

New mutation in ATM gen in patient whith Ataxia Telangiectasia. Clinical case

Nueva mutación en el gen ATM en paciente con ataxis telangiectasia. Caso clínico

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Abstract

Introduction: The ataxia telangiectasia syndrome (AT) is a genetic disease with an autosomal recessive inheritance pattern, with multisystem involvement and a broad clinical spectrum. It is caused by the mutation of the ATM gene, causing reduction or absence of the ATM proteinkinase, altering processes in the cell cycle, DNA repair and apoptosis. The objective of this article is to report the case of a patient with ataxia telangiectasia syndrome, caused by a mutation not previously reported in the literature. **Case report:** A 14 year-old patient native to Colombia, with classic clinical and phenotypical manifestations of AT syndrome, which started at 6 years of age with pondostatural alteration, recurrent respiratory infections, oculocutaneous telangiectasias and progressive neurological disorder that included: regression in her psychomotor development, ataxia and oculomotor apraxia. ATM gene sequencing is performed evidencing a homozygous mutation not reported in literature. **Discussion:** In Latin America are sparse the number of reports of patients with ataxia telangiectasia and only few of these describe their molecular findings. Molecular studies allow the diagnosis and a better orientation in the management and prognosis of patients with neurodegenerative diseases. The report of undescribed molecular variants is of great importance to establish the etiology of such diseases in diverse population groups, such as the countries of Latin America.

Keywords:

Ataxia-telangiectasia, cerebellar ataxia, medical genetic, neurodegenerative disease

Introduction

Ataxia telangiectasia syndrome (AT) is an autosomal recessive disease characterized by progressive neurological deficit, immunological involvement and a predisposition to cancer. It affects 1 out of every 44,000 to 100,000 people worldwide, with up to 2% of carriers reported in Caucasian Americans^{1,2}.

The first case was reported in 1926 by Syllaba and Henner³, however it was until 1964 that this disease was named AT by Dr. L. Martin. In 1988, Gatti and Cols⁴ map the ATM gene on chromosome 11q22.3-23.1; In 1995, Savitsky and cols.⁵ identified it as the gene responsible for AT syndrome.

The ATM protein is a 350 kDa polypeptide with catalytic activity and a characteristic motif of the kinase PI-3 family (PIKKs), which fulfills regulatory functions in signaling pathways in response to nutrients, growth factors, energy balance and even DNA repair. Also in homeostasis, it reported acts on metabolic pathways mediated by insulin, in the cell cycle and cellular senescence^{2,6,7}. Mutation of the ATM gene causes a decrease or absence of ATM protein, this is due to the accumulation of altered DNA in the cerebellum, which it results directly in cellular apoptosis, causing neurodegeneration, cerebellar atrophy and ataxia⁸⁻¹⁰.

The clinical manifestations of AT are observable in early childhood, with progressive cerebellar ataxia, which is the first to appear². Most of patients between 5 and 10 years present other severe alterations. Other clinical findings include: oculomotor apraxia, altered eye movements, cognitive dysfunction, and oculocutaneous telangiectasia^{1,9}; as well as dystonia and choreoathetosis in 90% of patients. Also, decreased cellular immune response secondary to thymic hypoplasia and peripheral lymphopenia is observable, a behavior that is similar to aging in the immune system⁶, primary endocrine disorders associated with delayed growth and onset of puberty and peripheral resistance to insulin^{2,6}.

This pathology has an autosomal recessive inheritance pattern, affecting men and women alike. Heterozygous carriers of the mutation are at increased risk of developing neoplasms in the breast, gastrointestinal system, bladder and skin, among others. In homozygotes, the risk of neoplasias is also higher, especially a cancer of lymphoreticular origin, non - Hodgkin's lymphoma, Hodgkin's lymphoma and various forms of T cell leukemia, which usually appear between the second and third decade of life. Solid tumors in reproductive and gastrointestinal organs have been reported in adult patients as well^{6,11-13}.

The objective of this article is to report the case of a Colombian patient, with ataxia telangiectasia syndrome, caused by a mutation not previously reported in the literature.

