

Reviews

More Than Ataxia: Hyperkinetic Movement Disorders in Childhood Autosomal Recessive Ataxia Syndromes

Toni S. Pearson*

Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA

Abstract

Background: The autosomal recessive ataxias are a heterogeneous group of disorders that are characterized by complex neurological features in addition to progressive ataxia. Hyperkinetic movement disorders occur in a significant proportion of patients, and may sometimes be the presenting motor symptom. Presentations with involuntary movements rather than ataxia are diagnostically challenging, and are likely under-recognized.

Methods: A PubMed literature search was performed in October 2015 utilizing pairwise combinations of disease-related terms (autosomal recessive ataxia, ataxia–telangiectasia, ataxia with oculomotor apraxia type 1 (AOA1), ataxia with oculomotor apraxia type 2 (AOA2), Friedreich ataxia, ataxia with vitamin E deficiency), and symptom-related terms (movement disorder, dystonia, chorea, choreoathetosis, myoclonus).

Results: Involuntary movements occur in the majority of patients with ataxia–telangiectasia and AOA1, and less frequently in patients with AOA2, Friedreich ataxia, and ataxia with vitamin E deficiency. Clinical presentations with an isolated hyperkinetic movement disorder in the absence of ataxia include dystonia or dystonia with myoclonus with predominant upper limb and cervical involvement (ataxia–telangiectasia, ataxia with vitamin E deficiency), and generalized chorea (ataxia with oculomotor apraxia type 1, ataxia–telangiectasia).

Discussion: An awareness of atypical presentations facilitates early and accurate diagnosis in these challenging cases. Recognition of involuntary movements is important not only for diagnosis, but also because of the potential for effective targeted symptomatic treatment.

Keywords: Choreoathetosis, ataxia with oculomotor apraxia, ataxia with vitamin E deficiency

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*To whom correspondence should be addressed. E-mail: tpearson@wustl.edu

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Introduction

The autosomal recessive cerebellar ataxias are a large and heterogeneous group of conditions that often present during childhood or adolescence. Many of these conditions are characterized by complex, mixed neurological syndromes that include sensorimotor peripheral neuropathy, spasticity, or loss of proprioception and vibration sense due to dorsal column degeneration, in addition to ataxia. Furthermore, ataxia may not be the sole movement abnormality. Hyperkinetic movement disorders, including dystonia, chorea, myoclonus, and tremor, occurred in about one-third of patients with progressive autosomal recessive ataxia in one cohort.¹ The severity of the accompanying involuntary movements may vary

from mild to severe. In some instances, the involuntary movements, rather than ataxia, may be the initial neurological symptom, making accurate and timely diagnosis particularly challenging.

The clinical and genetic characteristics of the autosomal recessive ataxias have been well described in several recent reviews^{2,3} and are summarized in Table 1. The spectrum of involuntary movements in the autosomal dominant spinocerebellar ataxias has also been described previously.⁴ The focus of this review is to describe the spectrum and, where possible, the frequency of involuntary movements associated with selected childhood-onset autosomal recessive ataxia syndromes in which involuntary movements are very common, or are under-recognized as a presenting feature of the disease: ataxia–telangiectasia (A-T), ataxia with

Table 1. Features of Ataxia Syndromes Associated with Involuntary Movements

Gene	Involuntary movements				Other clinical features	Laboratory findings
	Dystonia	Chorea	Myoclonus	Tremor (head, upper limbs)		
Ataxia-telangiectasia						
<i>ATM</i>	++	++	++	++	Immundeficiency, malignancy, telangiectasia, ± OMA	Elevated serum AFP ± CEA IgG deficiency (subclasses 2 and 4)
AOA1						
<i>APTX</i>	++	++			Oculomotor apraxia, areflexia, axonal sensorimotor neuropathy	Low serum albumin Elevated serum LDL ± elevated CK
AOA2						
<i>SETX</i>	+	+		+	Oculomotor apraxia, areflexia, axonal sensorimotor neuropathy	Elevated serum AFP
Friedreich's ataxia						
<i>FXN</i>	+	+	+	+	Areflexia, extensor plantar reflexes, scoliosis, pes cavus, deafness, cardiomyopathy, diabetes mellitus, loss of proprioception and vibration sense, axonal sensory neuropathy	
AVED						
<i>TTPA</i>	+			+	Areflexia, impaired proprioception and vibration sense with abnormal spinal SSEP; mild axonal sensory neuropathy in some patients	Low serum vitamin E (alpha-tocopherol)

