

Ataxia-Telangiectasia: guidelines for diagnosis and comprehensive care

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Abstract

Ataxia-Telangiectasia (A-T) is an autosomal recessive disease that coexists with progressive cerebellar ataxia, immunodeficiency, sinopulmonary infections and skin disorders, including oculocutaneous telangiectasiae, cancer susceptibility, radiosensitivity and early ageing. A-T is caused by mutations of the ATM gene. Laboratory findings include elevated alphaprotein, cerebellar atrophy on MRI, translocations involving chromosomes 7 and 14, absence or dysfunction of the ATM protein and radiosensitivity in CSA. According to recent reports, increased radiosensitivity together with ATM protein absence confirm the diagnosis of A-T. The last step in diagnosis is searching for mutation, which is time-consuming and expensive. As the ATM protein is very large, it influences many processes in organism, and consequently impairs functioning of different organs. Direct and simple guidelines are required for diagnosis and care of A-T patients.

Key words: Ataxia-Telangiectasia, ATM protein, radiosensitivity, x-rays, malignancy, immunodeficiency, dysphagia.

(*Centr Eur J Immunol* 2007; 32 (4): 234-238)

Introduction

Ataxia-Telangiectasia (A-T; MIM # 208900) is a rare autosomal recessive disorder caused by mutation in the *ATM* gene for Ataxia-Telangiectasia Mutated. Hallmarks of the disease comprise progressive cerebellar ataxia, oculocutaneous telangiectasiae, variable humoral and cellular deficiency, chromosomal instability, and increased risk of cancer and radiation sensitivity [1]. Epidemiologists estimate the frequency of A-T as 1 in 40 000 to 100 000 live births. The disease is found in all races. However, it is believed that many children with A-T, particularly those who die at young age, are never properly diagnosed. Therefore, this disease may actually be much more common. The responsible *ATM* gene, maps to chromosome 11q22-23 [2], and contains 66 exons [3]. The *ATM* product is a large (370-kd) serine/threonine kinase, with a phosphatidylinositol 3-kinase (Pi3K) domain, which localizes mainly to nuclei (lymphocytes, fibroblasts, germ cells) and is involved in the cellular responses to DNA double strand breaks, and damage-induced cell-cycle

checkpoints [2]. In cytoplasm ATM regulates redox state concerning especially neurons [4]. Over 400 mutations have been identified to date, which occur throughout the entire gene [5]. No curative strategy for this disease exists at present, but extensive research is being carried out in laboratories worldwide.

Basic clinical manifestation

A-T is one of a group of autosomal recessive cerebellar ataxias. The most debilitating feature of this disorder is the progressive neurodegeneration due to loss of Purkinje cells in the cerebellum and malfunction of other neuronal cells. The presence of early-onset cerebellar ataxia with oculocutaneous telangiectasiae permits diagnosis of A-T. Ataxia of both upper and lower limbs develops, usually by the age of 2 years. This clinical diagnosis becomes most apparent after age 10 years, when other symptoms such as dysarthric speech, oculomotor apraxia and choreoathetosis are fully expressed [6]. A-T diagnosis may become

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problematic before the appearance of telangiectasiae or when the characteristic neurological impairment is mild or delayed. In young infants the diagnosis may be elusive and easily confused with mild cerebellar palsy, acute infections, or episodic ataxia, ataxia with oculomotor apraxia or other rare genetic or mitochondrial diseases [7]. However, some patients are not recognized to have A-T until the second decade of life.

One of the main hallmarks of A-T – telangiectasiae appear most noticeably on the bulbar conjunctiva several years after onset of neurological symptoms (figure 1). They are noted, usually in the eyes, in almost all patients by age 10.

Additional supportive tests

The clinical diagnosis of A-T used to be based on early-onset progressive cerebellar ataxia and then development of oculocutaneous telangiectasia. There are additional blood or imaging tests which are supportive in making A-T diagnosis before any expensive and advanced methods are used.

AFP level

Serum alpha-fetoprotein (AFP) level is a useful tool to diagnose A-T, especially in young children. Elevated serum levels of AFP are found in 95% of patients [8]. However, false-positive findings are seen in children under age 2, whose levels remain slightly elevated from neonatal period. There are also some rare conditions of hereditary persistence of elevated AFP and association with some malignancies [4]. Thus if the serum AFP level is found to be elevated, A-T should be taken into consideration.

Immunological assessment

Dysgammaglobulinaemia, decreased cellular immune response and peripheral lymphopenia are on one hand the supportive findings but on the other hand are a variable feature in A-T patients. Most patients demonstrate immunoglobulin deficiencies involving IgA (in 60-70%), IgE (in 80%) and IgG especially IgG2 (in 80%) and IgG4 subclasses. One possible explanation for this variation is that different *ATM* mutations may have differing effects on immune gene rearrangements or cell survival [4]. Serum IgM levels are highly variable, and may change during disease progression. Hyper-IgM is seen in approximately 1-2% of patients with A-T worldwide and appears to be due to a polyclonal rather than a monoclonal gammopathy [9]. In patients with A-T hyper-IgM may represent an efficient or thwarted immunologic response to an infectious agent. Responses to polysaccharides antigen are reduced in almost all patients. The number of circulating T lymphocytes is usually reduced, and gamma/delta T-cell levels are usually elevated, probably reflecting a maturation defect in this pathway. B cells are normal or slightly elevated with poor in vitro response to mitogens.



