Ataxia-Telangiectasia in the south of Tunisia: A study of 11 cases

L'ataxie–télangiectasie dans le sud Tunisien: Etude de 11 cas

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RÉSUMÉ

Prérequis : L'ataxie télangiectasie (AT) associe un déficit immunitaire combiné à une ataxie cérébelleuse progressive. Elle est caractérisée par des signes neurologiques, des télangiectasies, une sensibilité accrue aux infections et un risque augmenté de cancers. L'AT est une maladie autosomique récessive due à une mutation du gène ATM.

But : Etudier les particularités cliniques, immunologiques et génétiques.

Méthodes : Nous avons mené une étude rétrospective à propos de tous les cas d'AT colligés dans le service de pédiatrie du CHU Hédi Chaker durant une période de 17 ans (1996-2012).

Résultats : nous avons colligé 11 cas d'AT. L'âge moyen de début de la symptomatologie était de 20 mois avec des extrêmes de 3 mois et 4 ans. Les signes inauguraux étaient dominés par le syndrome cérébelleux (8 cas) qui est apparu à un âge moyen de 2.8 ans. Les télangiectasies oculaires dans 2 cas. Les infections broncho pulmonaires ont affecté 7 patients à un âge moyen de survenue de 4.3 ans. Le déficit en IgA était le déficit immunitaire le plus fréquent. Une lymphopénie a été notée dans 7 cas et le déficit en CD4 dans 6 cas. Le caryotype sanguin a montré une instabilité chromosomique chez tous les patients, une translocation (7-14) chez d'entre eux. L'étude génétique effectuée chez 6 patients, a montré une mutation à l'état homozygote du gène ATM chez 4 enfants et une double mutation à l'état hétérozygote chez 2 autres. Après un recul moyen de 5 ans 6 mois, 7 patients sont décédés suite à des infections pulmonaires sévères.

Conclusion : l'AT est une maladie sévère dont le pronostic est essentiellement lié aux complications pulmonaires.

Mots-clés
Déficit immunitaire, ataxie télangiectasie, gène ATM

SUMMARY

Background : Ataxia-telangiectasia (A-T) is a multisystem disorder characterized by progressive neurologic impairment, variable immunodeficiency, impaired organ maturation, X-ray hypersensitivity, oculocutaneous telangiectasia, and a predisposition to malignancy.

Aim: We performed this study in order to describe clinical, immunological and molecular features of patients with AT followed in the south of Tunisia

Methods: we performed a retrospective study (1996-2012) in the south of Tunisia about all cases of A-T in order to describe their clinical, immunological and molecular features.

Results: 11 cases of AT were found. The mean age at onset of symptoms was 20 months with extremes varying from 3 months to 4 years. The median time to diagnosis was 3.6 years (range: 0-12 years).The main clinical feature of cerebellar syndrome, ataxia, was present at diagnosis in 8 patients and occurred at mean ages of 2.8 years. Ocular telangiectasia occurred at a mean age of 3.9 years (extremes: 3 months and 7 years). Recurrent sino-pulmonary infections that affected 7 children occurred at the mean age of 4.3 years. The most common humoral immune abnormality was serum IgA deficiency. Lymphopenia was found in 7 cases and lack of CD4 T in 6 cases. Cytogenetic analyses showed chromosomal instability in all children and a translocation (7–14) in two patients. A molecular diagnosis established in 6 patients from 4 families showed 5 different mutations of ATM gene. After an average decline of 5 years and 6 months, 7 patients died of severe pulmonary infection. Among them, 3 were ATM mutated.

Conclusion: Morbidity and mortality among patients with A- T are associated with ATM genotype.

Key-words
Immune deficiency, Ataxia-telangiectasia, ATMgene

Ataxia-telangiectasia (A-T) is a rare disorder with progressive ataxia, ocular telangiectasia, immune deficiency, and cancer predisposition, which is caused by biallelic germline mutations in the ATM gene. No curative strategy for this disease is currently available [1,2].

