

Short Communication

Variability of immunodeficiency associated with ataxia telangiectasia and clinical evolution in 12 affected patients

Claret Teruel G, Giner Muñoz MT, Plaza Martín AM, Martín Mateos MA, Piquer Gibert M, Sierra Martínez JI. Variability of immunodeficiency associated with ataxia telangiectasia and clinical evolution in 12 affected patients.

Pediatr Allergy Immunol 2005;16:615–618. © 2005 Blackwell Munksgaard

Ataxia telangiectasia (AT) is an infrequent condition, which is difficult to diagnose in children. The objective was to describe the evolution of all affected patients controlled in our hospital and to highlight the keys for an early diagnosis considering the variability of immunological disorders. The present study is a retrospective review of all patients diagnosed and controlled of AT in our hospital. Twelve patients were found, including two couples of siblings. The most frequent reason for consultation was unstable gait. Seven patients suffered repeated infections, being pneumonia the most frequent cause of infection, followed by sinusitis. One of the patients developed Burkitt's lymphoma, and another patient, Hodgkin's lymphoma, which caused the death of the patient at the age of 11. A couple of siblings aged 17 and 22 years developed insulin-resistant diabetes mellitus. The most frequent immunity disorders were the IgG deficiency and the decrease of T lymphocytes. Seven patients were treated with non-specific gamma-globulin. By the end of the follow-up, 8 patients (ages ranged 7 to 12 years) lost gait. Molecular genetic testing was conducted in patients who are still cared for in our hospital. Clinical suspicion of this entity will lead to an early diagnosis, the treatment of complications, and to provide genetic counselling for the families.

G. Claret Teruel, M. T. Giner Muñoz, A. M. Plaza Martín, M. A. Martín Mateos, M. Piquer Gibert and J. I. Sierra Martínez

Allergy and Clinical Immunology Section, Paediatrics Department, Integrated Unit Sant Joan de Déu – Clínic, Hospital Universitari Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

Key words: ataxia telangiectasia; alpha-fetoprotein; immunodeficiency; children

G. Claret Teruel, Allergy and Clinical Immunology Section, Paediatrics Department, Integrated Unit Sant Joan de Déu – Clínic, Hospital Universitari Sant Joan de Déu, Passeig Sant Joan de Déu 2, 08950 Esplugues (Barcelona), Spain
Tel.: +93 280 40 00
Fax: +93 203 39 59
E-mail: gclaret@hsjdbcn.org

Accepted 16 August 2005

Ataxia telangiectasia (AT) is a degenerative disorder characterized by a progressive cerebellar ataxia, oculo-cutaneous telangiectasia and combined immunodeficiency (1–4).

Both males and females are equally affected. The prevalence of the disease is estimated to be 1 in 40,000–100,000 births (1, 3). AT is present in all races and countries, with a variable prevalence. This variability depends, on one hand of the diagnostic methods and on the other hand, of the frequency of consanguinity. Consanguinity increases the risk, given its transmission by autosomal recessive inheritance (1–5).

The AT is a member of chromosomal breakage syndrome and is caused by a mutation in the AT gene (ATM) that encodes a protein important for cell cycle control and DNA repair after dam-

aging (3, 4). More than 400 mutations of the ATM gene have been described (1, 5).

The initial presentation of this disease is usually an early deterioration of the gait, between 1 and 4 yr of age, and mainly characterized by a progressive ataxia that will eventually avoid autonomous walking around age 10 (1). In 90% of the patients, telangiectasias appear several years after the neurological signs, usually in the conjunctive (1, 2, 6). An early occurrence of oculo-motor apraxia and dysarthria is frequent, but it may be difficult to assess in young children (1). Predisposition to sinopulmonary infections is a prominent feature of AT and pneumonia is a common cause of death (4). Children with AT tend to develop malignancies of blood system, particularly lymphoma and leukaemia and are

extremely sensible to ionizing radiation (1–3). Other features of the disease include diabetes mellitus, hypogonadism and growth retardation (2). Intelligence is normal.

