ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Ataxia-telangiectasia: an important cause of progressive ataxia and primary immunodeficiency in childhood

Ataxia-telangiectasia: uma causa importante de ataxia progressiva e imunodeficiência primária na infância

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ABSTRACT

Ataxia-telangiectasia (AT) is a rare autosomal recessive disorder caused by homozygous or compound heterozygous pathogenic variants in the ataxia telangiectasia mutated (*ATM*) gene, located at the 11q22-23 locus. This gene encodes a serine/threonine kinase involved in DNA double-strand break repair, genomic stability, cell cycle control, and apoptosis. The clinical manifestations of AT include cerebellar ataxia, oculocutaneous telangiectasia, primary immunodeficiency, and an increased risk of malignancies. The global incidence of AT ranges from 1:40,000 to 1:300,000 live births. In this report, we describe the case of a 6-year-old girl referred to the Medical Genetics Service for investigation of ataxia and primary immunodeficiency. She was the only child of a young, healthy, nonconsanguineous couple, with no family history of similar cases, malformations, or genetic diseases. The proband presented with the typical AT phenotype, including progressive gait ataxia in childhood, oculocutaneous telangiectasia, and primary immunodeficiency. The diagnosis of AT was confirmed through next-generation sequencing of the *ATM* gene with copy number variation analysis that identified 2 compound heterozygous pathogenic variants.

Keywords: Ataxia-telangiectasia, primary immunodeficiency diseases, DNA breaks, double-stranded, neoplasms.

RESUMO

A ataxia-telangiectasia (AT) é uma doença rara de herança autossômica recessiva causada pela presença de variantes patogênicas em homozigose ou heterozigose composta no gene *ATM*. Este gene, localizado na região cromossômica 11q22-23, codifica uma serina/treonina quinase, cujas funções estão relacionadas ao reparo de quebras de fita dupla do DNA, estabilidade genômica, controle do ciclo celular e apoptose. As manifestações clínicas são caracterizadas por ataxia cerebelar, telangiectasia oculocutânea, imunodeficiência primária e risco aumentado de malignidades. A incidência global de AT é de 1:40.000 a 1:300.000 nascimentos. Probanda, do sexo feminino, 6 anos, encaminhada ao serviço de Genética Médica para investigação de ataxia e imunodeficiência primária. Filha única de casal jovem, saudável, não consanguíneo, sem histórico familiar de outros casos semelhantes, malformações ou doenças genéticas. A probanda apresenta o fenótipo típico de AT com ataxia de marcha progressiva de início na infância, telangiectasia oculocutânea e imunodeficiência primária. O diagnóstico de AT foi confirmado através do sequenciamento por NGS (*Next-Generation Sequencing*) do gene *ATM* com análise de CNV (*Copy Number Variation*) que identificou duas variantes patogênicas em heterozigose composta.

Descritores: Ataxia telangiectasia, doenças da imunodeficiência primária, quebras de DNA de cadeia dupla, neoplasias.

Introduction

Ataxia-telangiectasia (AT) (OMIM #208900) was first described by Madame Louis-Bar in 1941 as a syndrome characterized by progressive cerebellar ataxia and oculocutaneous telangiectasia.[1] In 1957, Boder and Sedgwick documented 7 patients from the same family who exhibited increased susceptibility

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to recurrent pulmonary infections in association with the symptoms described above.[2] That same year, Wells and Shy reported cases of progressive familial choreoathetosis associated with cutaneous telangiectasia.[3]

AT is a rare autosomal recessive disorder caused by homozygous or compound heterozygous pathogenic variants in the ataxia telangiectasia mutated (*ATM*) gene, located at the 11q22–23 locus.[4] The ATM protein, a serine/threonine kinase, is involved in several molecular processes, being particularly important in DNA double-strand break repair, genomic stability, cell cycle control, and apoptosis.[5,6]

The clinical manifestations of AT are multisystemic and generally include progressive cerebellar ataxia in childhood, oculocutaneous telangiectasia, primary immunodeficiency, oculomotor apraxia, and sensitivity to ionizing radiation.[7] In addition, there is an increased lifetime risk of various neoplasms (such as leukemia and lymphomas), particularly in childhood, and cancers, including breast (in women and men), ovarian, pancreatic, gastric, colorectal, prostatic, and melanoma (Table 1).[8] Other findings that have also been described in patients with AT include pulmonary disease, recurrent sinopulmonary infections, diabetes mellitus, growth failure, delayed puberty, and gonadal dysfunction.[9-11] The incidence of AT ranges from 1:40,000 to 1:300,000 live births.[12] In Brazil, as in other South American countries, the incidence remains unknown due to underreporting.[13] Here, we report the case of a patient diagnosed with AT in childhood.