Clinical Case

Mix race (mestizo) patient, currently 14 years old, originally from Tambo, of Cauca Region (Colombia). The patient was the first gestation of non-consanguineous parents. Her* mother was 16 years old and her father was 25 years old at the time of gestation. Prenatal history did not show exposure to teratogens or any presence of other relevant pathologies. The ultrasound reports did not show any morphological alterations.

Vaginal delivery was performed at 34 weeks of gestation, due to premature rupture of membranes and onset of preterm labor. Weight of 2450 g (-1.86 SD), size 47 cm (-1.15 SD). There were no major congenital anomalies or other complications observed during his first moments after birth.

The patient presented normal psychomotor development with cephalic support at 4 months, sitting at 6 months, standing at 11 months and walking at 14 months. At 2 years of age, gait alteration was evidenced with an increase in the base of sustentation, instability and frequent falls.

At 6 years of age, she was evaluated by the endocrinologic unit for her low size for age, growth hormone treatment was implemented during 6 months without improvement, however, progression of ataxia and tremor was reported, reason for which the medication was suspended. By age 7, she was totally dependent, with poor postural control and distal tremor in 4 limbs, with limitations of her educational process.

During this period, the patient was evaluated in the pediatric and pediatric neurology services and some studies were carried out, including: Electroencephalogram, which it did not show alterations; Magnetic resonance imaging of the brain with atrophic cerebellar signs characterized by increased subarachnoid space interleaved and enlargement of the fourth ventricle (figure 1), which is abnormal for the patient's age, with signs of bulbar atrophy, with no other signs that could suggest atrophy of the rest of the brainstem and without significant alterations in the cerebral hemispheres; Alpha-fetoprotein 350 ng / ml (high); Evoked auditory potentials and immunoglobulins A, G, and M within normal limits.

Subsequently the patient was evaluated by the Service of Pediatric Dysmorphology and Genetics at 14 years of age. The physical examination presented a short stature 1.38 m (-4.06 SD) and low weight 27 kg (-4.76 SD), non-expressive facies, triangular face, oculocutaneous telangiectasia (figure 2), altered eye movements, trunk ataxia with positive cerebellar evidence, moderate to severe gait limitation and hypersensitivity

*TN: Patient's personal information is under protection, but we will refer as "she" from now on.

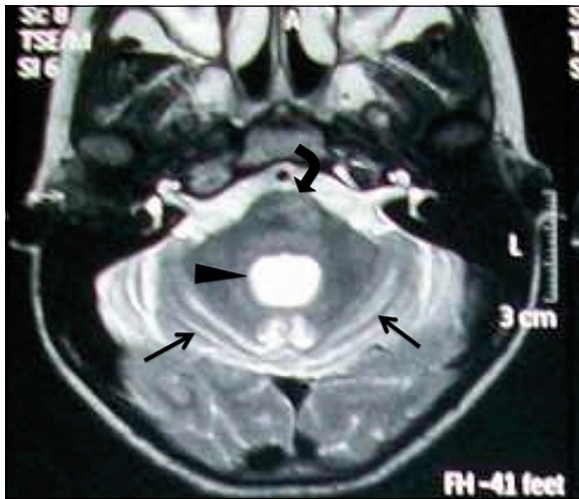


Figure 1. Brain Magnetic Resonance Imaging, enhanced T2 axial sequences evidencing enlargement of the subarachnoid space (arrows) and the fourth ventricle (arrowhead), as signs of cerebellar atrophy associated with moderate atrophy of the medulla oblongata (curved arrow), and some atrophic changes in the cerebellar peduncles.



Figure 2. A 14 year old patient, notice ocular telangiectasia.

to the sun. The system's review showed recurrent respiratory infections.

From these clinical findings described above, the patient's phenotype was considered to be compatible with Ataxia telangiectasia syndrome and, given the prognostic implications of this entity, sequencing was requested for the ATM gene using the AT NextGeneDx® panel. This test detected a change in homozygosity, consisting of a deletion of an A (c.7767delA), and a change in homozygosity, a transition from a T to a C (c.162T> C) resulting in a synonymous change in the protein (p.Tyr54Tyr).