Laboratory findings include elevated serum α -fetoprotein (AFP) in more than 95% of patients, immunological deficiencies and *in vitro* radiosensitivity (1, 7–9). AFP is a human fetal serum protein found at levels <10 ng/ml in children more than 1 yr of age (3). The radiosensitivity phenomenon is manifested by a decrease of the colony-forming units after exposure to ionizing radiation. It is abnormal in more than 99% of AT patients who present a colony survival assay score of $<21\%$ (8). It is highly sensitive for diagnosing AT but it has been recently suggested that it might be also manifested by other disorders of DNA repair, immunodeficiencies and tumours (1). Nowadays diagnosis is also possible measuring ATM protein, ATM kinase activity and ATM mutations (1, 8). Protein studies and gene sequencing has allowed us to reach a definitive diagnosis in cases with atypical manifestations (1).

The neuropathology of AT consists of a selective atrophy of the cerebellar cortex, which can be seen on magnetic resonance imaging (MRI) examination by 7–8 yr of age, because of a degeneration of granular and Purkinje's cells, caused by an unknown mechanism. Some researchers suggest that the patient's neurological deterioration is correlated to the degree of atrophy (10).

The AT is presently incurable and there is no way to slow the progression of the disease (1). Treatments are directed towards alleviating symptoms (1).

Objectives

- 1 A clinical descriptive study of the evolution of all patients diagnosed with AT that are or have been controlled in our centre.
- 2 To highlight the variability of the immunological disorders that may occur in patients with this disease.

Material and methods

We performed a retrospective review of all the patients with the diagnosis of AT controlled in the Allergy and Clinical Immunology Section of our hospital from 1978 to 2004. Clinical summaries and imaging studies were reviewed.

The following variables were collected: age at the first visit, and reason for consultation; age at diagnosis; time when the first telangiectasia

appeared; presence of infections or neoplasms; main immunity disorders and levels of AFP; karyotype disorders; clinical evolution and treatment.

Results

Twelve patients were collected, five boys and seven girls, including two couples of siblings. Three patients (two of them were brothers) had a family history of consanguinity. Except for one children who had an Arabic origin, the rest were Caucasians. The mean age at first visit in our hospital was 2 yr and 1 month (range: 13 months to 3 yr). All the patients were diagnosed in our hospital at a mean age of 2 yr and 8 months (range: 18 months to 4 yr and 8 months), excluding two patients in which diagnosis of AT was already made and were referred to our service for clinical follow up. In all cases, the reason of consultation was unstable gait, except for the youngest patient in our series (13 months old) who showed inability to sit with support.

The period between consultation and diagnosis ranged from 1 to 5 months (except for a case with a 3 yr and 7 months period). The onset of telangiectasias was at a mean age of 2 yr and 8 months (range: 15 months to 5 yr; Figs 1 and 2).

Eight patients (66.6%) suffered recurrent upper and/or lower respiratory tract infections and two of those also suffered repeated gastro-

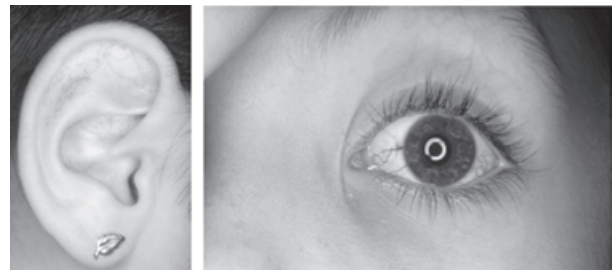


Fig. 1. Ataxia telangiectasia (AT) affected girl at the age of 5 yr.

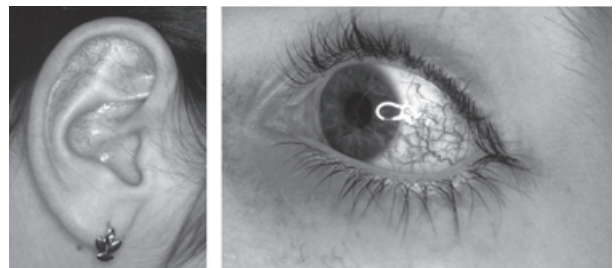


Fig. 2. The same girl at the age of 15 yr.