++, Common (>50% of patients); +, <50% of patients. Abbreviations: AFP, Alpha-fetoprotein; AOA, Ataxia with Oculomotor Apraxia; AVED, Ataxia with Vitamin E Deficiency; CEA, Carcinoembryonic Antigen; CK, Creatine Kinase; LDL_c, Low-density Lipoprotein; OMA, Oculomotor Apraxia; SSEP, Somatosensory Evoked Potential.

oculomotor apraxia types 1 and 2 (AOA1 and AOA2), Friedreich ataxia (FA), and ataxia with vitamin E deficiency (AVED). For each condition, presentations in which the hyperkinetic movement disorder is prominent are highlighted.

Methods

A literature search of the PubMed database was performed in October 2015, utilizing pairwise combinations of disease-related terms (autosomal recessive ataxia, A-T, ataxia with oculomotor apraxia type 1, AOA1, ataxia with oculomotor apraxia type 2, AOA2, Friedreich ataxia, ataxia with vitamin E deficiency) and symptom-related terms (movement disorder, dystonia, chorea, choreoathetosis, myoclonus). Case reports and case series published in peer-reviewed journals were included. The search was limited to English language publications, with the exception of one historical report on A-T in French.

Ataxia–telangiectasia

A-T is a multisystem disorder characterized by neurodegeneration, immunodeficiency and a predisposition to malignancy. It is caused by inactivating mutations in *ATM*, which encodes a serine-threonine kinase that plays a critical role in DNA repair.⁵ The classical phenotype is characterized by onset of axial and gait ataxia between 1 and 4 years of age after a period of normal motor development in early infancy. Affected children proceed to develop progressive ataxia, dysarthria, and oculomotor apraxia (an eye movement disorder characterized by impaired voluntary initiation of horizontal saccades). Oculocutaneous telangiectasias (small dilated blood vessels) usually appear several years after neurological symptom onset.

The term “variant A-T” is sometimes used to describe patients who have older age of onset, slower disease progression, and/or an incomplete phenotype. These milder phenotypes are typically associated with missense or splice site mutations that produce ATM protein with some residual kinase activity. In contrast, patients with the classic early-onset ataxia phenotype typically have truncating mutations that result in absent or non-functional ATM protein.^{6,7} In patients with milder disease, involuntary movements are often more prominent than ataxia.⁷

A-T is commonly associated with a mixed hyperkinetic movement disorder

Movement disorders, including dystonia, chorea, myoclonus, and parkinsonism are established clinical features of A-T, and were summarized in a recent review.⁸ Specifically, the longstanding recognition of a mixed hyperkinetic movement disorder in a majority of patients is illustrated by Sedgwick and Boder’s⁹ description, in 1960 of “variable choreoathetoid movements and posturing, [and] occasional myoclonic jerks” in 15 of 20 patients. Approximately 90% of adult and pediatric patients were observed to have involuntary movements in several subsequent large case series, with some variation in the precise characterization of the movements: choreoathetosis,¹⁰ or a variable combination of dystonia, chorea, and myoclonus.^{7,11}

Involuntary movements in A-T are variable and tend to be progressive. In children with classic, early-onset disease, the movements may remain mild compared with ataxia,⁹ but in patients with milder disease, progressive involuntary movements can be the dominant motor feature.⁷ Indeed, in what is now acknowledged to be the earliest published report of A-T, Syllaba and Henner¹² in 1926 described three siblings with childhood-onset, slowly progressive athetosis of the face and limbs who remained ambulatory throughout their teens.

