Dystonia in Ataxia Telangiectasia: A Case Report with Novel Mutations

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ABSTRACT
Ataxia telangiectasia (A-T) is a common, genetically inherited cause of early childhood-onset ataxia that is classically characterized by progressive cerebellar malfunction, oculocutaneous telangiectasia, genome instability, and immunodeficiency. There is vast phenotype variation in patients with A-T and recently, dystonia, an extrapyramidal movement disorder. Here, we report the case of a 10-year-old girl who had experienced repeated diarrhea and mild gait ataxia since the age of two years. At age seven, ataxia and ocular telangiectasia were evident and immunoglobulin level assessment showed hyper IgM immune phenotype, thus a diagnosis of A-T was made based on clinical and laboratory findings, and she was started on intravenous immunoglobulin therapy. Generalized dystonia appeared when she was 10-years-old. Molecular analysis revealed two heterozygous mutations, c.6259delG and c.6658C>T, in the ATM gene of which one (c.6259delG) is novel. Dystonia can be part of the clinical picture in the A-T disorder and may even mask ataxia. This should be considered as a major feature mainly in variant A-T, which may occur without general ataxia and may be misdiagnosed in adults with primary dystonia.

Ataxia telangiectasia (A-T) [OMIM #208900] is an autosomal recessive multisystem disorder that is typically characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, variable immunodeficiency, increased alpha-fetoprotein levels, and hypersensitivity to ionizing radiations. A-T occurs at a frequency ranging from one in 40,000 to one in 100,000 births worldwide and ATM [OMIM *607585], an important player in DNA damage response/repair, is the only gene known to be associated with this disease.1

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.2,3 Here, we report a patient with classical A-T phenotype, hyper immunoglobulin (IgM) immune phenotype, and generalized dystonia, and literature review of reported cases with dystonia.

CASE REPORT
The 10-year-old girl was born to non-consanguineous, healthy, Iranian parents after an uneventful gestation and delivery. Her older sister was healthy, and there was no family history of neurological disease or malignancy. The first symptom that was noticed by parents was repeated diarrhea, which started when she was six months old until she turned two years old. At that time, inflammatory bowel disease was diagnosed by physicians based on diarrhea, failure to thrive and underweight, and the results of laboratory tests. She walked at about 16 months old, but after eight months (aged two years old), she manifested mild gait ataxia (abnormal swaying of the head and trunk). Her walk has improved since her parents started occupational therapy and her speech, fine motor and social skills were normal, but diarrhea continued. By the age of five years, cerebellar ataxia had progressed, and her speech had become dysarthric. At seven years old, when she was...
referred to our hospital, she had lost the ability of independent ambulation, and ocular telangiectasia was evident. Diagnosis of A-T was made based on clinical and laboratory findings and she was started on intravenous immunoglobulin therapy (IVIG).

Laboratory finding showed serum IgG 5 mg/dL (normal: 800–1600), IgM 208 mg/dL (normal: 40–230), IgA 1 mg/dL (normal: 70–400), IgE 1 mg/dL (normal: up to 52); serum alpha-fetoprotein (AFP) levels 104.7 IU/mL (normal: < 5.5); and increased induced radiosensitivity as assessed by the G2 chromosomal radiosensitivity assay [Figure 1].

When the patient was 10-years-old, she was no longer able to walk and received granulocyte-colony stimulating factor (G-CSF, two times) and antibiotic prophylaxis due to neutropenia and lymphadenopathy granulomatous. During this year, she experienced brief episodes of involuntary head extension and rotation, and her cervical dystonia worsened and extended to the limbs and trunk, mostly on the right side, causing an abnormal movement.

**Figure 1:** G2-chromosomal radiosensitivity assay results in a patient with ataxia telangiectasia and her parents. Individual radiosensitivity (IRS) estimated as IRS = \[1 - \frac{(G2_{caf} - G2)}{G2_{caf}} \] \times 100%.

**Figure 2:** Genetic study of ATM in ataxia telangiectasia patient. (a) Pedigree of the patient. (b) Confirmatory Sanger sequencing of proband for identified variants of the ATM gene. (c) Representation of mutation on ATM protein domains showing defect on FAT domain at amino acids region 1960 to 2566.
posture. Brain magnetic resonance imaging showed mild cerebral atrophy, mainly in the lower cerebellar hemisphere. The cerebellar vermis was intact, whereas the fourth ventricle showed some dilation. Therapeutic trials using trihexyphenidyl HCl and subsequently baclofen were initiated but were both ineffective. However, trihexyphenidyl with clonazepam relatively reduced the symptoms.

