Case Report

Dopa-Responsive Dystonia: An Early Presentation of Ataxia-Telangiectasia

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Abstract

Ataxia-telangiectasia (AT) is a complex genetic neurodegenerative disease with autosomal recessive inheritance. The typical initial features of ataxia telangiectasia include ataxia, cutaneous telangiectasia, and immune deficiency with recurrent infections. Usually, movement disorder occurs late in the course of the disease. A diagnosis of variant or atypical ataxia-telangiectasia (variant AT) is considered in case of any deviation from the normal course of illness giving rise to variable presentations of the disease. Only a few cases of variant AT with predominant movement disorder have been reported worldwide. A knowledge of atypical presentations helps in early diagnosis and thus to initiate management and counselling of the family at the earliest. Here, we report a case of genetically confirmed ataxia-telangiectasia with an initial presentation of dopamine responsive dystonia.

Keywords: Dystonia, exome sequencing, genetic counselling, rare diseases

Introduction

Ataxia-telangiectasia (AT) is a genetic neurodegenerative disease with autosomal recessive inheritance. It usually manifests in late infancy or early childhood with ataxia, cutaneous telangiectasia, and impaired functioning of immune system resulting in increased susceptibility to infections and higher risk of malignancies.[1] Patients with AT may also develop various movement disorders, including choreoathetosis, myoclonus, and dystonia later in the course of illness. Any deviation from the normal course of illness is considered as variant or atypical AT.[2] Dopa-responsive dystonia (DRD) is an uncommon treatable condition that can be a rare presentation of a few genetic disorders. The current report highlights a genetically proven case of AT with an initial presentation of DRD.

Case Details

A four-year-old male child, born to non-consanguineous Indian parents, presented at two-years of age with gait imbalance. Although the child achieved independent walking by 12 months, he developed progressively worsening abnormal gait in the form of abnormal posturing and dragging of the right foot with frequent falls [Video 1]. The fine motor, social, cognitive, and language milestones were age-appropriate, although his speech was unclear. Antenatal, natal, and postnatal history were non-contributory.

On examination, anthropometry was normal. He had asymmetrical generalized dystonia with predominant lower limb involvement, Oro-motor dystonia with dysarthric speech, drooling, and central hypotonia. External ocular movements were complete. No apraxia, nystagmus, or telangiectasia were observed.

Basic biochemistry, metabolic work-up, and magnetic resonance imaging (MRI) of the brain returned normal. Suspecting a neurotransmitter disorder, an empiric trial of low dose levodopa was initiated at an initial dose of 2 mg/kg/day and increased to 4 mg/kg/day, with best results at 2.5 mg/kg/day. As neurotransmitter analysis was not easily available, simultaneous whole exome sequencing (WES) was ordered. On three-month follow-up, parents reported relief in drooling and oromotor dystonia immediately, with significant gradual improvement in generalized dystonia, gait, and balance. Clinically, the child behaved like a case of dopa-responsive dystonia (DRD).

WES detected homozygous, two base-pair deletions in exon-61 of *ATM* (NM_000051.3:c.8833_8834del; depth: 67x) that resulted in frame-shift variant and premature protein truncation, (p.Leu2945ValfsTer10)

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[Supplimentary Figure 1]. This variant was classified as pathogenic (according to the American College of Medical Genetics and Genomics [ACMG] guidelines).[3] Serum alfa-fetoprotein (AFP) was high (106 ng/ml, normal range 0–8); immunoglobulin profile returned normal. Targeted parental Sanger sequencing revealed a heterozygous state in the mother while the father carried wild-type *ATM* allele [Supplimentary Figures 2 and 3]. Short-tandem-repeats profile proved the biological relatedness of the child [Supplimentary Figure 4]. Thus, the proband had maternally inherited a single *ATM* variant while the other likely occurred *de novo*, thereby confirming a diagnosis of variant-AT associated with DRD.

Further follow-up over the next one year showed progressive improvement in gait, balance, and dystonia, with mild persistence of gait asymmetry. Levodopa was erroneously discontinued by another physician, only to worsen the child's dystonic features. A reintroduction of levodopa showed the same clinical benefits, re-enforcing the dopa responsiveness. Over time, the child achieved running, climb stairs, and jumping independently [Video 2].

Post-test genetic counseling outlined the disease prognosis, role of onco-surveillance for breast cancer in the carrier mother, and available reproductive options.[1]

Discussion

DRD is an uncommon but treatable condition showing a dramatic and sustained response to levodopa. It is usually seen in disorders affecting the dopaminergic pathways (dopamine synthesis defects, transportopathies). DRD can rarely be an initial presentation of disorders not affecting the nigrostriatal dopaminergic system (e.g. *DYT1*-related disorders, GLUT1-deficiency, AT).[4]

Variant-AT is a milder form of AT with variable initial presentations, later age of onset, and slower rate of progression. Although the classical features of AT including ocular telangiectasia and immunodeficiency are infrequent and less prominent, the burden of malignancies is high.[2,5] Our case represents one of the rare clinical reports of variant-AT with DRD in a young child; the first from India, as per our knowledge.