Ataxia-telangiectasia is reported in all regions of the world. The incidence of ataxia-telangiectasia is about 1 case in 100,000 births and may differ among countries according their mean consanguinity rates [3]. The frequency of ataxia-telangiectasia mutant alleles heterozygosity was reported to be 1.4-2% of the general population [3]. In most cases, it is caused by mutations in the ataxia-telangiectasia mutated (ATM) gene leading to a truncated protein product [4], which encodes the protein kinaseATM, the master regulator of the cellular responses to double strand breaks in the DNA [5-8]. A-T demonstrates the typical consequences of defects in the DNA damage response (DDR): degeneration of specific tissues affecting particularly the nervous and immune systems, chromosomal instability, sensitivity to specific DNA damaging agents, and a cellular phenotype that reflects the missing DDR player. During the last 5 decades A-T has attracted the attention of numerous clinicians and investigators, who recognized the important biological function flagged by its striking phenotype [9].

Previous studies showed that in Tunisia ataxia-telangiectasia is more prevalent among primary immunodeficiency disorders than in most of countries [10]. However the age at diagnosis is still late. So we performed this study in order to describe clinical, immunological and molecular features of patients with AT followed in the south of Tunisia.

METHODS

We reviewed in a retrospective study, all patients with A-T followed in the pediatrics department of Hedi Chaker University Hospital in Sfax, all coming from the south of Tunisia, during a period of 15 years (1996-2010). The diagnosis of A-T was made according to typical clinical findings plus one of the following: (1) a proven mutation in the ATM gene; (2) elevated α-fetoprotein, cerebellar atrophy on MRI, chromosomal instability, and immune deficiency.

RESULTS

Diagnosis and sociodemographic characteristics

From January 1996 to December 2008, 11 cases of A-T were confirmed according to the described diagnostic criteria in our department. AT was diagnosed based on clinical, laboratory, and molecular criteria in 6 cases and based on clinical and laboratory criteria in 5 cases (table I). The mean age at onset of symptoms was 20 months with extremes varying from 3 months to 4years.The median age at diagnosis was 6 years(extremes: 2 months and14 years) (table I). So that, the median time to diagnosis was 3.6years (range: 0-12 years).

We have noticed a slight predominance of males: 6 boys against 5 girls. Parental consanguinity was reported in all cases among our patients and familial history of AT was noted in 5 cases. There were one family with 2 affected children and another family with 3 affected children. Family History of leukemia was reported in one family (patients 4-6).

Clinical Manifestations

The main clinical events and ages at onset are reported in table I. The main clinical feature of cerebellar syndrome, ataxia, was present at diagnosis in 8 patients and occurred at mean ages of 2.8 years (extremes: 13 months and 6 years). Oculomotor apraxia (reported in 8 cases) and dysarthria (reported in 7 cases) were first observed at mean ages of 8.2 years and 10,2 years respectively. Loss of ability to walk occurred at a mean age of 11.3 years. Extra-pyramidal syndrome was noted in 9 children and occurred at 4 ± 2 years. Ocular telangiectasiae were observed in 10 patients at diagnosis (Figure 1).

Figure 1 : Occular telangiectasiae

They occurred at a mean age of 3.9 years (extremes: 3 months and 7 years). Oculomotor apraxia was noted in 4 cases. Recurrent sino-pulmonary infections (RSPI) affected 7children. They occurred at the mean age of 4.3 years (range: 5 months-8 years). Children usually suffered from focal pneumonia. Four children had haemoptysis. Microbiological analysis of expectoration often isolated Pseudomonas aeruginosa (four children), Hemophilusinfluenza (two children), Streptococcus pneumoniae (two children). Lung imaging diagnosed bronchiectasis in a child at age of 8 years. Chronic respiratory insufficiency occurred in two childrenat the age of 7 and 14 years (patients 7 and 11). Recurrent diarrhea was seen in 1 patient who developed equally a herpetic meningoencephalitis at the age of 2 years (patient 4). Five patients were wheelchairbound at an age between 12 and 15 years. Growth retardation occurred in 6 children at a mean age of 8± 3 years.