Whole exome sequencing identified a compound heterozygous mutation in the $ATM$ gene (c.6259delG and c.6658C>T) and was confirmed by Sanger sequencing in the patient and her parents. Both variants were located in the FAT domain (the name derived from FRAP, ATM, and TRRAP) of the ATM protein (p.Glu2087LysfsTer and p.Gln2220Ter; [Figure 2]). Bioinformatical tools support the pathological involvement of these variants (frequency: 0 in all databases, combined annotation-dependent depletion (CADD) scores: 35.00 and 45.00, respectively, and the mutation significance cutoff of ATM: 0.001).

**DISCUSSION**

Biallelic mutations in ATM are associated with classical and milder forms (variant A-T) of A-T. The variant A-T does not present the cardinal features of the disease, or they become apparent only later in life with incomplete, atypical, and highly variable manifestations. The neurological aspects of A-T are unfortunately still poorly understood, and is the main aspect of the disease and is not recapitulated in mice with complete deficiency of the murine ATM ortholog. Impairment of the extrapyramidal movement system with signs including dystonia, myoclonus, chorea, parkinsonism, and both postural, rest, and kinetic tremor is also common among patients with A-T. Recently, reports of different types of dystonia related to $ATM$ gene mutations have attracted great attention [Table 1, 2, and 3].

Dystonia is a movement disorder characterized by involuntary sustained or intermittent muscle contractions producing abnormal postures, repetitive movements, or both. Dystonic movements are usually manifested by twisting and may show a tremulous pattern. Before designating A-T as a distinct disease, dystonia was reported by Syllaba and Henner in three adolescent Czech siblings in association with ocular telangiectasia. After this report, the non-primary (secondary) dystonia was described in other articles repeatedly before and after [Table 2] and [Table 3] identification of the $ATM$ gene in patients with A-T. The dystonia frequency in patients with A-T vary in different case series [Table 1], and since myoclonic dystonia can easily be mistaken for chorea, the exact frequency is not known, but at least in variant A-T it accounts for 86% of cases with prominent cervical, cranial, and brachial involvement [Table 1, 2, and 3]. Although dystonia has been manifested in both classic A-T and variant A-T at different ages with different body involvements, it has received great attention in the variant form, as dystonia is more frequent in this form of the disease and may in fact be the only symptom in variant A-T. Currently, the treatment of dystonia in A-T patients remains symptomatic [Table 4]. Due to the marked heterogeneity of A-T, we have limited knowledge about the basis of individual responses to a given therapy.

Dystonia, like other extrapyramidal features, is usually more prominent in late manifestations of classical A-T. However, it may also be the initial or even the most prominent manifestation of A-T, potentially masking ataxia symptoms. This symptom mostly appears as an early-onset form of dystonia, and in variant forms without frank cerebellar involvement.

| Year<sup>4</sup> | Patient number (age range, years) | A-T cases | Percentage (n) | Frequent location of dystonia |
|-----------------|----------------------------------|-----------|----------------|-----------------------------|
| 1992<sup>1</sup> | 70 (2–42) Classic (62 cases) and variant (8) | 78% (55/70) | Limbs, face, trunk, oromandibular |
| 2009<sup>2</sup> | 13 (NA) Variant | 72% (8/11) | - |
| 2011<sup>4</sup> | 57 (2–19) Classic | 15.8% (9/57) | - |
| 2014<sup>4</sup> | 22 (2.7–19.7) Classic | 50% (10/20) | - |
| 2014<sup>4</sup> | 14 (21–36) Variant | 86% (12/14) | Upper limbs, neck |
it may mimic other forms of early-onset primary torsion dystonias or present mildly without any notice. In contrast to what we observed in our patient, dystonia is often associated with myoclonic jerks and may be induced/worsened by specific motor or cognitive tasks and, similar to ataxia, it is progressive with age as expected in a neurodegenerative disorder.

The genotype-phenotype relation in dystonia of a-T patients is not well understood. It is accepted that mutations with severe loss of aTm protein (truncating/null mutations) cause severe disease, and mild mutations (usually missense) with a residual level of protein may cause milder forms or appear late in life. In classical A-T with truncating mutation, most neurological symptoms including dystonia are similar between patients. However, in variant A-T, symptoms differ due to “milder” mutations, various combinations of compound heterozygous mutations, individual allelic expression pattern, possible modifier genes, and alternative RNA splicing. In addition, ATM enzymatic activity levels do not fully correlate with the milder phenotypes of variant A-T. Accordingly, although the genotype and phenotype comparison in A-T contributes to improved insight into the pathological mechanisms in A-T, it remains to be studied further.

