Diferent clinical and laboratory evolutions in ataxia-telangiectasia syndrome: report of four cases

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ABSTRACT

We report four patients with ataxia-telangiectasia syndrome that presented varied neurologic evolution. Three patients initially presented neurologic alterations of slow progression, evolving to late immunocompromised conditions. The fourth patient presented, from symptom onset, immune and neurologic debilitation, that were both severe and of fast progression. The chronological sequence of the most commonly observed immunocompromised conditions were in our patients, in ascending order, IgA deficiency, IgG2 deficiency and the neutrophil phagocytosis stage and common variable immunodeficiency.

The first two reports are of sisters in whom the diagnosis was done between the ages of three and six years, having ocular apraxia, cerebellar ataxia and telangiectasia. Slow progression of neurologic debilitation was observed, without presentation of intermittent infections. The patients began presenting accentuated immunocompromised conditions at the ages of 14 and 17 years, dying at the ages of 16 and 20 years, respectively, due to severe infections that were resistant to treatment. The diagnosis of the third case was established when the patient was two years old, presenting ataxia and telangiectasia. Syndrome progression was slow, presenting at the age of eight years more accentuated neurologic disorders and IgA deficiency. The fourth case presented significant neurologic compromise at the age of five, simultaneous to IgA and IgG2 deficiency, and repeating pneumonias and sinusitis. At this time, intravenous gammaglobulin reposition was done. The neurologic and immune disorders progressed rapidly, and at the age of eight presented the inability to walk. At this time inversion of the CD4/CD8 ration was verified through laboratory tests.

Key words: Ataxia. Telangiectasia. IgA deficiency. IgG2 deficiency. Phagocytic deficiency. Neurologic alterations.

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RESUMEN

Se presentan cuatro pacientes portadores del síndrome de ataxia telangiectasia que tuvieron diferente evolución neurológica y inmunológica. Tres pacientes empezaron el cuadro clínico con alteraciones neurológicas de progresión lenta y compromiso inmunológico tardío. La cuarta paciente desde el inicio presentó alteraciones inmunológicas y neurológicas graves y de rápida progresión. La secuencia cronológica de las alteraciones inmunológicos más observadas fue la siguiente: 1.º deficiencia de IgA; 2.º deficiencia de IgG2 y de la etapa de acción fagocítica de los neutrófilos; 3.º inmunodeficiencia común variable.

Los dos primeros casos son dos hermanas en las que el diagnóstico fue hecho a los tres y seis años de edad, observándose apraxia ocular, ataxia cerebelar y telangiectasias. Hubo progresión lenta del cuadro neurológico, sin infecciones paralelas. Las pacientes empezaron a presentar alteración inmunológica acentuada a los 17 y 14 años, falleciendo a los 20 y 16 años respectivamente, por infecciones graves y

resistentes al tratamiento. El diagnóstico del tercer caso fue establecido a los dos años de edad con la presencia de ataxia y telangectasias. La progresión del síndrome fue lenta, presentando trastornos neurológicos más acentuados y deficiencia de IgA a los ocho años de edad. La cuarta paciente presentó un importante compromiso neurológico a los cinco años de edad, simultáneamente a la deficiencia de IgA e IgG2, sinusitis y neumonías de repetición. En esa ocasión fue iniciada reposición de gammaglobulina endovenosa. Los trastornos neurológicos e inmunológicos progresaron rápidamente, observándose incapacidad de marcha e inversión de la relación CD4/CD8 a los ocho años de edad.

Palabras clave: Ataxia. Telangiectasia. Deficiencia de IgA. Deficiencia de IgG2. Deficiencia fagocítica. Alteraciones neurológicas.

INTRODUCTION

Ataxia-telangiectasia (AT) was first reported as a neurologic disorder associated with cerebellar ataxia, delay in ocular movement in relation to head movement (ocular-motor apraxia), ocular-cutaneous telangiectasia and repeating infections[1-3]. Cytogenetic studies revealed specific chromosome instability with multiple rearrangements between chromosomes 7 and 14[4,5]. Research has demonstrated pleiotropic heredity, with more detailed molecular based studies done after the AT gene was cloned in 1995[3]. It is currently considered a recessive autosomal disease, affecting different sections of the body, still uncorrelated, mainly the neurologic and immune system[6,7]. The distribution of this disease is global, occurring in all ethnicities, with an estimated frequency ranging between 1:40,000 and 1:100,000[8].