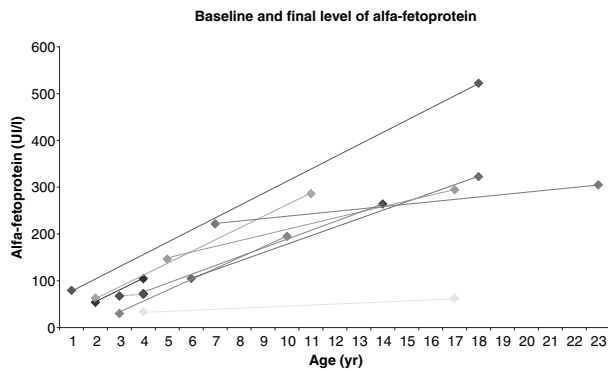


Fig. 3. Baseline and final level of α -fetoprotein in ataxia telangiectasia (AT) affected children.

enteritis. The most frequent infection was pneumonia (in four cases), followed by chronic sinusitis (three patients) and repeated otitis (two cases).

Two types of neoplasms occurred in our patients; Burkitt's lymphoma in one case and Hodgkin's lymphoma in another case (which caused the death of the patient at 11 yr of age). A couple of siblings aged 17 and 22 yr developed type II diabetes mellitus, because of a peripheral resistance to insulin, and were successfully treated with oral antidiabetics.

Immunological abnormalities were present in all patients of our series. The most common humoral immune disorder was serum immunoglobulin (Ig)G₂ deficiency found in eight patients (66.6%), followed by IgA deficiency in seven cases (58.3%), IgE in six cases (50%) and IgG₄ in three cases (25%). Among patients with IgA deficiency only one had isolated IgA deficiency, one had IgG₄ deficiency, one had IgM deficiency, three had IgG₂ deficiency, five had IgGE deficiency and two had total IgG deficiency. Regarding cellular immunity, the majority of patients (75%) had decreased levels of T4 lymphocytes, and in five cases (41.6%) there was a reduced *in vitro* response to mitogens (concanavalin A, Pokeweed mitogen, phytohaemagglutinin) in lymphoblastic transformation test. Determinations of AFP showed high levels in all patients (Fig. 3).

A karyotype study was conducted in eight patients and in seven cases chromosome fragility was found. Molecular genetic testing was conducted in seven patients resulting 8977C>T mutation (in one case in homozygosis and in two siblings in heterozygosis), 9010del128 mutation (in one case in homozygosis), the 715delT mutation (in one case in homozygosis) and the 3712del5 mutation (in one case in heterozygosis).

Seven patients (58.3%) received replacement therapy with intravenous immunoglobulin

(IVIG). The mean age at initiation of the therapy was 5 yr and half (range: 1–10 yr). None of our patients received antibiotic prophylaxis.

End of follow up occurred after change of address or because of referral to adult patient centres. Six patients are still controlled in our hospital. Two of the children in our series died (16.6%), one of them because of Hodgkin's lymphoma at the age of 11 yr and the other due to a relapse of chronic respiratory failure secondary to repeated infection episodes, at the age of 18 yr. Most patients ($n = 8$; 66.6%) were unable to walk at ages ranging from 7 to 12 yr. At the end of the follow-up period, four patients were able to walk, but with clear ataxia (two of them aged 14 yr, other 6 yr and the last aged 4 yr and 7 months).

Discussion

According to literature telangiectasias often do not appear until the patients are 6–8 yr old (2) but in our series they appear earlier (mean 2 yr and 8 months). Age of diagnosis in previous reports was closely associated with recognition of ocular telangiectasias (3). In our series four patients were diagnosed before their apparition. This could be probably because of the growing interest in AT, reflected in the highest number of references in the literature that allows a better knowledge and earlier recognition of the disease (5).

Although early publications correlated AT basically with the selective deficiency of IgA, the immunity disorders that these patients can show are very diverse, and do not always correlate with the clinical expression of the immunodeficiency (1, 4, 11). In our series, we report four patients (33.3%) who did not suffer relevant infective processes, despite disorders of the humoral and cellular immunity were found in all of them. The percentage of patients free of recurrent infections varies broadly in the literature, with authors reporting rates of 80%, while other sources report to have found equal number of infections in the AT-affected twin compared with the twin not affected (4). The most frequent humoral immunity disorder in our series is IgG₂ deficiency (66.6%) followed by IgA (68.3%) and IgE (50%) deficiency while in the literature the most frequent humoral immunity disorder is IgG₄ deficiency, present only in 25% of our patients (4). None of our patients developed hypergammaglobulinaemia or gammopathy. Probably, the case of the later diagnosis was due to the lack of an IgA deficiency, which was invariably considered and was associated with

this disease some years ago (11). Regarding cellular immunity the T-lymphocyte deficiency is the most common deficiency in our series reaching the 75% of the patients while the literature reports only 57% (4). Reduced responses to mitogens were present in our patients in a similar percentage than reported in the literature (4).

