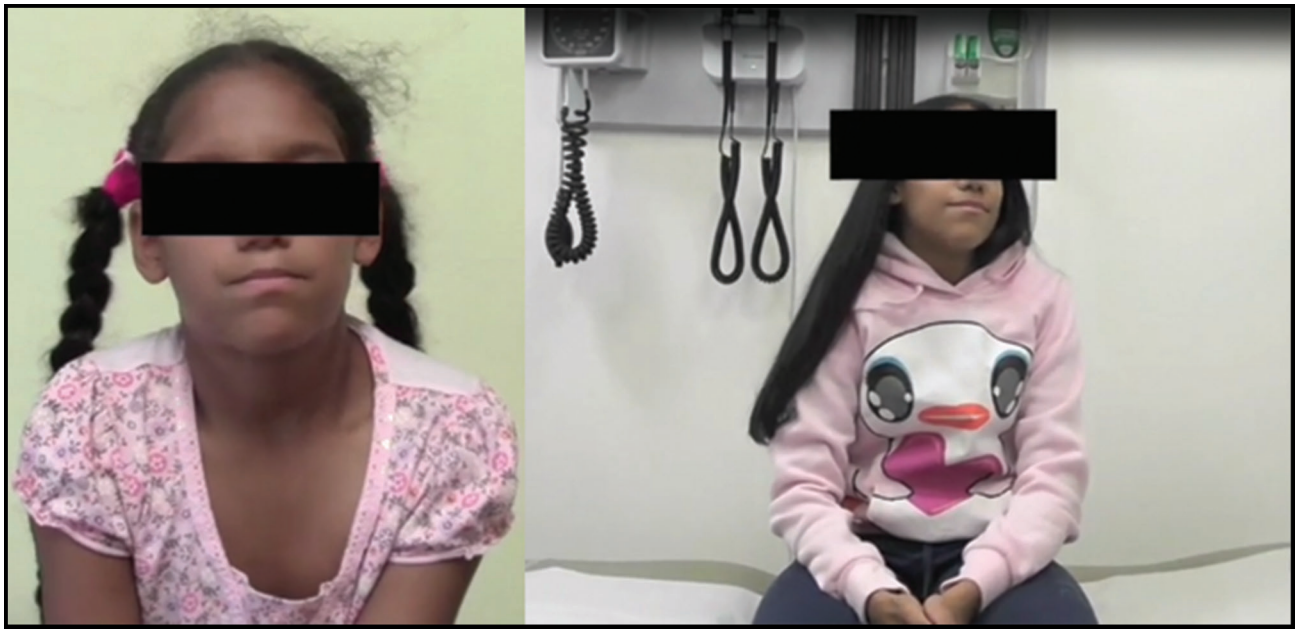
Dystonia occurs rarely in AVED and has been described as a presenting feature only once previously, in a child who presented with a syndrome that resembled myoclonic dystonia.[5] We present the clinical and genetic features and initial treatment response of two siblings with AVED who presented atypically with dystonia.

Case report

Two siblings (male, 14.5 years, and female, 11 years) presented for evaluation of head tremor. Perinatal history and development had been normal for both siblings until age 11 years, when they each developed involuntary shaky movements of the head that worsened during times of stress. Each had also experienced new mild school difficulties requiring special education services at age 11 or 12 years. The male also had symptoms of depression.

The female was examined 6 months after symptom onset (Video 1 seg.1: 00:21). She had cervical dystonia and an irregular, horizontal, jerky head tremor of variable amplitude consistent with dystonic tremor. She also had bilateral postural arm dystonia, most pronounced in the left arm during writing. Her gait was narrow-based and steady.

The male was examined 2–3 years after symptom onset (Video 2, Segment 1). He had intermittent head tremor and generalized dystonia involving the neck, trunk, and limbs. Dystonic contractions of abdominal



Video 1. **Segment 1. Sister at Presentation, Age 11.** This video demonstrates cervical dystonia and dystonic tremor, no dysmetria on the finger-to-nose test, left arm dystonia while writing, a narrow-based, steady gait, and normal tandem gait. **Segment 2. Sister Post Treatment, Age 13.5.** Treatment consisted of vitamin E (inconsistently for 10 months) and trihexyphenidyl (for 2.5 years). This video demonstrates intermittent head tremor, cervical dystonia, and no dysmetria on reaching, which was stable from the prior segment. There is subtle gait ataxia with impaired tandem gait.

muscles were present at rest, and shoulder and limb dystonia worsened with action, particularly walking. Dystonia did not respond to any sensory tricks. There was mild bilateral weakness of ankle dorsiflexion. His gait was normal-based and steady, but tandem gait was mildly impaired, attributed at the time to his dystonia and distal weakness.