There is some suggestion that chorea is more common than dystonia in childhood (60% vs. 15% in one series of 57 children aged 2–19 years¹³), while dystonia becomes more apparent with advancing age. One recent study of 14 adults with childhood-onset A-T reported dystonia in 86%, myoclonus in 70%, but chorea in none.¹⁴

Myoclonus is reported to occur in 60–95% of patients.^{7,13,14} Myoclonus may occur in body regions affected by dystonia,^{14–16} or in distinct regions.^{14,17,18} The trunk, neck, and upper limbs are most frequently affected, and jerks worsen with action. Characterization of the movements with surface electromyography revealed a burst duration of 30–80 ms in one case,¹⁸ and longer duration bursts of >50 ms in others.¹⁴ These findings suggest myoclonus of subcortical origin. In rare cases, myoclonus may become the predominant motor finding, several years after initial onset of ataxia (Myoclonus in A-T: <http://dx.doi.org/10.1016/j.braindev.2014.06.001>; <http://dx.doi.org/10.7916/D88P5Z9X>).^{15,17,18} There are anecdotal reports of symptomatic improvement of myoclonus following treatment with either levetiracetam¹⁷ or clonazepam.¹⁸

Overall, the data suggest that dystonia in A-T is frequently accompanied by jerky movements due to chorea, myoclonus, or both. These clinical observations are supported by a recent kinematic analysis of upper limb movements in patients with A-T, in which both slow and rapid non-rhythmic adventitious movements were recorded using an accelerometer attached to the hand during rest, posture-holding, and finger-to-nose reaching movements.¹⁹ The same study additionally documented rhythmic oscillatory movements, consistent with upper limb postural and action tremor, in the vast majority of patients (79/80).

Involuntary movements as the presenting symptom in A-T

The presence of subtle dystonia or chorea may provide an early clue to the diagnosis in very young children with classic A-T when overt signs of progressive ataxia are lacking.^{11,20} Initial motor symptoms are often quite non-specific. Many infants have a history of walking on time, but continue to appear clumsy or unsteady through the second year of life, prompting neurological evaluation. On examination, the gait is usually narrow-based, but patients veer off course, and dystonic posturing of the upper or lower limbs is often observed.²⁰ Chorea may appear as mild fidgety movements of the hands and feet at this age.²⁰ A small number of patients with prominent, jerky chorea involving the face or the whole body in early childhood as the dominant presenting feature have been reported.^{21,22} Confirmation of the diagnosis of A-T at this early stage can have important implications for genetic counseling and family planning, and also permits recognition of the potential risk of adverse consequences from future cancer treatment.²²

Table 2. Involuntary Movements as the Presenting Motor Abnormality

Distribution of Movements	
Chorea	
Ataxia–telangiectasia	
AOA1	Limbs ± face and trunk
AOA2	
Friedreich's ataxia	
Dystonia	
Ataxia–telangiectasia	Limbs (young children); cervical, upper limbs (older children)
AVED	Cervical, upper limbs most common
AOA2	Upper limbs
Dystonia with myoclonus	
Ataxia–telangiectasia	
AVED	Cervical, upper limbs
Postural tremor	
AVED	
AOA2	Head

Abbreviations: AOA, Ataxia with Oculomotor Apraxia; AVED, Ataxia with Vitamin E Deficiency.

A-T may present with isolated dystonia (Table 2). Age of onset as young as 2 years has been documented,²³ although in most reported cases, dystonia onset occurred later in childhood. The neck and upper limbs were the most frequent initial sites of dystonia.^{14,24–28} In two patients, dystonia was later accompanied by myoclonus of the head, trunk, or upper limbs, mimicking myoclonus–dystonia (Dystonia and dystonia with myoclonus in A-T: <http://dx.doi.org/10.1016/j.parkreldis.2013.08.013>; <http://dx.doi.org/10.1212/WNL.0b013e3182494d51>).^{16,23,27} Some patients developed progressive generalized dystonia.^{14,25,29} Dystonia improved markedly with levodopa therapy in three siblings with adolescent-onset cervical dystonia,²⁶ but levodopa response was more modest¹⁵ or absent^{29–31} in other cases.