Fig. 1. Ocular telangiectasiae

Imaging studies

Magnetic resonance imaging (MRI) of the cerebellum shows atrophy, usually by age 10, which is progressive.

Karyotype

Karyotyping reveals characteristic chromosomal aberrations, such as t(7;14), translocations and telomeric fusion and increased rate of telomeric shortening [4].

Diagnosis

Much progress has been made in early diagnosis since the *ATM* gene was cloned in 1995 [2]. The European Society for Immunodeficiency Disorders (ESID) has established diagnostic criteria for clinicians for better recognition of A-T (table 1). They are divided into three categories: possible, probable and definitive. Possible and probable categories comprise clinical features such as cerebellar ataxia and ocular or facial telangiectasia, together with laboratory tests like: serum IgA at least 2 SD below normal for age, alpha fetoprotein at least 2 SD above normal for age and increased radiation-induced chromosomal breakage in cultured cells.

Radiosensitivity test

As mentioned above, A-T cells are hypersensitive to ionizing radiation. The colony survival assay (CSA) is the only measurement of radiosensitivity that has been validated for clinical use. The CSA identifies radiosensitivity in approximately 90% of patients with A-T [10].

ATM protein

A-T cells are typically deficient of *ATM* protein due to null mutations in both copies of the *ATM* gene. This characteristic has recently been validated as a diagnostic criterion for identifying A-T [1]. Immunoblotting (i.e. Western blot) of nuclear lysates from A-T cells is a semi-quantitative

Table 1. ESID criteria of Ataxia-Telangiectasia

DEFINITIVE
Male or female patient with either increased radiation-induced chromosomal breakage in cultured cells, or progressive cerebellar ataxia, who has disabling mutations on both alleles of ATM
PROBABLE
Male or female patient with progressive cerebellar ataxia and three out of the following four findings: <ul style="list-style-type: none">• ocular or facial telangiectasia• serum IgA at least 2 SD below normal for age• alpha fetoprotein at least 2 SD above normal for age• increased radiation induced chromosomal breakage in cultured cells
POSSIBLE
Male or female patient with progressive cerebellar ataxia and at least one of the following four findings: <ul style="list-style-type: none">• ocular or facial telangiectasia• serum IgA at least 2 SD below normal for age• alpha fetoprotein more than 2 SD above normal for age• increased chromosomal breakage after exposure to irradiation
DIFFERENTIAL DIAGNOSIS
Nijmegen breakage syndrome Bloom syndrome

measurement of ATM protein, with >98% sensitivity and specificity. When they are studied, lack of ATM protein is noted in >95% of patients with A-T [11]. The lack of detectable ATM protein levels by immunoblotting analysis and the abnormal radiosensitivity testing (CSA) results offer strong support for a clinical diagnosis of A-T.

Genetic analysis

More than 400 mutations in the *ATM* gene have been described in A-T patients [12]. The reported A-T mutations are evenly distributed throughout the gene, affecting every coding exon [13]. The majority of A-T patients carry unique mutations. Most patients present a classic form of A-T resulting from the presence of two truncating mutations, leading to total loss of the ATM protein. Genetic analysis of new A-T patients comprises sequencing four most common Polish mutations, 5932G>T, IVS53-2A>C, 6095G>A and 1563delAG, which covers about 25% of the untyped patients [14]. This is performed in Department of Pathology and Laboratory Medicine, Los Angeles, USA, thanks to close cooperation with Professor Richard Gatti. These facts, taken together with the large size of the ATM gene, make the screening for mutations expensive and labor intensive, using currently available methods.

Comprehensive care and future treatment

The prognosis for individuals with A-T is poor. However, some patients live to their forties or even fifties. Main problems of A-T patients facing clinicians, comprise progressive cerebellar ataxia, recurrent respiratory infections, delay of growth and puberty and last but not least predisposition to develop cancer (www.atcp.org).

Neurology care

As A-T is a progressive disorder, patients should be neurologically evaluated regularly by an experienced specialist. In many cases proper and multidirectional rehabilitation can slow the progress of the neurodegeneration and positively influence the psychological background. It is very important to note that A-T children, if evaluated properly, are not retarded in mental skills. Most patients begin to have difficulty walking at the end of the first year of life and are wheelchair-bound by the teenage years [15]. At this time, recommendation of a proper wheel-chair, with accompanied social support if needed, is essential.

Swallowing problems

Feeding and dysphagia problems often develop as A-T patients get older. The neurological changes in A-T may interfere with the timing or coordination of the pharyngeal phase of swallowing, which may result in aspiration of the saliva, food or liquids. This is why frequent coughing during meals should serve as a warning sign of dysfunctional swallowing and possible aspiration. However, many individuals with A-T present with silent aspiration, which is said to be a term describing the failure to cough when aspiration occurs. It is dangerous as silent aspiration may increase the risk of pneumonia.