Laboratory Features

Alpha fetoprotein (AFP) was increased in all patients, with mean level of 165.1 kU/L (range 36–308). The most common humoral immune abnormality was serum IgA deficiency (9 cases). Three patients had IgG deficiency and 4 had high levels of IgM. Serum level of IgG2 checked in three patients was low in one case (0.093g/l). We found lymphopenia in 7 cases and lack of CD4 T (< 500 µl/L) in 6 cases. T-cell subset analysis, by immunologic flow cytometry, showed a

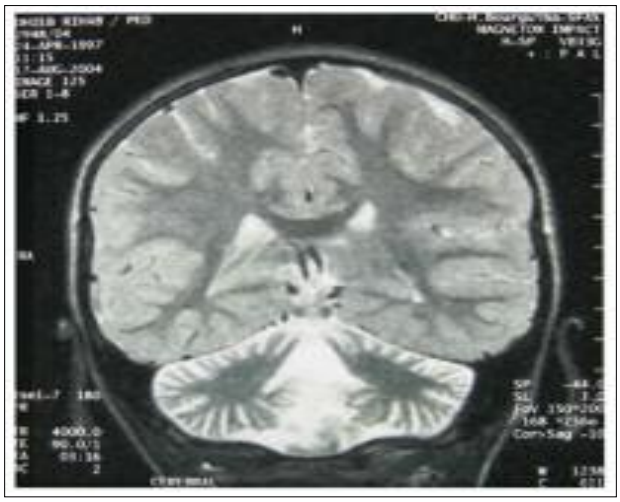
Table I : Summary of clinical, immunological, molecular and outcome features of patients with AT followed in the south of Tunisia

Patient	*Familial cases*	*Age at diagnosis*	clinical features at diagnosis	*Age at onset of ataxia*	*Age at onset of Téleng.*	Lung disease *(Age at onset)*	AFP kUI/L at diagnosis	Immune function	Cytogenetic analyses	Molecular diagnosis	average decline / *Evolution*
1	1. sister AT (patient.2)	7 years	cerebellar syndrome	5 years	3 months	–	222	Lymphopenia IgA deficiency	chromosomal instability	*c.6415_6415 delG&p.Glu2139Hefs*X6 *c.3894dupT&p.Ala1299Cysfs*X3	7 years/ Loss of ability to walk at 12 years
2	1. brother AT (patient1)	5 years	RSPI	6years	5 years	RSPI (4 years) haemoptysis	175,2	Lymphopenia IgA deficiency	chromosomal instability	*c.6415_6415 delG&p.Glu2139Hefs*X6 *c.3894dupT&p.Ala1299Cysfs*X3	7 years/ Loss of ability to walk at 12 years
3	–	3 years	cerebellar syndrome.	3 years	3 years	–	170	Lymphopenia IgG2 deficiency. CD4 deficiency	chromosomal instability	*c.8781 delB (c.8671_8786 del115&p.Gly2891Asnfs*X9) *(HMZ)*	13years/ Loss of ability to walk at 14 years Death at 16 years of age
4	1sister AT (patient5) 1 brother leukemia	2 years	RSPI Recurrent diarrhea	–	3 years	RSPI (5 months)	130	Lymphopenia IgA deficiency High IgM level CD4 deficiency	chromosomal instability	–	3years/ Death at 5 years of age
5	1 sister AT (patient4) 1brother leukemia	7 years	cerebellar syndrome	20 months	7 years	–	164,1	Lymphopenia IgA deficiency High IgM level CD4 deficiency	chromosomal instability	*c.6100C>T&Arg2034X (HMZ)*	7 years/ Loss of ability to walk at 12 years Death at 14 years of age
6	2 sisters AT (patient4,5) 1brother leukemia	2 months Néonatal screening	Néonatal screening	18 months	3 years	–	36	Lymphopenia IgA deficiency High IgM level	chromosomal instability	*c.6100C>T&Arg2034X (HMZ)*	4 years
7	–	6 years	cerebellar syndrome	18 months	4 years	RSPI (6 years) haemoptysis	170,9	Lymphopenia IgA deficiency reversed CD4/CD8 ratio	Chromosomal instability t(7,14)	*c.3894dupT&p.Ala1299Cysfs*X3 *(HMZ)*	11years/ Loss of ability to walk at 14 years Chronic respiratory insufficiency Death at 17 years
8	–	6 years	cerebellar syndrome RSPI	5 years	5 years	RSPI (3 years)	220	IgA deficiency. CD4 deficiency reversed CD4/CD8 ratio	Chromosomal instability t(7,14)	not done	Lost of follow up
9	–	6 years	cerebellar syndrome	19 months	6 years	RSPI (5 years) haemoptysis	308	IgA, Ig G deficiency High Ig M level CD4 deficiency reversed CD4/CD8 ratio	chromosomal instability	not done	4 years/ bronchiectasi death (10 years)
10	–	14 years	cerebellar syndrome Téleng. RSPI	4 years	2 years	RSPI (8 years) haemoptysis	190	IgA deficiency CD4 deficiency reversed CD4/CD8 ratio	chromosomal instability	not done	4 years/ Loss of ability to walk at 15 years bronchiectasis death (18 years)
11	–	7 years	cerebellar syndrome Téleng. RSPI	13 months	4 years	RSPI (4 years)	170	IgA, Ig G deficiency High Ig M level CD4 deficiency reversed CD4/CD8 ratio	chromosomal instability	not done	1 year/ Chronic respiratory insufficiency death (8years)