A specific homozygous founder missense mutation in the Canadian Mennonite population (c.6200 C>A) is associated with a pure dystonia or myoclonus–dystonia-like phenotype with predominant cervical and upper limb involvement (Dystonia and dystonia with myoclonus in A-T: <http://dx.doi.org/10.1016/j.parkreldis.2013.08.013>; <http://dx.doi.org/10.1212/WNL.0b013e3182494d51>).^{16,23} In this population, the 12 reported patients experienced onset of dystonia between ages 1 and 20 years. Over half of the patients eventually developed generalized dystonia, but none developed ataxia in adulthood.

Ataxia with oculomotor apraxia type I

AOA1 is caused by mutations in *APTX*, which encodes aprataxin, a nuclear protein involved in DNA strand-break repair³² (Table 1). Symptom onset in AOA1 typically occurs in the first decade of life. The initial manifestation in most patients is gait ataxia, followed by dysarthria and upper limb dysmetria, and oculomotor apraxia. The ataxia is slowly progressive, and all patients also develop an axonal sensorimotor neuropathy that leads to eventual quadriparesis and loss of ambulation approximately 7–10 years after disease onset.^{32,33}

Chorea and dystonia both occur commonly in AOA1 (Dystonia and chorea in AOA1; <http://dx.doi.org/10.1056/NEJMra1006610>)². Chorea is present in up to 80% of patients at onset,³⁴ and is usually most severe early in the disease course.^{34,35} The movements can affect the face, laryngo-pharynx, and limbs. Chorea often subsides as the disease progresses, and may disappear entirely in some patients, particularly those who later develop severe neuropathy-related weakness. Chorea remains persistent and disabling in a minority of patients.³⁴

Dystonia is present in about 50% of patients,³⁶ and may be apparent soon after disease onset,^{34,36,37} or develop several years into the disease course.³⁸ Most patients have upper limb dystonia that is less prominent than either the ataxia or neuropathy. However, two Japanese patients

with progressive generalized dystonia as the dominant feature have been described.^{37,38} In one of those two patients, dystonia improved with clonazepam treatment (4 mg/day), but was not responsive to either levodopa-carbidopa (250–25 mg/day) or trihexyphenidyl (15 mg/day).³⁷

Involuntary movements at presentation

Chorea was the most prominent presenting neurological feature in six of the 14 patients in one series, leading to initial investigation in five patients for Sydenham chorea, Huntington disease, or benign hereditary chorea (Table 2).³⁴

Ataxia with oculomotor apraxia type 2

AOA2 is caused by mutations in *SETX*, which encodes the protein senataxin. Senataxin has a RNA-interacting helicase domain and a protein-interacting amino-terminal domain, and plays important roles in RNA processing and the maintenance of genomic stability.³⁹ The AOA2 clinical syndrome is characterized by slowly progressive ataxia, oculomotor apraxia, and axonal sensorimotor peripheral neuropathy (Table 1). Symptom onset occurs later than in AOA1, commonly during the second decade of life. Gait ataxia is the most common initial symptom.^{40–42}

Hyperkinetic movement disorders are less prevalent in AOA2 than in AOA1, but they do occur. In the 90-patient series of Anheim et al.,⁴³ dystonia was detected in 14%, head tremor in 14%, and chorea in 10% of patients. A slightly higher prevalence of 20–25% for dystonia and chorea⁴⁰ and for head tremor⁴² was reported in two smaller series. Dystonia usually affects the hands,⁴³ but trunk involvement has also been reported.⁴¹ A few patients have a combination of chorea and dystonia.^{40,41} Movements may either remain stable⁴⁰ or diminish over time.^{41,44} The relative stability of movements in some cases may be attributable to the slower rate of progression of weakness in AOA2 than in AOA1.

