Abnormal Saccades Differentiate Adolescent Onset Variant Ataxia Telangiectasia from Other Myoclonus Dystonia

Sir,

Ataxia telangiectasia (A-T) is an autosomal recessive disorder caused by inactivating mutations in the ataxia telangiectasia mutated (*ATM*) gene, which encodes the ATM kinase protein.[1] A-T patients usually present before 2 years of age with ataxia, extrapyramidal (EP) movement disorders, oculomotor apraxia (OMA), and peripheral neuropathy leading to wheelchair dependency before end of first decade of life.[2] This classic A-T presentation is characterized by telangiectasias, immunodeficiency, radiosensitivity, and increased serum α-fetoprotein (AFP) levels along with a predisposition to cancer.[2] Besides this prototype, a milder phenotype with later age of onset, slower progression and prolonged survival exists called variant A-T[3] which is associated with mutations that leave some residual ATM kinase activity, whereas it is fully absent in the classic subtype.[4] Variant A-T may rarely present as myoclonus dystonia (M-D).

Case Report

A 30-year-old gentleman presented with involuntary neck movements since 12 years of age and involuntary movements of both upper limbs since 18 years of age. His neck movements were intermittent, nonrhythmic, and horizontal with rotational jerks to left, which were aggravated with stress and anxiety and reduced with sensory tricks. He had intermittent, brief, jerky, shock-like movements of neck and both hands (right > left) with abnormal posture during writing and holding, affecting his ability to do fine work. These movements were exacerbated by somatosensory and auditory stimuli. There were no diurnal fluctuations or paroxysms. Family history was negative.

On examination, there was no oculocutaneous telangiectasia. He had cervical dystonia in the form of left rotacollis with right laterocollis and neck myoclonus [Video 1]. Upper extremities showed asymmetric dystonic posturing of both hands along with myoclonic jerks. He had slow vertical saccade and hypometric horizontal saccades without OMA. Gait ataxia and cerebellar signs were conspicuously absent. His routine blood investigations (hemogram, biochemistry) were normal. KF ring was absent; serum ceruloplasmin and 24-h urinary copper were normal. Ultrasonogram of abdomen–pelvis and magnetic resonance imaging (MRI) of brain were normal. Genetic studies for DYT 1,11 and SCA 1,2,3 were negative. Clinical whole-exome sequencing showed a homozygous missense mutation (c. 9156G > C; p.Trp3052Cys) in exon 63 of *ATM* gene on chromosome 11q22. His serum AFP levels were high at 317.2 ng/ml (normal <10 ng/ml). The same variant was detected by next-generation sequencing in heterozygous condition in the father of the index patient, which was confirmed by Sanger sequencing.

Discussion

Our case shows that as compared to classic A-T, variant A-T presents predominantly as an EP syndrome (isolated dystonia

Table 1: Showing key differences between classic and variant A-T

Characteristics	Classic A-T	Variant A-T
ATM gene mutation	Usually splicing mutation; severe phenotype (no functional ATM protein)	Usually missense mutation; milder phenotype (small amount of residual ATM protein)
Clinical phenotype	Ataxia dominant; more malignant course	Extrapyramidal features dominant; more benign course
Cerebellar ataxia	Cardinal feature (nearly all patients)	Can be absent; if present, mild
Telangiectasia	Present in almost all	Seen in 50%. If present, mild
Immunodeficiency	Present in almost all	No immunodeficiency
Oculomotor apraxia	In virtually all patients	Can be absent in up to 50%
MRI brain	Cerebellar atrophy (vermian)	Normal in 60% patients
Serum AFP	Usually high	Can be normal or mild increased