In many cases the clinical manifestations begin with a delay in neuropsychomotor development, which may not be noticed by the parents, mainly due to the absence of mental retardation[9]. Usually, cerebellar ataxia follows, and is of difficult diagnosis if the symptoms coincide with the beginning of walking[10]. Ataxia is progressive culminating with the inability to walk[11]. The telangiectasias are the second most marking characteristic of the disease and are present in nearly all patients with AT[8]. The telangiectasias mainly appear in the subpapillary venous plexus, around the ages of three and five years and are more evident in the internal parts of the bulbar conjunctiva, auricular pavilions, cervical region and dorsal region of the nose[6]. They may appear in other regions of the integumentary system, always symmetrical in form or may manifest in internal organs as well. Serum α fetoprotein is increased in 90 to 95 % of the cases, and is considered a disease marker[12]. The repeating infections are the consequence of the several immunodeficiencies, with IgA deficiency the most frequent, followed by the deficiencies of the IgG subclasses and common variable immunodeficiency, with the inversion of the CD4/CD8 ratio[13,14]. Infectious processes are the main causes of death; however, death may rarely be consequent of neoplasias due to the higher susceptibility presented by these patients[15].

CASE REPORTS

First case

A.P.M.S., female, proceeding from São Paulo, Brazil, sister also has ataxia-telangiectasia, co-sanguineous parents (first degree cousins). Ataxic gait/walk was diagnosed at the age of 16 months, remaining stable until the age of three years, when it became progressive, becoming accentuated at the age 8 years and was unable to walk at the age of 15 years, concomitant with vitiligo manifestations. Bilateral ocular telangiectasia and ocular-motor apraxia manifested at the age of eight years. The onset of respiratory tract infections began at the age of nine, with the subsequent diagnosis of IgA deficiency. At the age of 17 years presented deficiency in the neutrophil phagocytosis digestion stage, followed by the decrease of CD4 + cells, with the inversion of the CD4/CD8 ration. The infectious aspects persisted with oral monoliasis that were of difficult treatment and severe pneumonias that culminated in death at the age of 20 years.

Second case

C.M.S., female, sister of the patient of the first report. Neurologic manifestations began around the age of six with ataxic gait and widened base tending to fall to the right along with slight, involuntary movements of the lips and superior limbs. At the age of seven years there was the onset of ocular telangiectasia, with extrapyrimidal alterations and infection of the superior respiratory tract, and presenting IgA serum deficiency. At the age of 14 years began presenting deficiency in the phagocytosis by neutrophils phase. At the age of 16 years repeating

pneumonias began along with IgG2 deficiency, and started intravenous gammaglobulin treatment; six months later presented inversion of the CD4/CD8 ration due to a reduction in the number of CD4 + cells. The patient died at the age of 16 due to severe pulmonary infection.

Third case

S.C., female proceeding from São Paulo, Brazil, co-sanguineous parents (second degree cousins). At the age of two years presented difficulty in walking and conjunctiva telangiectasia. At the age of four years began to present repeating infections in the respiratory tract associated to bronchospasm. At the age of five years showed compromise in stature development. At the age of eight there was worsening of the neurologic condition, with equilibrium and walking being affected, maintaining bronchospasm concomitant to the repeating sinopulmonary infections, associated to IgA deficiency. Currently the patient is nine years old, maintaining the same clinical and laboratory conditions.

Fourth case

G.F.A, female, proceeding from São Paulo Brazil, non co-sanguineous parents. At the age of two presented ataxic gait and repeating bronchopneumonias began. She only began speech development at the age of three years. At the age of five, conjunctiva telangiectasia appears in the auricular pavilion, appendicular ataxia, and ocular-motor apraxia. At the age of five years the repeating pneumonias became more aggravated, in association with IgA and IGg2 deficiency, and was when she began to receive intravenous gammaglobulin, At the age of eight years presented a reduction in CD4 + cells. Worsening of the neurologic condition continues to progress and currently, at the age of nine years, is unable to walk.

RESULTS

The four patients presented an increase in serum α fetoprotein and reduction in serum IgA, with values under 7mg/dL. In the first and second case reports a reduction in the ingestion of zymosan by neutrophils was acquired through three assays using zymosan, zymosan and homologous serum, and zymosan and autologous serum[16,17]. The nitroblue tetrazolium (NBT) tests did not demonstrate any alterations in the neutrophil digestion phase. Chemotactic and phagocytic responses of monocytes were also studied[18], with no alterations observed in these exams. The values of IgG serum, C3 and C4 complement components were obtained through simple radial immunodiffusion. For T, B, CD4 + and CD8 + lymphocytes, anti-CD3, anti-CD19, anti-CD8 monoclonal antibodies were used, respectively. The values obtained were compared with the standard curves according to the age of each patient, throughout the course of patient follow-up[19,20].