Table 1
Neoplasms with increased risk in patients with AT

Type of cancer	Probability
Female breast – invasive ductal carcinoma	2.03
Female breast – ductal carcinoma *in situ*	1.80
Male breast	1.72
Ovarian	1.57
Pancreatic	4.21
Gastric	2.97
Colorectal	1.49
Prostatic	2.58
Melanoma	1.46

AT = ataxia-telangiectasia. Adapted from Hall et al.[8].

Case report

A 6-year-old girl was referred to the Medical Genetics Service by the Immunology Department for investigation of ataxia and primary immunodeficiency. At age 1, she experienced an episode of bronchiolitis that required hospitalization. At age 2, she began to show progressive cerebellar ataxia and recurrent skin infections secondary to insect bites. Between the ages of 4 and 5, she had recurrent episodes of pneumonia and upper respiratory tract infections, which were treated on an outpatient basis.

The patient was the only child of a healthy, nonconsanguineous couple, with no family history of similar cases, malformations, or genetic diseases. Pregnancy was uneventful, and the patient was delivered vaginally at 39 weeks of gestation, with no signs of perinatal asphyxia (Apgar scores of 9 and 9 at 1 and 5 minutes, respectively). Her birth weight was 2.78 kg (10th-25th percentile), length 47 cm (10th-25th percentile), and head circumference 33 cm (25th-50th percentile), all within normal ranges for the gestational age. There were no perinatal complications, and the patient was discharged from the maternity ward at 2 days old. Neuropsychomotor development milestones during the first year of life were also within the expected range for her age.

Clinical and morphological examination showed normal height, normocephaly, and Tanner stages M1/P1. However, the patient also exhibited gait ataxia, head tilting, oculomotor apraxia, oculocutaneous telangiectasia (Figure 1), slurred speech, hypoplastic nasal alae, and left clubfoot.

Genetic analysis identified a karyotype of 46,XX [10]. Sequence analysis of the *ATM*, including copy number variation (CNV) analysis, identified two heterozygous pathogenic variants: c.3894dup (p.Ala1299Cysfs*3) and c.3802del (p.Val1268*). Additional examinations of the proband are described in Table 2.

Following initiation of human immunoglobulin (Ig) therapy for immunodeficiency, there was a significant reduction in the frequency of infectious episodes. Despite this, the levels of IgA, IgE, and IgG (including the IgG1, IgG2, and IgG3 subclasses) remained low, whereas α-fetoprotein levels were significantly elevated. Gait ataxia worsened, leading to significant fatigue during ambulation, with a wheelchair being

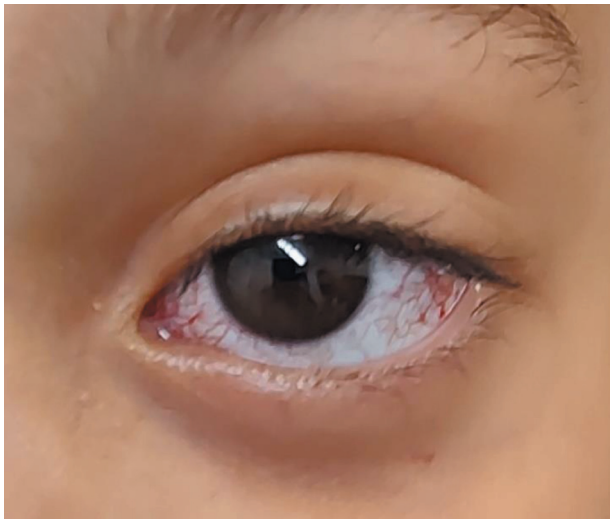

Figure 1
Ocular telangiectasia in the proband

required for distances > 100 m. Additional symptoms included dysphagia for liquids (with frequent choking), sialorrhea, and difficulties with speech, writing, and drawing. Bilateral tympanoplasty was performed to treat recurrent otitis media, yielding good results.

The patient is currently undergoing integrated rehabilitation therapy with a multidisciplinary team, including motor and respiratory physical therapy and nutritional support, as well as interdisciplinary follow-up involving pediatrics, pulmonology, immunology, genetics, and neurology.