AFP = α-Fetoprotein; ATM = ataxia telangiectasia mutated

Table 2: Genes with myoclonus dystonia phenotype and differentiating features

Gene (gene product)	Differentiating features in phenotype
ATM (ATM kinase protein)	AR, adolescent onset, mildly progressive course, with no alcohol responsiveness
	myoclonus of neck + dystonia of neck and UEs
	ataxia, telangiectasia, oculomotor apraxia, and immunodeficiency can be present in up to half the subjects
	milder degrees of supranuclear eye movement abnormalities (slow or hypometric saccades), parental consanguinity, modest elevation in serum α-fetoprotein will help to differentiate
SGCE (epsilon sarcoglycan)	AD, adolescent onset; myoclonus of UEs (proximal > distal) and neck
	Myoclonus more prominent and debilitating than dystonia, psychiatric abnormalities, and exquisite alcohol response will help to differentiate
Maternal uniparental disomy (mUPD7)	Features similar to epsilon sarcoglycan (same chromosome 7)
	Short stature, triangular facies, and postnatal growth retardation, association with Silver-Russell syndrome will help to differentiate
ADCY5 (adenyl cyclase 5)	AD, first decade onset; dystonia is often generalized and progressive
	Saccadic abnormalities may be seen
	Nocturnal aggravation of movement disorder, facial dyskinesia, axial hypotonia, delayed milestones, dysarthria, episodic painful dystonic posturing aggravated by stress or illness help in differentiating
RELN (reelin)	AD, third decade onset
	Have psychiatric abnormalities and response to alcohol similar to epsilon sarcoglycan patients though with a milder disease course
	Enhanced startle, later age of onset will help to differentiate
GNAL (guanine nucleotide binding protein G (olf), subunit α) known as DYT25	AD, fourth decade onset with progressive course
	No alcohol responsiveness or psychiatric features
	Myoclonus of UEs; dystonia of neck, oromandibular region, larynx associated with tremor of head, UEs help to differentiate
ANO3 (Anoctamin 3) also known as DYT24	AD, first to fourth decade onset, slowly progressive
	Myoclonus affects neck, UEs
	Dystonia involves cervical, oro-mandibular region, larynx, blepharospasm
	Tremor affecting head, UEs >> voice help to differentiate
GCH1 (GTP cyclohydrolase I)	AD, first decade onset
	Myoclonus onset in UEs, then spreading to LLs, face, trunk plus dystonia in neck, UEs
	Parkinsonian features and excellent response to levodopa will help to differentiate

AD = autosomal dominant; AR = autosomal recessive; UEs = upper extremities; LL = lower limbs

or M-D with or without choreoathetosis and tremor). Ataxia, telangiectasia, OMA and immunodeficiency can be absent in up to half the variant A-T cases [Table 1]. MRI brain can be normal in 60% of patients while serum AFP elevation is usually mild to moderate. Lesser degrees of supranuclear eye movement abnormalities (slow or hypometric saccades) with modest elevation in serum AFP, as seen in our case, will help to differentiate it from similar presentation of other genetic diseases, namely, dystonia due to epsilon sarcoglycan mutation (DYT-11). Saccadic abnormalities may be seen in M-D due to *ADCY5* mutation; however, nocturnal aggravation of movement disorder, facial dyskinesia, axial hypotonia, episodic painful dystonic posturing aggravated by stress or illness, and delayed developmental milestones help in differentiating it from variant A-T [Table 2].[5]

A unique dominant M-D like syndrome with cardiac arrhythmias, was initially linked to a mutation in the *CACNA1B* gene, coding for neuronal voltage-gated calcium channels.[6] However, this was refuted by a large European multicentric cohort study.[7] In a study on DYT11-negative patients with M-D

phenotype, rare missense variants in *RELN* were identified. *RELN* mutations segregate in an autosomal dominant fashion and the product reelin is a large secreted glycoprotein that plays essential roles in the cytoarchitecture of laminated brain structures. *RELN* mutation-positive patients have a higher age at onset and a milder course of disease compared to epsilon sarcoglycan M-D patients though psychiatric abnormalities and response to alcohol were common among both.[8]

Similar M-D like presentation of A-T, with onset in second decade similar to ours, was first reported from India in 2002, however it was not genetically proven.[9] In the largest series of A-T from India consisting of 100 patients, presentation with dystonic crisis was seen in one and 29 subjects had choreoathetosis as initial feature. Neither myoclonus nor M-D phenotype was observed in their cohort.[10]

Our case of genetically proven variant A-T highlights the fact that mild degrees of supranuclear eye movement abnormalities with modest elevation in serum α-fetoprotein will help to differentiate M-D like phenotype from similar presentation of other genetic diseases. Variant A-T needs follow-up due to an increased risk for malignancy compared to others with similar M-D phenotype.

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Conflicts of interest

There are no conflicts of interest.

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