Compared to other causes of dystonia, DRD associated with variant-AT presents earlier (median 12 years; range 1–20 years) with progressive dystonia, tremors, and variable myoclonus. Appendicular, cervical, and cranial dystonia are more commonly appreciated. DRD associated with variant-AT and with disease onset of <5 years usually has predominant neck and leg dystonia initially, similar to our patient.[2]

Schneider *et al*.[6] reported a family of cervical DRD with three affected siblings. All relevant work-up, including genetic tests for *GCH-1*, *TH*, and *SPR*, returned negative. Years later, WES detected causative compound-heterozygous variants in *ATM* (frameshift deletion and missense variant) in these siblings.[7] In another Canadian cohort of 35 patients with dystonia, 13 had homozygous *ATM* variants. In another case, a homozygous frameshift *ATM* variant with premature truncation of translation was found in a two-year-old girl with predominant DRD and no typical features of AT.[8] In previously reported cases, as part of reserve phenotyping, the levels of serum AFP and immunoglobulins were not uniformly mentioned; but a few of them had high serum AFP levels.

Our case also highlights a seemingly obvious but sometimes overlooked aspect of parental segregation, even in scenarios of clear pathogenicity. The child had inherited one variant from the mother while the second variant occurred likely *de novo*, though the possibility of paternal gonadal mosaicism cannot be ruled out.

This case serves as a reminder for laboratories to include the *ATM* gene in dystonia panels. We also suggest that clinicians be sensitized about AT as a rare but plausible etiology in cases of DRD. The measurement of serum AFP can serve as a cost-effective screening in outpatient services for patients presenting with DRD. Better understanding of such expanded spectra of AT would help to truncate the tiring diagnostic odysseys borne by families. The benefits of early diagnosis are manifold, given the positive therapeutic impact of a timely diagnosis as well as the role of reproductive counseling. It is noteworthy that the *ATM* gene is considered a moderate penetrance breast cancer susceptibility gene, with more than two-fold increase in risk of developing breast cancer in female *ATM*-carriers compared to the general population.[1] Early diagnosis thus aids regular onco-surveillance in as-yet unaffected family members.

Thus, the current case reminds us of the genetic heterogeneity of dopa-responsive dystonia and the impact of early diagnosis in cases of rare disorders.

Acknowledgements

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What is known: Dopa-responsive dystonia is usually seen in disorders affecting dopaminergic pathways (dopamine synthesis defects, transportopathies).

What is new: Dopa-responsive dystonia as an initial presentation of ataxia-telangiectasia highlights the expanded genetic spectrum of dopa-responsive dystonia phenotype and impact of early genetic diagnosis.

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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Nil.

Conflicts of interest
There are no conflicts of interest.