AFP: alpha fetoprotein Téleng.: telangiectasias RSPI: Recurrent sino-pulmonary infections HMZ: homozygous

Radiology features
Cerebral MRI, performed in 6 children, showed cerebellar atrophy in all cases (Figure2).

Figure 2 : Cerebral MRI: cerebellar atrophy



Cytogenetic analyses
Cytogenetic analyses performed in all patients, showed chromosomal instability in all children. Translocation 7–14 was present in two patients (patients 7-8).

Molecular diagnosis
A molecular diagnosis was established in 6 patients from 4 families. We identified 5 different mutations. A homozygous mutation was detected in 4 cases (Table 1).

Treatment
Treatment was consisted on respiratory physical therapy and antibiotic prophylaxis in all patients. Intravenous Ig had been administered in two patients every month since they were 3 years old. One of them who had IgA defects developed an anaphylaxis incident so that the Intravenous Ig were stopped (patient 3). The recurrent respiratory infections decreased in frequency, duration and severity in the second patient (patient 4).

Evolution
After an average decline of 5 years and 6 months (range,1-13years), 7 patients died of severe pulmonary infection. The mean age at death was 12,4 years (range, 5-18 years).

DISCUSSION

A-T is primarily an early-onset, progressive, neurodegenerative disorder [11] that is transmitted as an autosomal recessive disorder with a frequency of 1/100,000live births [3].
A-T is seen among all ethnic groups and is most prominent when there isa high consanguinity rate, which increase the risk of autosomal recessive disorders and multifactorial diseases [12].
Consanguineous marriages have been a long-standing social habit among Tunisians (the overall rate of consanguineous marriage is 32.71% [13]. In our study, consanguinity was present in all cases.
Ataxia is usually a first diagnostic hallmark, starting at walking age and leading to wheelchair dependency toward the second decade of life [11,14-16]. The median age at onset of ataxia in our patients was 2.8 years (extremes: 13 months and 6 years).Among the other classic early features of A-T slurred speech, oculomotorapraxia, and choreoathetosis, which are seen in most of our patients. In all of them, these neurologic problems were progressive and nothing could be done except supportive care such as physiotherapy and other rehabilitative therapies. Cognitive abilities are relatively conserved, but academic achievement is impaired [15].
Oculocutaneous telangiectasia, the second diagnostic hallmark of ataxia-telangiectasia, usually has a later onset than the ataxia [16,17]. The onset of telangiectasiae usually follows ataxia by several years typically at age 3-6 years. The median age at onset of telangiectasia in our patients was 3,9 years. While telangiectasiae are usually seen over the bulbar conjunctiva, they can occur in other places as well, notably over the bridge of the nose, pinnae of the ears, the antecubital fossae, knuckles and behind the knee in the popliteal fossae. However, some A-T patients never develop prominent telangiectasia [18].
Ataxia-telangiectasia patients are prone to recurrent sinopulmonary infections as a result of a variety of cellular and humoral immunodeficiencies[19]. Pulmonary status is a prognosis factor of A-T: 50% of patients die in adolescence from over whelming bronchopulmonary disease[19]. Pulmonary infections in A-T are usually caused by viruses during the first two years of life, and by common bacterialpathogens in later childhood, such as Hemophilus influenzae, Streptococcus pneumoniae, Pseudomonas aeruginosaand Staphylococcus aureus [20].
These common infections are often correlated with the severity of humoral defect, and hence the rationale for using gamma-globulin [20]. Variable immunodeficiencies involving the function of T lymphocytes are common in A-T. Nevertheless, mycobacteria and opportunist pathogens (such as fungi or pneumocystis) rarely cause pulmonary infection in AT. Recurrent pneumonias result in progressive bronchiectasis and advanced lung disease [21]. Some researchers have noted a correlation between the severity of pulmonary status and humoral immunodeficiencies. The most common humoral immunological defects are diminished or absent serum IgA which was found in 9 of our patients and IgG2, and impaired antibody responses to vaccines [22]. Serum IgG level is generally normal even when some IgG subclasses are reduced. Patients with IgG2or IgG4 appear to be at higher risk for infection [20]. Increased IgM levels may occur in A-T. It was found in 4 patients in our study.
Cellular immunity can also be affected in A-T: abnormal development of the thymus, with absence of Hassal corpuscles and cortico-medullary differentiation, impaired delayed hypersensitivity reactions or lymphoproliferative responses to mitogens, and diminishing numbers of CD4 lymphocytes [23]. An elevated serum α fetoprotein level is a useful screening test for ataxia-telangiectasia. AFP is reported to be elevated in about 90% of -A-T patients [11].
A-T is caused by biallelic mutations in the ATM gene, which is located at 11q22.3 [4,11].