Discussion

The AT is an autosomal recessive inheritance pathology, with a multisystem commitment. Its diagnosis is usually based on a clinical triad of neurological

signs, prioritized by an evolutionary cerebellar syndrome, consisting of dysnergia, intentional tremor, adeno-kinesias, and generalized hypotonia that causes loss of gait. Other findings include oculocutaneous alterations, such as the presence of telangiectasias, and Café au lait spots; variable cellular and humoral immunodeficiency responsible for recurrent respiratory infections, high incidence of neoplasias, hypersensitivity to ionic radiation, delayed growth, gonadal dysgenesis, and high levels of alpha fetoprotein^{2,14-17}.

The neurological symptoms of AT can be explained by the systematic elimination of certain cell populations. This is expressed as progressive atrophy of the cerebellar cortex, destruction of the basal ganglia, demyelination of the posterior columns and loss of neurons inside the anterior horn of the spinal cord. Oculocutaneous signs are secondary to neurological manifestations. Telangiectasias usually occur in the eyes at first, subsequently affecting the skin, particularly the lobes of the ears¹⁸.

Although these phenotypic findings are classically described in the literature, the clinical spectrum of AT is very extensive, with non-classical presentations that may or may not exhibit neurological abnormalities, motor alterations, cerebellar ataxia, and no ocular telangiectasias. This leads to difficulties in the diagnosis process, especially in some cases².

In this report, we present the case of a Colombian patient, with a classic AT phenotype. When performing the diagnostic molecular panel, a change in homozygosity was reported, consisting of a deletion of an A (c.7767delA) that produces a change in the reading frame producing a premature stop codon (p.Lys2589Asnfs * 17). This deletion has not previously been described in the literature, however, when simulation of the effect on the protein (PolyPhen 2) is detrimental, it is considered pathological.

Concomitantly the panel identified a change in homozygosity, a transition from a T to a C (c.162T> C), which produces a synonymous change in the protein (p.Tyr54Tyr). This change has been previously reported in databases such as dbSNP, ClinVar, and NCBI (rs3218690); and is considered probably benign in its clinical significance. However, it is noteworthy that this change was previously reported in another patient with a diagnosis of AT¹⁹.

Currently, there is no effective treatment for AT. However, clinical management for this pathology focus on a symptomatic and supportive approach, and the prevention of early manifestations of AT has not been satisfactory to date. Therapeutic interventions, such as early and continuous physical therapy, could minimize the occurrence of contractures, which appear over time in almost all affected patients. Intravenous immunoglobulin replacement therapy has redu-

ced the number and severity of infections in patients who present them. Rehabilitation and support care is needed, including physical, occupational, language and deglutition therapy²⁰.

Regular pulmonary monitoring is recommended, in case of detecting hypoxemia long-term oxygen therapy is required and radiographic follow-up is minimized¹⁶.

The predisposition to malignancy suggests the need for preventive medical check-ups, in search of early signs. The use and doses to initiate radiation therapy or chemotherapy are controversial and difficult to establish, due to the hypersensitivity that these patients present to ionizing radiation. Thus, it is suggested that the oncological management must be performed in specialized centers^{16,20}.

Although this pathology is widely described in the literature, we count with few reported cases from Latin America, the majority of these reports focus on the clinical follow-up of patients, or on the description of atypical clinical presentations, being scarce those describing the molecular findings or mutations²¹⁻²⁷.

It is considered that the inclusion of molecular studies in the diagnosis of patients with clinical features that include neuromotor symptoms are of great importance, especially in Latin American countries. This is not only to confirm the diagnosis in cases with classic clinical features, or to guide the diagnosis in atypical presentations, but also to identify new molecular variants (polymorphisms and mutations) which could contribute to the etiology and appearance of rare pathologies in this population group, Nonetheless these variants persist unidentified due to the lack of access to these studies or by the lack of report in the literature. All these remain unknown, due to the lack of access to these studies and the lack of reports in the literature.

Conclusions

This clinical case raises the need to perform molecular tests in patients with neurodegenerative diseases, which are a highly important tool that eases the diagnosis, and allows for a better orientation in the management and prognosis of patients, as well as offering genetic counseling to their parents. The report of unknown molecular is vital to determine the causes and contribution to the etiology of genetic pathologies in population groups of different origin and races, as it happens in Latin American countries.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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