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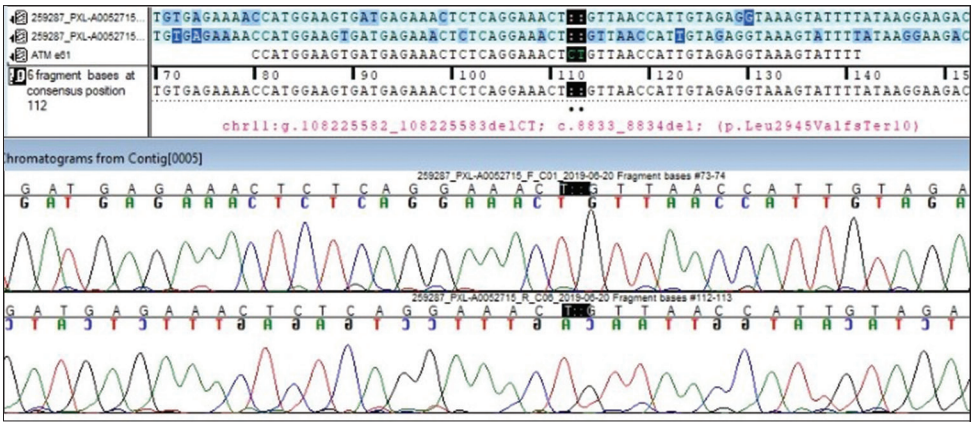
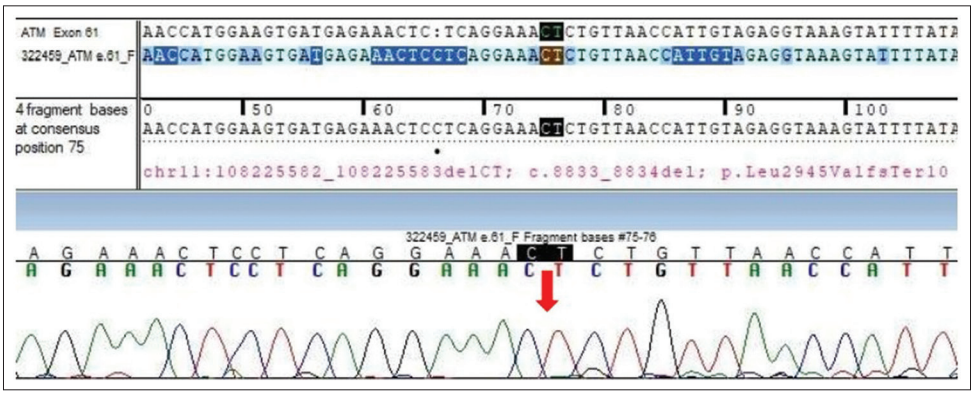
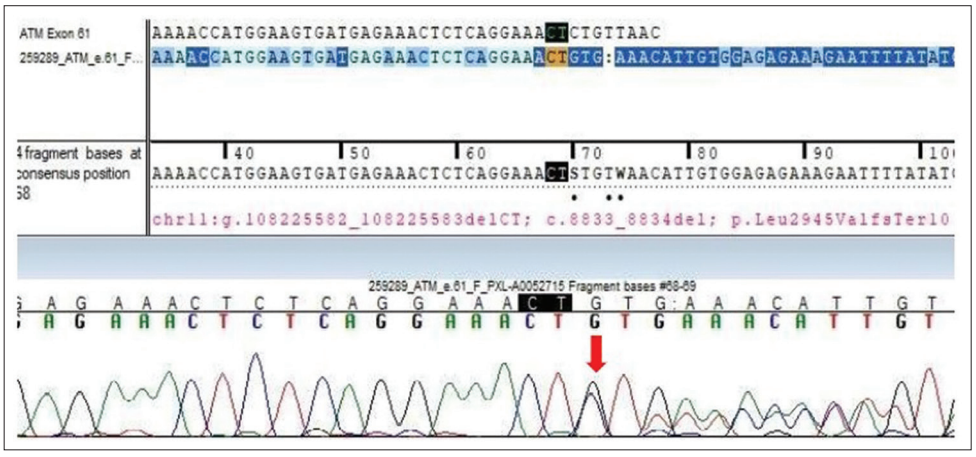


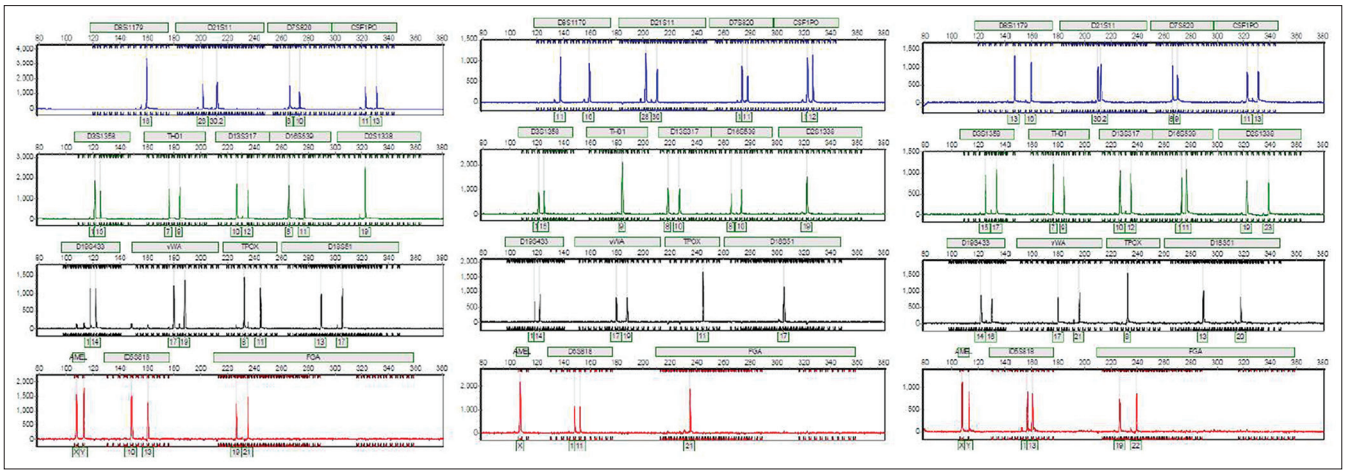
Supplementary Figure 1: Sanger sequencing of the *ATM* variant in the proband (NC_000011.9:g.108225584_108225585del)



Supplementary Figure 2: Sanger sequencing of the ATM variant in the proband's father (NC_000011.9:g.108225584_108225585del)



Supplementary Figure 3: Sanger sequencing of the *ATM* variant in the proband's mother (NC_000011.9:g.108225584_108225585del)



Supplementary Figure 4: Representative profile of short-tandem-repeat (STR) markers allele electropherogram