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A Rare and Unusual Case of Ataxia Telangiectasia with Cervical Dystonia from India

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ABSTRACT

We reported a rare and unusual case ATM gene variant responsible of familial Ataxia-Telangiectasia (A-T) with cervical dystonia rather than ataxia as hall mark clinical manifestations in 18-year-old male patient from India. Patient was presented with clinical indications of neck rotatory movements in the last 2 years. Initially intermittent, slowly become constant with more backwards turning and painful movements with severe disability. Examination findings revealed no conjunctival telangiectasia and neurological examination findings suggestive of cervical dystonia with severe retro collis. The patient has a family history of dystonia, his sister started noticing involuntary neck movement in the last 1.5 years with gradual progression. Her physical examination revealed no evidence of conjunctival lesions and neurological examination suggestive of cervical dystonia with lateral collis. MRI findings of patient were normal. Both the patient and her sister are siblings of a consanguineous product. Patient has been referred for whole exome sequencing. The exome data analysis identified a novel homozygous missense variant c.5751A>T, p.Arg1917Ser (chr11:108307973A>T) in ATM gene responsible for familial A-T with cervical dystonia without chorea as hall mark clinical manifestations. In conclusion, to the best of our literature knowledge this is the rare and unusual case from India wherein we are reporting a novel homozygous missense variant c.5751A>T, p.Arg1917Ser (chr11:108307973A>T) in ATM gene responsible for familial A-T with cervical dystonia rather than ataxia as hall mark clinical manifestations affecting both brother and sister in the same family. Thus, early onset of cervical dystonia should be taken into account as a key characteristic of variant A-T, which can manifest without general ataxia and may cause adults with primary dystonia to receive an incorrect diagnosis.

Keywords: *Ataxia-Telangiectasia; ATM gene; Homozygous; Cervical dystonia; Chorea.*

Introduction

Ataxia-telangiectasia (A-T) is an autosomal recessive disorder characterized by progressive ataxia, choreoathetosis and immunodeficiency beginning in early childhood. The estimated prevalence of the disease ranges from 1/40,000 to 1/300,000 people worldwide, depending on the geographic or ethnic region evaluated. A-T is caused by biallelic mutations in the ataxia telangiectasia mutated (ATM) gene in chromosome 11q22.3 [1]. A-T is characterized by respiratory complaints such as bronchitis, bronchiectasis, and sinusitis; neurological complaints such as poor muscle coordination (clumsiness); and

movement disorders such as dystonia, choreoathetosis, myoclonus, and tremors. General physical appearance is characterized by the presence of short stature, café au lait spots, progeric skin and hair changes, oculocutaneous telangiectasia, horizontal head thrusts due to difficulty in initiating horizontal saccades (both voluntary and reflex saccades are affected), ocular apraxia, diabetes mellitus, and features of glucose intolerance like acanthosis nigricans, hypogonadism, lymphocytopenias, predisposition to malignancy, hypoimmunoglobulinemia, and other immune defects [2].

Different forms of A-T have been described in the literature, with those more severe variably categorized as "classic", "typical", "early onset" or "childhood onset" AT, while milder forms have been referred to as "variant", "atypical", "late onset" or "adult onset" A-T [3]. The classical A-T patient phenotype shows progressive cerebellar ataxia, oculomotor apraxia, altered eye movements, cognitive dysfunction, oculocutaneous telangiectasia, dystonia, choreoathetosis, immunodeficiency, and recurrent sinopulmonary infections in early childhood [4].

There is a wide spectrum of phenotypic manifestations in patients with A-T. Recently, there is growing evidence that ATM mutations, can manifest generalized or focal dystonia with or without of the classical signs of A-T [5,6]. Herein, we report an unusual case of A-T with cervical dystonia in a patient from India,

Case Presentation

An 18-year-old male patient from South India, presented with clinical indications of neck rotatory movements in the last 2 years. Initially intermittent, slowly became constant with more of backwards turning and painful movements with severe disability. Examination findings revealed no conjunctival telangiectasia and neurological examination findings suggestive of cervical dystonia with severe retro collis (Figure 1). There were no ataxia or chorea form movements noticed. Brain MRI findings were normal.

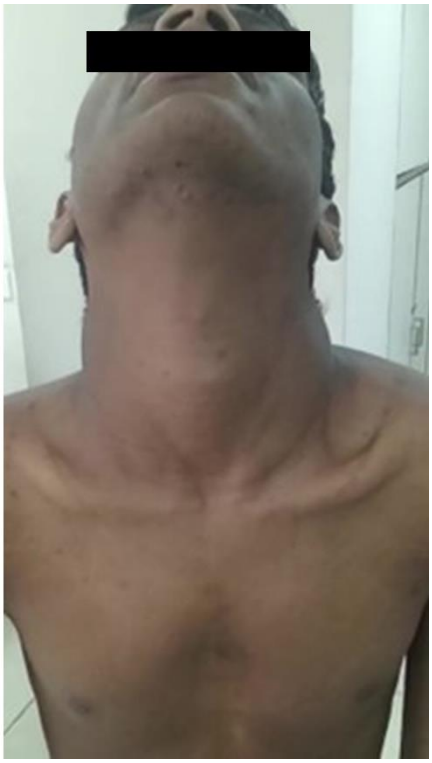

Figure 1: Symptoms of cervical dystonia.

