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      | 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 |
| GNAI (guanine nucleotide binding protein G (olf), subunit a) 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 1)      | 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].

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. However, this was refuted by a large European multicentric cohort study. 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.

References
1. Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, et al. A single ataxia telangiectasia gene with a product similar to Pt-3 kinase. Science 1995;268:1749-53.
2. van Os NJH, Hensiek A, van Gaalen J, Taylor AMR, van Deuren M, Weemaes CMR, et al. Trajectories of motor abnormalities in milder phenotypes of ataxia telangiectasia. Neurology 2019;92:e19-29.
3. Verhagen MMM, Abdo WF, Willemsen MAAP, Hogervorst FBL, Sneeuws DFCM, Hiel JAP, et al. Clinical spectrum of ataxia-telangiectasia in adulthood. Neurology 2009;73:430-7.
4. Saunders-Pullman RJ, Gatti R. Ataxia-telangiectasia: Without ataxia or telangiectasia? Neurology 2009;73:414-5.
5. Chang FC, Westenberger A, Dale RC, Smith M, Pall HS, Perez-Dueñas B, et al. Phenotypic insights into ADCY5-associated disease. Mov Disord 2016;31:1033-40.
6. Groen JL, Andrade A, Ritz K, Jalalzadeh H, Haagmans M, Bradley TE, et al. CACNA1B mutation is linked to unique myoclonus-dystonia syndrome. Hum Mol Genet 2015;24:987-93.
7. Mencacci NE, R'bibo L, Bandres-Ciga S, Carecchio M, Zorzi G, Nardocci N, et al. The CACNA1B R1389H variant is not associated with myoclonus-dystonia in a large European multicentric cohort. Hum Mol Genet 2015;24:5326-9.
8. Groen JL, Ritz K, Jalalzadeh H, van der Salm SMA, Jongejan A, Mook OR, et al. RELN rare variants in myoclonus-dystonia. Mov Disord 2015;30:415-9.
9. Goyal V, Behari M. Dystonia as presenting manifestation of ataxia telangiectasia: A case report. Neurol India 2002;50:187-9.
10. Mahadevappa M, Kamble N, Santhosh Kumar DV, Yadav R, Netravathi M, Pal PK. A clinical profile of 100 patients with ataxia telangiectasia seen at a tertiary care center. Ann Mov Disord 2020;3:33-8.