Immunoglobulin class-switch recombination deficiency (CSR-D), previously known as hyperIgM syndrome, is a heterogeneous group of primary immunodeficiencies characterized by the presence of elevated or normal serum IgM levels and low or absent serum levels of the switched isotypes (IgG, IgA, and IgE). Elevated IgM is seen in 10–21% of A-T patients and due to mild or delayed neurologic symptoms may be misdiagnosed with CSR-D. Most patients with classic A-T demonstrate immunoglobulin deficiency, but it is relatively infrequent in mild A-T forms, but may still be helpful for diagnosis. Based on previous
Table 3: Dystonia reports in ataxia telangiectasia cases with confirmed ATM mutation.

| Year       | Classic/variant | Cases | Dystonia location | Dystonia onset (age, years) | First symptom | Ataxia onset, years | Cerebellar (age, years) | AFP (ng/mL) | Serum Ig | Radio sensitivity |
|------------|-----------------|-------|-------------------|-------------------------------|---------------|---------------------|--------------------------|-------------|-----------|------------------|
| 2008       | V               | 1     | N, LL             | Early (14)                    | N             | 14                  | Atrophy (42)             | Slightly high | Normal   | NA               |
| 2009       | V               | 1     | CC, O             | Early (15)                    | N             | No ataxia           | Mild atrophy (18)        | High        | NA        | Normal           |
| 2009–2014  | V               | 12    | N, L, C           | Early (~12)                   | Cervical     | Late-onset mild ataxia | Mild atrophy (NA)        | High        | NA        | NA               |
| 2013       | V               | 3     | CR                | Early (~13)                   | Cervical     | No ataxia           | NA                       | High        | NA        | NA               |
| 2013       | V               | 1     | F, N              | Early (~7)                    | NA            | No ataxia           | Normal (16)              | High        | IgA-Low   | Yes (MN assay)   |
| 2013       | V               | 1     | L, N, T           | Early (2)                     | L             | No ataxia           | Normal (48)              | High        | NA        | Yes (ICBA)       |
| 2013       | V               | 3     | N, L, T           | Early (NA)                    | Cervicobrachial | No ataxia          | Normal (NA)              | High        | NA        | Yes (CSA)        |
| 2013       | V               | 1     | Dystonia          | Early (NA)                    | NA            | No ataxia           | Atrophy (41)             | High        | IgA-Low   | Yes (CSA)        |
| 2014       | V               | 1     | LL, T             | Early (8)                     | LL            | 4                   | Mild atrophy (7)         | High        | IgE-Low   | NA               |
| 2015       | V               | 1     | N, T, O           | Late (45)                     | N             | No ataxia           | Normal (45)              | High        | IgA-Low   | NA               |
| 2015       | V               | 3     | N, RUL            | Late (25)                     | N             | No ataxia           | Normal (~40)             | High        | NA        | NA               |
| 2016       | C               | 1     | N                 | Early (5)                     | N, T          | Childhood           | Atrophy (25)             | High        | NA        | NA               |

Ig: immunoglobulin; N: neck; NA: not available; T: trunk; UL: upper limb; LL: lower limb; CC: cranio cervical; F: face; O: oromandibular; CR: cranial; L: limbs; H: hand; RUL: right upper limb; G: generalized; C: classic; V: variant; MN assay: S-G2 micronucleus assay; ICBA: induced chromosome breakage assay; CSA: colony survival assay.

*prevalent ones.
publications, our patient is the first dystonic A-T with a class switching defect, causing hyper IgM immune phenotype.

**CONCLUSION**

Dystonia can be part of the clinical picture in A-T and may even mask ataxia. In clinical practice, early-onset dystonia with slow progression may be indicative of A-T. This is more important for the diagnosis of patients with the variant form of A-T, because, despite overall milder neurologic disease, the burden of malignancy remains high as for A-T, so patients will need surveillance of immunodeficiency and malignancies, as well as measures to lessen accumulating DNA damage from radiologic exposure and chemotherapeutic agents. Therefore, early-onset dystonia with cervical and brachial onset and prominent cranial involvement should be considered as a major feature of variant A-T, which may occur without general ataxia and may thus be misdiagnosed in adults with primary dystonia.

**Disclosure**
The authors declared no conflicts of interest.

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