Patients was 3rd of siblings of a consanguineous product and he has family history of dystonia. His sister 17-year-old, 4th of siblings of a consanguineous product started noticing involuntary neck movement in the last 1.5 years with gradual progression. Physical examination revealed no evidence of conjunctival lesions and neurological examination suggestive of cervical dystonia with lateral collis (Figure 2).

Figure 2: Symptoms of cervical dystonia in 17 year old girl.

Patient was referred for whole exome sequencing. The total genomic DNA was extracted from the biological sample using column-based method and DNA quality and quantity were assessed using electrophoretic and Qubit method. The quality control qualified genomic DNA was randomly fragmented and ligating sequencing adapters were added to both ends of DNA fragments. Sequencing libraries were size-selected using beads to optimal template size and amplified by polymerase chain reaction. The regions of interest (exons and flanking intronic targets) are targeted by hybridization-based target capture method. Sequencing libraries that passed the quality control were sequenced on Ultra-high-depth Whole Genome Sequencing instrument (Model: DNBSEQ-T10x4RS; Make: MGI) using paired-end chemistry. Reads were assembled and are aligned to reference sequences based on National Center for Biotechnology Information (NCBI) Ref Seq transcripts and human genome build GRCh38. Data was filtered and analyzed to identify variants of interest related to patients' clinical phenotype.

The exome data analysis identified a homozygous missense variant c.5751A>T, p.Arg1917Ser (chr11:108307973A>T) in ATM gene as represented in Table 1.

Table 1: Variants in ATM gene

Gene and Transcript	Exon	Variant Nomenclature	Zygosity	Disease	Inheritance
ATM NM_000051.4	38	c.5751A>T p.Arg1917Ser Chr11:108307973A>T	Homozygous	Ataxia-telangiectasia (OMIM#208900)	Autosomal recessive

Discussion

The ATM gene codes for a kinase protein which acts as a recognition and signalling molecule for DNA damage from ionizing radiation. A-Tis usually caused by homozygous or compound heterozygous mutations of the ATM gene, which leads to a reduced or complete absence of kinase enzyme activity. The level of kinase activity is a major determinant of the clinical phenotype of the patients. Most pathogenic or potentially pathogenic mutations in ATM gene exome sequences are non-conservative missense mutations, deletions, frameshift mutations, or putative loss of function mutations [7]. The mutations in atypical A-T segregate within families, and the affected members of the family as a whole may present with movement problems rather than ataxia as the major hallmark of the condition. Dystonia occurs more often in atypical A-T than in classic A-T. It usually appears during childhood or adolescence and tends to affect multiple systems over time [8,9]. In concurrence with literature findings, in our case study, a homozygous missense variant c.5751A>T, p.Arg1917Ser (chr11:108307973A>T) in ATM gene caused a phenotypic cervical dystonic atrophy without

classical signs of A-T in 3rd and 4th siblings of a consanguineous product. Saunders-Pullman et al., reported 13 patients from 3 Canadian Mennonite families with variant A-T due to a homozygous missense mutation in the ATM gene. The patients had onset of dystonia in the first 2 decades (range, 1-20 years). Dystonia mostly affected the neck, face, tongue, and limbs, and became generalized in 60% of patients [10]. Similar clinical manifestations of dystonia were observed in our case study in 3rd and 4th siblings of a consanguineous product. Furthermore, Gatti et al., pointed out that 'a significant proportion of older patients in their twenties and early thirties develop progressive spinal muscular atrophy, affecting mostly hands and feet, and dystonia.' Interosseous muscular atrophy in the hands in combination with the early-onset dystonic posturing leads to striking combined flexion-extension contractures of the fingers, which they illustrated [11].

Conclusion

In conclusion, we are reporting a novel homozygous missense variant c.5751A>T, p.Arg1917Ser (chr11:108307973A>T) in ATM gene responsible for familial A-T with cervical dystonia rather than ataxia as hall mark clinical manifestations affecting both brother and sister in the same family. This case study delineated that dystonia can be part of the clinical picture in A-T and may even mask ataxia. In clinical practice, early-onset of cervical dystonia with slow progression could be indicative of A-T. Hence, early onset of cervical dystonia should be taken into account as a key characteristic of variant A-T, which can manifest without general ataxia and may cause adults with primary dystonia to receive an incorrect diagnosis.

Patient Consent Declaration

Authors hereby declare that they have obtained patient consent.

Conflict of Interest

None.

Funding

None to declare.

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