Both siblings had diminished upper extremity and patellar tendon reflexes but normal ankle jerks and downgoing plantar responses. Neurologic examinations and ophthalmologic examinations were otherwise normal, specifically without evidence of limb dysmetria, nystagmus, dysarthria, or impaired vibration or proprioception. The

Video 2. **Segment 1. Brother at Presentation, Age 14.5.** This video demonstrates irregular head tremor at rest and dystonia of the neck, upper limb, and trunk that increases during reaching. There is subtle intention tremor on finger-to-nose test. Gait is normal-based and steady, with generalized dystonia, particularly involving the right shoulder, left arm, and both lower limbs. **Segment 2. Brother 18 Months after Presentation, Age 16.** Eighteen months after presentation, the patient has a broad-based, unsteady gait and dysdiadochokinesia. Generalized dystonia is unchanged. **Segment 3. Brother Post Treatment, Age 17.** Treatment consisted of vitamin E (for 10 months) and trihexyphenidyl (for 2.5 years). The patient's dysdiadochokinesia has improved significantly. He has residual upper limb dysmetria on the finger-to-nose test. Gait ataxia and generalized dystonia were unchanged.

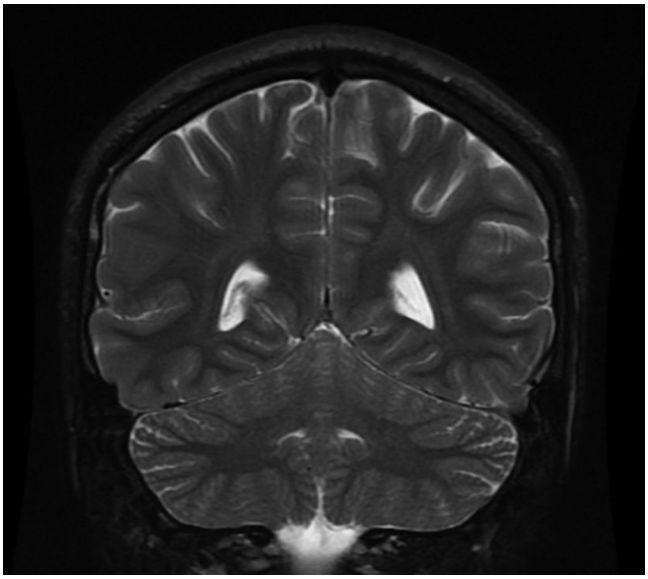


Figure 1. **Magnetic Resonance Imaging (Brother**). Coronal T2-weighted magnetic resonance imaging showing normal cerebellum.

initial clinical impression was of a progressive neurological disorder characterized by dystonia, mild cognitive dysfunction, and weakness of neuromuscular origin.

Initial investigations, including serum copper, ceruloplasmin, alpha-fetoprotein, serum and cerebrospinal fluid lactate concentrations, and brain magnetic resonance imaging were all normal (Figure 1). Nerve conduction studies as well as muscle, nerve and skin biopsies were performed in the brother. The nerve conduction study, skin biopsy, and nerve biopsy were normal; his muscle biopsy revealed rare myofibrillar derangement and mild, non-specific cytoarchitectural abnormalities consistent with mild myopathic changes. Treatment with trihexyphenidyl was initiated in both siblings. The dose in the sister was 6 mg per day, and for the brother, 15 mg per day. The head tremor improved in the sister; the brother reported subjective improvement in walking, but examination findings did not clearly improve.

One year after presentation, the brother developed dysarthria, dysdiadochokinesia, limb dysmetria, and gait ataxia (Video 2, Segment 2). The plasma alpha-tocopherol (vitamin E) level was found to be low in both siblings (<0.5 mg/L; reference range 5.5–18.0 mg/L). Compound heterozygous frameshift mutations in the *TTPA* gene (c.161_164del, p.R54fs and c.487delT, p.W163fs) were detected in both siblings, confirming the diagnosis of AVED.

The siblings were started on high-dose vitamin E supplementation. Ten months later, on 2,400 IU/day, plasma vitamin E levels were in the normal range for both (brother, 7.4–10.4 μg/mL; sister, 7.0–7.8 μg/mL). Follow up examination demonstrated improved dysarthria and dysdiadochokinesia in the brother (Video 2, Segment 3). His dystonia and ataxic gait did not improve. The sister had developed mild gait ataxia on examination (Video 1 seg 2: 00:46), although she did not notice any impairment of balance, gait, or coordination in daily life. Her new gait ataxia was explained, in retrospect, by a delay in the proper initiation of her treatment because of intermittent medication non-compliance.

Discussion

Our patients had an atypical presentation of AVED, with initial cervical dystonia and mild cognitive dysfunction in the absence of ataxia. Dystonia has been described in only 10 previous patients with AVED (Table 1). In only one previous case was dystonia the presenting symptom, in an 8-year-old patient with head jerks and cervical dystonia that resembled myoclonus–dystonia.[5] Our cases reinforce that dystonia may precede the onset of ataxia, and highlight cervical distribution as a characteristic feature of dystonia in AVED.