The risk of cancer in these patients is estimated to be 200 times higher than in the general population, affecting to a third of them (1). In our series, by the end of the study, only one-sixth of the patients showed it. Among those without cancer, one of the patients had lost a sister because of lymphoma. The previously healthy child who presents with a malignancy atypical for the patient's age, or with atypical histology or location should make us think on the possibility of an underlying and undiagnosed immunodeficiency disorder (1). Close relatives of AT patients should be revised regularly, as heterozygotes have an increased risk of developing cancer (12).

All of our patients presented high levels of AFP and increase with age but we have not found a significant correlation between AFP levels and the severity of the disease as some researchers have proposed (11). In absence of other reasons that might explain the increased values of this parameter (liver, testicle and pancreas cancer and transitorily elevation only during the recovery of an acute necrotic liver disease) this is a key data for the early diagnosis of AT. AFP testing has been recommend by some researchers in all toddlers and children with undiagnosed progressive ataxia (1, 3).

As described in the literature, most of our patients inherit different mutations from each parent (1, 2). Only in one case the 8977C>T mutation was found in homozygosis. There is a great interest in finding relationships between genotype and phenotype but this is nowadays difficult because both mutations are defined only in a few cases (1).

Although we do not have the possibility to stop the disease or to slow its progression an early diagnose is necessary to detect cancer in patients and relatives, design effective palliative treatments, to limit the exposure to ultraviolet light and diagnostic radiographs and to allow the opportunity for genetic counselling (3).

References

1. CHUN HH, GATTI RA. Ataxia telangiectasia, an evolving phenotype. *DNA Repair* 2004; 3: 1187–96.
2. MURPHY RC, BERDON WE, RUZAL-SHAPIRO C, et al. Malignancies in pediatric patients with ataxia telangiectasia. *Pediatr Radiol* 1999; 29: 225–30.
3. CABANA MD, CRAWFORD TO, WINKELSTEIN JA, et al. Consequences of delayed diagnosis of ataxia telangiectasia. *Pediatrics* 1998; 102: 98–100.
4. NOWAK-WĘGRZYN A, CRAWFORD TO, WINKELSTEIN JA, CARSON KA, LEDERMAN HM. Immunodeficiency and infections in ataxia telangiectasia. *J Pediatr* 2004; 144: 505–11.
5. LAVIN MF, CONCANNON P, GATTI RA. Eighth International Workshop on ataxia telangiectasia (ATW8). *Cancer Res* 1999; 59: 3845–9.
6. FARR AK, SHALEV B, CRAWFORD TO, LEDERMAN HM, WINKELSTEIN JA, REPKA MX. Ocular manifestations of ataxia telangiectasia. *Am J Ophthalmol* 2002; 134: 891–6.
7. SUN X, BECKER-CATANIA SG, CHUN HH, et al. Early diagnosis of ataxia telangiectasia using radiosensitivity testing. *J Pediatr* 2002; 140: 724–31.
8. CHU HH, SUN X, NAHAS SA, et al. Improved diagnostic testing for ataxia telangiectasia by immunoblotting of nuclear lysates for ATM protein expression. *Mol Genet Metab* 2003; 80: 437–43.
9. MEYTS I, WEEMAES C, DE WOLF-PEETERS C, et al. Unusual and severe disease course in a child with ataxia telangiectasia. *Pediatr Allergy Immunol* 2003; 14: 330–3.
10. TAVANI F, ZIMMERMAN RA, BERRY GT, SULLIVAN K, GATTI R, BINGHAM P. Ataxia telangiectasia: the pattern of cerebellar atrophy on MRI. *Neuroradiology* 2003; 45: 315–9.
11. AYACHE R, NAJJAR MF, OBEID H, POUSSE H, GUEDDICHE MN. Ataxia telangiectasia. Clinical and biological study in 17 cases. *Ann Biol Clin* 1994; 52: 117–20.
12. CAVACIUTI E, LAUGÉ A, JANIN N, et al. Cancer risk according to type and location of ATM mutation in ataxia telangiectasia families. *Genes Chromosomes Cancer* 2005; 42: 1–9.