Discussion

The rarity of AT makes its diagnosis challenging. Clinical suspicion should be considered in children who present with early-onset progressive gait ataxia, oculocutaneous telangiectasia, and recurrent sinopulmonary infections. However, AT exhibits phenotypic variability, with some patients manifesting milder symptoms only in adulthood. These cases, referred to as "atypical AT," are generally associated with a longer life expectancy.[14] The diagnosis of AT is primarily based on clinical features and then confirmed through molecular techniques that detect homozygous or compound heterozygous pathogenic variants of the *ATM* gene.[15] In few cases, AT may involve chromosomal alterations, such as translocation between chromosomes 7p and 14q, which can be visualized by karyotyping. It may also involve submicroscopic alterations, such as microdeletions or microduplications in the DNA segment, which can be identified using techniques such as multiplex ligation-dependent probe amplification or array comparative genomic hybridization.[16,17] Furthermore, reports have demonstrated that during karyotyping, the presence of breakage sites in bands 2p11, 2p12, 7p14, 7q35, 14qter, and 22q11-q12 have been implicated in AT, within the detection limits of standard light microscopy.[18,19]

Table 2
Additional examinations of the proband

Test	Results	Reference ranges
α-Fetoprotein	509.5 µg/L	< 7.5 µg/L
Glucose	77 mg/dL	70-99 mg/dL
Hb1Ac	5.7%	< 5.7%
TSH	3.95 mUI/L	0.9-6.5 m IU/L
Free T4	1.37 ng/dL	0.7-1.8 ng/dL
AST	35 U/L	5-40 U/L
ALT	22 U/L	7-56 U/L
IgA	7 mg/dL	15-250 mg/dL
IgM	45.2 mg/dL	45-300 mg/dL
IgE	< 1 UI/mL	≤ 52 IU/mL
IgG	51 mg/dL	340-1,600 mg/dL
IgG1	47 mg/dL	288-918 mg/dL
IgG2	< 2 mg/dL	44-375 mg/dL
IgG3	6.8 mg/dL	15-85.3 mg/dL
IgG4	0.7 mg/Dl	0.4-99.2 mg/dL
Absolute CD19	27/µL	236-646/µL
CD19%	4.2%	9.7-20.7%
Absolute CD3	399/µL	1,260-2,610/µL
CD3%	61.4%	61.1-77.4%
CH50, Complement	79.61 U/mL	41.68-95.06 U/mL
C3, Complement	139 mg/dL	90-180 mg/dL
C4, Complement	25.2 mg/dL	10-40 mg/dL
Vitamin B12	999 pg/mL	197-771 pg/mL
Anti-HIV antibody	Nonreactive	Nonreactive

The AT phenotype observed in our patient corresponded to that described in the literature, including early-onset progressive gait ataxia, oculocutaneous telangiectasia, oculomotor apraxia, slurred speech, primary immunodeficiency, and recurrent sinopulmonary infections. These findings supported the suspicion and clinical diagnosis of AT. The patient's karyotype was normal, consistent with the lack of consanguinity between the parents and the absence of other cases in the family. However, because this test does not detect microdeletions, microduplications, or submicroscopic rearrangements, the diagnostic investigation was expanded to include sequence analysis of the *ATM* gene and CNV analysis. This approach identified 2 compound heterozygous pathogenic variants, thereby confirming the diagnosis of AT.

There is currently no treatment for AT, although therapeutic trials are underway.[20] Because AT may present a wide variety of clinical manifestations, patients should receive counseling from a multidisciplinary team involving a pediatrician, neurologist, geneticist, immunologist, pulmonologist, endocrinologist, hematologist, oncologist, and nutritionist.[21] Addressing specific AT-related symptoms is crucial. Patients and parents should be advised to avoid exposure to harmful factors, such as ionizing radiation (unnecessary exposure to sunlight, radiography, and computed tomography), and to monitor for signs or symptoms suggestive of malignancy. Immunizations with inactivated vaccines are safe for all individuals with AT and should be performed to prevent infections. However, rubella vaccination should be avoided in those with severe immunodeficiency due to the increased risk of granuloma formation.[22] These measures can improve quality of life, prolong survival, and minimize potentially fatal complications.

Genetic counseling and risk estimation for familial recurrence was not possible because the parents were divorced, precluding the sequencing of the *ATM* gene in both parents to determine whether the proband's pathogenic variants were inherited or the result of a *de novo* mutation. Given that the genetic alterations found in the proband were compound heterozygous, the possibility of new variants cannot be excluded, underscoring the need for parental sequencing. Since AT has an autosomal recessive pattern of inheritance, the couple theoretically has a 25% risk of recurrence with each pregnancy.

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