In the 12 reported cases of dystonia in patients with AVED (our two included), the development of ataxia preceded dystonia in the majority of patients. The average age at onset of symptoms was 9.5 years, and the average at onset of dystonia was 15.8 years. The latency from initial neurological symptom onset to dystonia onset was highly variable, ranging from 0 to 26 years (nine patients included). Dystonia occurred most frequently in the neck (75%), followed by upper limbs (62.5%), lower limbs (50%), trunk (50%), and face (37.5%). Half of the patients developed generalized dystonia (Table 1). Additionally, features of dystonia may be more prevalent than previously recognized in AVED. In one series,[3] head tremor has been reported in up to 44% of patients with AVED, and it is possible that at least some of these patients had cervical dystonia with dystonic tremor rather than head titubation.

The mechanism of neurologic dysfunction in AVED is unknown, but neuronal oxidative injury has been hypothesized. Brain imaging demonstrates cerebellar atrophy in up to 50% of cases.[3,4] Other brain regions are also affected. Animal models of AVED and post-mortem studies of humans with secondary vitamin E deficiency have shown evidence of degenerative changes in the substantia nigra, posterior column, nerve roots, and peripheral nervous system.[6–12] Post-mortem studies of patients with AVED demonstrate loss of cerebellar Purkinje cells, dying back-type posterior column degeneration with spheroids and corpora amylacea, and lipofuscin accumulation.[13,14] Ataxia in AVED is likely caused by a combination of cerebellar and posterior column degeneration. Whether dystonia in AVED is attributable to injury of nigrostriatal, cerebellar, or other circuits is uncertain.

High-dose vitamin E supplementation may stop disease progression and, in some cases, result in clinical improvement, especially in patients with shorter disease duration.[3,4] Primary prevention in mutation-positive pre-symptomatic patients has also been reported.[15] Without treatment, most patients with disease onset during childhood (age <18 years) become wheelchair-bound within 5–20 years of disease onset. The brother in our report started treatment approximately 4 years after symptom onset, when he had developed significant generalized dystonia and ataxia. After 10 months of treatment, he had moderate improvement in hand coordination and speech, but his gait ataxia and dystonia remained unchanged.

Table 1. **Clinical Characteristics and Treatment Response in Patients with AVED and Dystonia**

Study	Age at Onset (years)	Initial Symptoms	Age at Dystonia Onset (years)	Dystonia Distribution	Vitamin E Treatment (target dose/day; total duration)	Clinical Course
Krendel et al.[17]	7	Gait difficulty, clumsiness, dysarthria	19	GD Neck UE LE	3,600 IU; 5 mo	Stable
Stumpf et al.[18]	4	Unsteady gait,	30	Face	800 mg; 6 mo	Stable
Amiel et al.[15]	7	Ataxia	16	Face UE	1,000 mg; 5 yr	Improved: social contact, speech
Jackson et al.[19]	7	Head and hand tremor	22	GD Face Neck Trunk LE	1,200 IU; 3 yr	Stable
Yokota et al.[20]	30	ND	ND	ND	ND	Stable
Cavalier et al.[21]	3	ND	ND	ND	ND	ND
Schuelke et al.[22]	9	Clumsiness	13	ND	40 mg/kg; 18 mo	Improved: psychiatric, cognitive, ataxia, dysarthria, sensation, Deep tendon reflex's
Angelini et al.[5]	8	Cervical myoclonus-dystonia	At onset	Neck Trunk	2,400 mg; 1.75 yr	Improved: ataxia, dystonia, myoclonus
Roubertie et al.[16]	8.6	Gait instability, clumsiness, slurred/ scanning speech	11.75	GD Neck Trunk UE LE	2,000 mg; 5 yr	Improved: ataxia Onset: progressive dystonia
Mariotti et al.[3]	8	ND	ND	ND	2,400 mg; 5 yr	Improved: ataxia, dystonia
Our case: female	11	Dystonic head tremor	At onset	Neck UE	2,400 IU; 10 mo	Onset: ataxia
Our case: male	11	Dystonic head tremor	At onset	GD Neck Trunk UE LE	2,400 IU; 10 mo	Improved: dysarthria, dysdiadochokinesia

Abbreviations: AVED, Ataxia with Vitamin E Deficiency; GD, Generalized Dystonia (defined as combination of segmental crural plus other area of body); LE, Lower Extremity; mo, Months; ND, Not Described; UE, Upper Extremity; yr, Years.

The specific response of dystonia in AVED to vitamin E treatment is variable. Dystonia has been reported to improve in two patients,[3,5] and most patients with dystonia as a feature of their disease had stabilization or improvement of their other symptoms on high dose vitamin E (Table 1). One patient, however, experienced progressive dystonia despite escalating doses of vitamin E supplementation.[16] There are anecdotal reports of dystonia improvement in response to symptomatic treatment with botulinum toxin, trihexyphenidyl,[16] and clonazepam.[5] The sister in our report clearly improved with trihexyphenidyl treatment. Since AVED may be treatable if diagnosed early, it should be considered in the differential diagnosis of progressive dystonia, particularly when the dystonia is cervical, or is accompanied by head tremor.

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