Dystonia in AOA2 has been reported to occur more frequently in patients with milder disease. Milder phenotypes correlate with missense mutations in the helicase domain of *SETX* (frequency of dystonia: 41.7%), while more severe disease is associated with missense mutations outside the helicase domain, truncating mutations, or deletions (frequency of dystonia: <10%).⁴³

There is a single report of symptomatic treatment with bilateral pallidal deep brain stimulation (DBS) in a 19-year-old patient with upper and lower limb dystonia, bilateral rest and action tremor of the arms, and jerky arm movements suggestive of myoclonus.⁴⁵ The patient's arm tremor and myoclonus improved, although there was no change in the Unified Dystonia Rating Scale (UDRS) score.

Involuntary movements at presentation

Rarely, involuntary movements have been reported as a prominent presenting symptom of AOA2, although they are accompanied by ataxia in almost all cases (Table 2). Two patients had upper limb dystonia as an initial symptom.^{40,42} Two siblings presented with

prominent chorea of the trunk and face.⁴⁴ One patient had isolated head tremor as the initial symptom at age 9 years.⁴²

Friedreich ataxia

FA is the most common autosomal recessive ataxia in Caucasian populations. The neurological syndrome is characterized by progressive ataxia, dysarthria, limb weakness, impaired proprioception and vibration sense, areflexia, and extensor plantar responses (Table 1). Homozygous GAA triplet repeat expansions in exon 1 of the frataxin gene (*FXN*) are detected in over 90% of patients. The remaining patients have an abnormal GAA expansion on one allele coupled with another pathogenic variant on the other allele.

Involuntary movements are not uncommon in FA, but only rarely are they the dominant feature. Of 29 patients with FA in one series, 17% had postural tremor of the upper limbs or head, and 45% had mild upper limb dystonia.⁴⁶ The dystonia was observed on examination, but was usually unnoticed by patients, overshadowed by their other motor symptoms.

A handful of case reports describe prominent dystonia in patients with FA who had initially presented with ataxia. One 20-year-old patient had fixed rotational torticollis together with episodic exercise-induced dystonic head tremor.⁴⁷ Two patients in their late teens experienced trunk spasms and writer's cramp.⁴⁸ Rare reports of chorea as an early disease feature also exist (see below).^{49–51}

Involuntary movements at presentation

An atypical presentation of generalized chorea without ataxia has been described in three patients (Table 2). The first two had symptom onset at ages 19 and 12 years and were both homozygous for the typical intronic GAA expansion.⁴⁹ The third, with compound heterozygous mutations, experienced atypically early onset at age 4 years with progressive trunk and limb chorea prior to the onset of ataxia at age 12.⁵¹ Simultaneous onset of apparently acute ataxia with chorea of the tongue and hands has also been reported in one 10 year old boy with compound heterozygous mutations.⁵⁰

Ataxia with vitamin E deficiency

AVED is one of the few treatable neurodegenerative diseases, making prompt diagnosis critical. Patients have low levels of plasma vitamin E as a result of mutations in *TTPA*, the gene encoding the α -tocopherol transfer protein, which normally incorporates α -tocopherol into very low density lipoproteins in the liver for secretion into the circulation.⁵² Treatment with high-dose vitamin E supplementation prevents disease progression, and may partially reverse symptoms in some cases.^{53,54}

AVED is often characterized as a FA-like syndrome. The diseases share the common features of progressive gait ataxia, dysarthria, areflexia, and impaired proprioception and vibration sense (Table 1). A distinguishing motor feature in AVED, not observed in patients with FA, is a postural head tremor (i.e., tremor that is present when the patient is upright), reported in 28%⁵⁵ and 44%⁵⁴ of patients in two respective series (Table 2).

Dystonia was observed in 13% of patients with AVED in the largest published series to date.⁵⁵ Additional case reports demonstrate that dystonia may be a prominent finding.^{56–60} The face and neck were the most commonly affected body regions, but in half of the 10 patients reported to date, dystonia spread to become generalized.^{58,59,61} Dystonia usually emerged after patients had already developed progressive cerebellar symptoms.