The number of unique ATM mutations in A-T patients now exceeds 400. Most patients inherit different mutations from each parent; they are compound heterozygotes. Approximately 85% of these mutations are either nonsense or splicing types, creating mainly frame shifts and premature termination codons that result in null mutations. These occur over the entire gene and none accounts for more than 3% frequency [14]. Patients with biallelic mutations in ATM that cause total loss of expression or gene-product function have a higher risk for cancer (mainly hematologic malignancies) at younger ages than patients with 1 hypomorphic mutation in ATM, who have greater mortality from RSPI [9,14,24,25]. It is well accepted that mutations causing severe loss of ATM protein (truncating/null mutations) cause severe disease, and mild mutations (usually missense) with residual protein may cause milder or later ataxia. However, there are no data on how mutations affect other aspects of the neurologic presentation (ie, are there mutations that are more prone to cause extrapyramidal involvement?).

The treatment of A-T remains based in medical management (of immunodeficiencies and sinopulmonary infections, neurologic dysfunction, and malignancy) and neuro rehabilitation (physical, occupational, and speech/swallowing therapy; adaptive equipment; and nutritional counseling). Physiotherapy advice regarding which techniques to adopt and optimise anatomical lobar drainage and supervision of airway clearance methods before irreversible structural lung damage occur is desirable. In addition to optimal immunoglobulin dosing and physiotherapy, the use, duration and dosage of antibiotic treatment or prophylaxis should be considered for each patient.

In patients with ataxia-telangiectasia, early death is frequently due to pulmonary disease, but malignancies are also a common cause. According to other studies, the incidence of malignancy is 60-300 times higher than in healthy persons, and, on autopsy report, 49% of cases had malignant tumors [26]. In the present study, however, no patients had malignancies. This may be due to our brief follow-up period (5 years and 6 months). For type of tumor, previous data that show lympho reticular malignancies as the most common tumors seen in ataxia-telangiectasia patients, especially non-Hodgkin lymphomas or leukemias, but other kinds of tumors also occur[27,28]. The life time risk of cancer among patients with A-T has been estimated to be 10-38%, which is about 100-fold more than the population rate [16]. In the absence of chronic bronchopulmonary disease and lympho reticular malignancy, however, A-T is consistent with survival into the fifth or sixth decade.

CONCLUSION

It is important to inform the general population about the dangers of consanguinity, which is very common in some areas such as Tunisia. Morbidity and mortality among patients with A-T are associated with ATM genotype. This information could improve our prognostic ability and lead to adapted therapeutic strategies. Prospective studies should be performed to determine the outcomes of various chemotherapy protocols and prophylactic antibiotic and immunoglobulin replacement therapies, as well as to prevent neurologic impairments, in patients with A-T.

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