The general guidelines for dysphagia problems in A-T patients involve:

- Choking or coughing when eating or drinking.
- Poor weight gain or weight loss.
- Excessive drooling.
- Mealtimes lasting longer than 40 minutes.
- Refusing foods or drinks.

- Chewing problems.
- Increased frequency or severity of lung infections.

After recognizing, dysphagia problem, the patient should be examined by a speech/language pathologist or pulmonologist.

Immunology care

Frequent upper and lower respiratory tract infections are observed in approximately one-third of A-T patients [16]. They often precede neurological complications and immunodeficiency is the main, but not the only, etiology for lung disease in A-T. So, comprehensive evaluation of the immune system should always be performed in newly recognized individual with A-T. Due to humoral immunodeficiency and sino-pulmonary infections, 20% to 25% of patients require regular immunoglobulin replacement therapy. A-T patients, except those receiving gamma globulin, and members of their close family, should receive an influenza vaccine every year. Preventing pneumonia requires two kinds of vaccines against *Streptococcus pneumoniae*, which are used under different circumstances. All A-T patients should receive 2 doses of conjugated vaccine with a 2-month interval between doses. One to two months after second dose, concentration of specific antibodies should be tested. If the individual does not produce antibodies, s/he should be directed to an immunologist. If the individual produces antibodies to the vaccine, one dose of polysaccharide vaccine should be given 6-12 months later. Booster shots of polysaccharide vaccine should be given every 5 years thereafter.

Live vaccines (rubella, mumps, measles, BCG, varicella) should be considered individually, depending on current immunological status of A-T patients.

A-T and puberty delay

Many young A-T women have irregular menstrual periods or stop having menses at an early age. A few never complete puberty development to the point of starting menstrual periods. Accumulation of the tissue that lines in uterus (endometrium) increases risk of the development of endometrial cancer. If the lack of menstrual periods is caused by a deficiency of estrogen, there can be a long-term risk of development of osteoporosis.

The general guidelines for estrogen replacement in A-T females are:

- Progesterone 10-14 days every 1-3 months, to prevent accumulation of endometrial tissue.
- On-going therapy recommended to provide normal menstrual cycles.
- Alternative use of standard birth control pills.
- Estrogen as an alternative.
- Recommended daily allowance of Calcium (1200 mg) Vitamin D units (400 units).

A-T and cancer risk

Malignancy frequently occurs in patients with A-T. They are said to have 100 fold higher risk of cancer than the general population. One in three A-T patients will develop a malignancy at some time during their lives [17]. Eighty-five percent of these cancers are lymphoid, either leukemia or lymphoma, which are characteristic in younger patients. Older patients tend to also develop malignant solid tumors such as stomach, breast, liver or ovarian cancer [18]. An occasional A-T patient may develop cancer before a diagnosis of A-T is suspected. Absence of routine screening tests requires good knowledge of warning signs of probable malignancy.

Warning signs of lymphoma and leukemia:

- Recurrent or persistent fever without explanation.
- Bruising and/or bleeding.
- Unusually pale complexion.
- Enlarged lymph nodes.
- Body aches and bone pain.

Leukemias and lymphomas are treatable if are supervised by experienced oncologist. The treatment and prognosis of the cancers depend on the properties of the affected lymphocyte and not on the extent of disease at the time of diagnosis. A very simple blood test – morphology with manual smear should be performed at any time malignancy is suspected. Consequently, the therapy of malignancies is complicated by the fact of conventional doses of radiation therapy as well as conventional chemotherapy.

Treatment of cancer in A-T-modified intensive chemotherapy:

- Radiomimetic drugs (such as Bleomycin) should be avoided.
- Neurotoxicity drugs (such as Vincristine) should be avoided.

A-T and X-rays

Patients with A-T and their cultured cells are unusually sensitive to X-ray [19]. Therefore, X-rays should be used only when the result is likely to affect a medical treatment decision.

Guidelines for the use of diagnostic X-rays in A-T:

- Avoid X-rays whenever possible.
- Alternative tests (MRI scan or ultrasonogram), may provide equivalent information without requiring X-rays.
- Routine screening dental X-rays should be avoided.
- Radiation therapy should never be given to an A-T patient.

Future treatment

Since it seems likely that oxidative stress may contribute to the neurodegeneration in A-T, potential therapies based on the use of antioxidants offer some hope. Currently, patients are advice to take alfa-lipolic acid in doses of 100-200 mg per day. Future treatment strategies vary, depending on type of mutation. They are focused on restoring ATM protein function with the use of compounds such as aminoglycosides, which have the potential to read through premature termination

codons [20]. Further research is being done on curing splicing mutations (unpublished data).

A-T patients require interdisciplinary care of specialists in pediatrics/internal medicine, neurology, oncology, pneumonology, physiotherapist and psychology under the clinical immunologist's supervision.

Acknowledgement

This study was supported by project S100/2006, "The Children's Memorial Health Institute", grant from the Polish Ministry of Science PBZ-KBN-1190/P05/04 and grant EURO-POLICY-PID SP23-CT-2005-006411.

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