Involuntary movements at presentation

Importantly, dystonia as the presenting symptom of AVED has been described in three patients in two separate reports.^{57,62} In all three cases, the dystonia was cervical and associated with irregular head tremor (Dystonia in AVED; <http://dx.doi.org/10.7916/D8B85820>)⁶². In one patient, the combination of posturing and jerky head movements mimicked myoclonus–dystonia (Table 2).⁵⁷ The involuntary movements preceded the onset of ataxia by 3–6 years, suggesting that we should screen for vitamin E deficiency not just in the context of ataxia, but also in patients with progressive dystonia or dystonia with myoclonus, particularly when the neck is involved.

The specific response of dystonia to treatment with vitamin E appears to vary, and is not always specifically described. Dystonia improved with treatment in at least two cases.^{54,57} However, dystonia progressed despite treatment in a patient who developed dystonia 2 years after ataxia onset, while on high-dose vitamin E supplementation.⁵⁹ The patient's dystonia responded partially to symptomatic treatment with botulinum toxin injections and trihexyphenidyl.

Data about the long-term response of other symptoms, including head tremor and ataxia, to vitamin E therapy are limited. Head tremor tended to improve,⁵³ while improvements in gait ataxia were more limited in two studies that describe treatment response.^{53,54} A few patients experienced progressive ataxia despite vitamin E therapy.⁵⁴ Most patients seem to experience stabilization rather than a significant reversal of symptoms,⁵⁴ highlighting the importance of prompt diagnosis.

Pathophysiology of involuntary movements in ataxia syndromes

The pathophysiological basis of the involuntary movements observed in the diseases described above remains unknown. Involuntary movements have traditionally been associated with dysfunction of the basal ganglia. Does the presence of involuntary movements therefore imply basal ganglia involvement in these ataxia syndromes? An alternative hypothesis is that cerebellar pathology may be implicated in some way in the pathogenesis of involuntary movements such as dystonia and chorea.

The main common pathological finding in brain in A-T, AOA1, AOA2, and AVED is a marked loss of cerebellar Purkinje cells.^{63,65} In FA, Purkinje cell loss is relatively mild, and ataxia is attributed to severe atrophy of the dentate nucleus,⁶⁶ in combination with proprioceptive sensory loss from dorsal column degeneration.

What evidence is there for basal ganglia dysfunction or pathology? Data from one fludeoxyglucose positron emission tomography study of adult patients with A-T demonstrated hyperactivity in the globus

pallidus that correlated inversely with subjects' motor performance.⁶⁷ However, evidence of basal ganglia pathology on post-mortem examination in A-T (the most extensively characterized of the disorders, with published neuropathological reports from over 30 patients) is scarce.^{64,65,68,69} The possibility of abnormal basal ganglia neuronal function without detectable cell loss remains possible.

There has been recent interest in a possible role of the cerebellum in the pathogenesis of involuntary movements via the interaction of cerebellar and basal ganglia circuits. In the past decade, results from anatomical experiments have provided evidence for disynaptic pathways connecting the dentate nucleus and striatum,⁷⁰ and the subthalamic nucleus and cerebellar cortex.⁷¹ A potential role of the cerebellum in the pathogenesis of dystonia has been a particular topic of study and debate,⁷² (reviewed by Prudente et al.⁷³).

Conclusions

Involuntary movements occur in the majority of patients with A-T and AOA1, and less frequently in patients with AOA2, FA, and AVED. Occasionally, the hyperkinetic movement disorder, rather than ataxia, may be the most prominent initial motor finding. Presentations with isolated dystonia, dystonia with myoclonus, and generalized chorea do occur. In a child or adolescent with progressive dystonia, particularly in a craniocervical or upper limb distribution, A-T and AVED should be considered in the differential diagnosis.

Recognition of hyperkinetic movement disorders in these diseases has important implications for diagnosis, genetic counseling, and treatment. In the appropriate clinical context, screening laboratory investigations may rapidly guide further diagnostic testing (Table 1). When movement symptoms are severe and functionally disabling, accurate characterization is also important for treatment. In contrast to the functional deficits resulting from cerebellar degeneration and motor neuropathy, involuntary movements are often amenable to symptomatic treatment.

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