DISCUSSION

Our patients presented an increase of α fetoprotein, as well as ataxia and other neurologic alterations, telangiectasia, repeating infections and immune deficiencies that were diagnosed through laboratory assays, confirming the diagnosis of ataxia-telangiectasia syndrome, with the onset of symptoms occurring between the ages of 16 months and nine years.

Serum IgA deficiency was the first immune alteration presented by all four patients, with values below 7 mg/dL, which persisted throughout disease evolution. Sequentially, the immune alterations were the reduction of serum IgG levels, presented by two patients, and deficiency in the neutrophil phagocytosis digestion stage, observed in two patients as well. In chronological order, there was the inversion of the CD4/CD8 ration, presented by three patients in the advanced forms of the syndrome. The B lymphocytes, C3 and C4 complement components as well as chemotactic and phagocytic activity for monocytes were normal throughout the evolution. The sequence in IgA deficiency, followed by IgG subclass deficiency and inversion of the CD4/CD8 ration is comparable to that which has already been documented in the literature[13,14]. It is also compatible to the hypothesis that IgA deficiency may have, in sequence, IgG subclass deficiency and common variable immunodeficiency[21]. In the literature, cases were not found of ataxia-telangiectasia having deficiency in the phagocytic activity of polymorphonuclears, which was observed in two of our patients, as well as not finding studies regarding such alteration in this syndrome. The phagocytosis alterations, which were observed in a laboratory environment, were concomitant with the clinical worsening of the infectious processes presented by our patients.

The first two case reports were of two sisters, demonstrating the hereditary nature of the disease. From the beginning, these two patients presented neurologic alterations of slow progression, posteriorly leading to the inability to walk. The infections ap-

peared later, with repeating sinusitis, followed by pneumonias that throughout the course of their presentation became increasingly harder to control, coinciding with the deficiency in the phagocytic ingestion phase by neutrophils and the reduction in serum IgG2 levels. It is well know that the reduction in neutrophil activity propitiates an inadequate defense against *Staphylococcus aureus*[22], in the same manner that deficiency in the IgG2 subclass makes the patient more susceptible to *Streptococcus pneumoniae* and *Haemophilus influenzae*. The three types of bacteria mentioned constitute the main etiologies of the pneumonias, thus being coherent with the laboratory and clinical findings observed in our patients. Encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* require the union of the Fab portion of IgG2 for opsonization mediated by Fcγ receptors found in polymorphonuclear neutrophils[23]. The deaths of the two sisters were in consequence of the severe infectious processes, which are also well described in the literature[15]. The ataxia-telangiectasia syndrome presented by the two sisters evolved in a similar manner; such similarity may suggest that the genetic heredity may contribute with the form of evolution of the disease.

The third case shows the disease with a similar evolution to that of the two sisters: initial neurologic alterations with slow evolution and a delayed immunocompromised situation with IgA deficiency. This propitiates susceptibility to superior respiratory tract infections, which may trigger bronchospasm. In this manner, IgA permits greater mucosae allergen penetration, triggering respiratory atopies. Therefore, the bronchospasms associated to the repeating sinus infections presented by the patient may be in consequence of the observed IgA deficiency.

The evolution was quite different in the fourth case report. The patient presented, from the onset of symptoms, repeating infections concomitant with the neurologic alterations. From the beginning, she presented IgA deficiency as well as that of IgG2. The initial cerebellar ataxia rapidly evolved leading to the complete inability to walk six years after the initial diagnosis.

All of the patients were treated with antibiotics whenever necessary. The treatment chosen for our patients that evolved with IgG2 subclass deficiency along with repeating pneumonias was that which is commonly recommended: intravenous gammaglobulin administration every three to four weeks[24]. In patients with ataxia-telangiectasia with cellular alteration, bone marrow transplant can be opted for, being many times not chosen due to the severe neurologic impairments that occur in AT.

We conclude that ataxia-telangiectasia can present different forms of evolution, both in relation to the neurologic and immune conditions. In the first three case reports the patients evolved with slow and progressive neurologic alteration, with a delayed immunocompromised condition, while the fourth patient presented fast and concomitant evolution of neurologic and immune alterations. Furthermore, we conclude that the chronological sequence of the observed immunodeficiencies observed in the four cases were IgA deficiency, IgG2 deficiency and phagocytic ingestion by neutrophils phase, and, lastly, common variable immunodeficiency. It is possible that the type of evolution and disease progression is also associated to specific inherited genetics, as is suggested from the reports of the two sisters.

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