Ataxia telangiectasia: clinical manifestation and diagnosis

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Abstract

Ataxia-telangiectasia (AT) is an autosomal recessive disease that coexist with progressive cerebellar ataxia, immunodeficiency, sinopulmonary infections, skin disorders, including oculocutaneous telangiectasiae, cancer susceptibility, radiosensitivity and early aging. AT 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, radiosensitivity in CSA. Patients with AT present with an undetectable intracellular ATM protein level or absence of catalytic activity. According to last reports increased radiosensitivity together with ATM protein absence confirm the diagnosis of AT. ATM gene is very large and searching for mutations is time-consuming and expensive.

Key words: ataxia telangiectasia, ATM protein, CSA, radiosensitivity

Introduction

Ataxia telangiectasia (AT; 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, increased risk of cancer and radiation sensitivity (12). Epidemiologists estimate the frequency of AT as 1 in 40 000 to 100 000 live births. However, it is believed that many children with AT, particularly those who die at young age, have been never properly diagnosed. Therefore, this disease may actually be much more common. The responsible gene ATM, maps to chromosome 11q22-23 (15), and contains 66 exons (8). 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 strain breaks, damage-induced cell-cycle checkpoints (15). In cytoplasm ATM regulates redox state concerning especially neurons (9). Over 400 mutations have been identified to date which occur throughout the entire gene (10). No curative strategy for this disease exist nowadays, however extensive work is being carried out in laboratories worldwide.

Clinical manifestation

AT 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 AT. 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, ocu-lomotor apraxia and choreoathetosis are fully expressed (2). By teenage most patients require a wheelchair for mobility. However, AT diagnosis may become problematic before the appearance of telangiectasiae or when the characteristic neurological impairment is mild or delayed. Most patients begin...
to have difficulty walking at the end of the first year of life and are wheelchair-bound by the teenage years (13). However, some patients are not recognized to have AT until the second decade of life. In young infants the diagnosis may be elusive and easily confused with mild cerebellar palsy, acute infectious, or episodic ataxia, ataxia with oculomotor apraxia or other rare genetic or mitochondrial diseases (1).

One of the main hallmarks of AT – telangiectasias appear most noticeably on the bulbar conjunctiva several years after onset of neurological symptoms (Fig. 1). They are noted, usually in the eyes, in almost all patients by age 10 years. Frequent sinopulmonary infections are observed in approximately one-third of AT patients (6). They often precede neurological complications and immunodeficiency is the main, but not the only, etiology for lung disease in AT. Malignancy occurs frequently in patients with AT. They are said to have 100 fold higher risk of cancer than the general population. One in the three AT patients will develop a malignancy at some time during their lives (5). The 85% of cancers are lymphoid, either leukaemia or lymphoma, which are characteristic for younger patients. Whereas older patients tend to develop also malignant solid tumors such as stomach, breast, liver or ovarian cancer (5). An occasional AT patient may first develop cancer, before a diagnosis of AT is suspected. Patients with AT and their cultured cells are unusually sensitive to x-ray (17). Consequently, the therapy of malignancies is complicated by the fact of conventional doses of radiation therapy as well as chemotherapy with radiomimetic agents.

AT children if evaluated properly are not retarded in mental skills. The prognosis for individuals with AT is poor, however some patients live to forties or even fifties. Treatment has focused on slowing the progress of the neurodegeneration; devising approaches for treatment of tumours while minimizing side effects and treatment with immunoglobulin for the immunodeficiency. Additionally, since it seems likely that oxidative stress may contribute to the neurodegeneration in AT, potential therapies based on the use of antioxidants offer some hope.

**Diagnosis**

The clinical diagnosis of AT used to be based on progressive cerebellar ataxia of early onset and then development of oculocutaneous telangiectasia. Serum level of alpha fetal protein (AFP) is a useful tool to diagnose AT especially in young children. Elevated serum levels of AFP are found in 95% of patients (7). However false-positive findings are seen in children under age 2 years, whose levels remain slightly elevated from neonatal period. There are also some rare condition of hereditary persistence of elevated AFP and association with some malignancies (8). So each time the serum AFP level is elevated, AT should be taken into consideration.

Dysgammaglobulinemia, decreased cellular immune response and peripheral lymphopenia are on one hand the supportive findings but on the other a variable feature of AT 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 (9). Due to humoral immunodeficiency and sino-pulmonary infections, 20% to 25% of patients with AT require regular immunoglobulin replacement therapy. Serum IgM levels are highly variable, may change during disease progression. Hyper-IgM is seen in approximately 1%–2% of patients with AT worldwide and appears to be due to a polyclonal rather than a monoclonal gammopathy (14). In patients with AT 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, 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.

Magnetic resonance imaging (MRI) of the cerebellum shows atrophy usually by age 10. Karyotyping reveals characteristic chromosomal aberrations, such as t (7; 14), translocations and telomeric fusion and increased rate of telomeric shortening (17).

Much progress has been made in the early diagnosis since the ATM gene was cloned in 1995 (8). As mentioned above, AT cells are hypersensitive to ionizing radiation. The colony survival assay (CSA) is the only measure of radiosensitivity that has been validated for clinical use. It measures the survival fraction of Epstein-Barr virus-transformed lymphoblastoid cell lines (LCLs) established from patient samples, following exposure to 1 Gray gamma radiation. Survival fractions for classical AT usually score below 21%, signifying radiosensitivity; a normal response to irradiation (IR) is > 36%. The CSA identifies radiosensitivity in approximately 90% of patients with A-T (16) (Fig. 2).

European Society for Immunodeficiency Disorders (ESID) created diagnostic criteria for clinicians for better recognizing of AT. They are divided into three categories: definitive possible, and probable (Table 1). Possible and pro-

![Fig. 1. Ocular telangiectasiea in AT patient](image_url)
bale categories comprise clinical features as cerebellar ataxia and ocular or facial telangiectasia together with laboratory tests like: serum IgA at least 2 SD below normal for age, AFP at least 2 SD above normal for age and increased radiation induced chromosomal breakage in cultured cells.

AT 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 AT (12). Western blot of nuclear lysates from AT cells is a semi-quantitative measurement of ATM protein, with > 98% sensitivity and specificity. The immunoblotting is not practical for testing samples from young infants unless LCLs are first established. When they are studied, lack of ATM protein is noted in >95% of patients with AT (3). The lack of detectable ATM protein levels by immunoblotting analysis and the abnormal CSA results offer strong support for a clinical diagnosis of AT. Very small amounts of ATM protein are seen in some patients. Equally, there is 1% of AT patients with normal amounts of ATM protein, which is functionally impaired. Here, we can analyze of the many substrates of ATM kinase activity to determine whether the expected serine or threonine residues have been phosphorylated. Assays of PI-3 kinase activity can be used (3). More than 400 mutations in the ATM gene have been described in AT patients (10). The reported AT mutations are evenly distributed throughout the gene, affecting every coding exon (4). The majority of AT patients carry unique mutations. Most patients present a classic form of AT resulting from the presence of two truncating mutations, leading to total loss of the ATM protein (11). These facts, taken together with the large size of the ATM gene, make the screening for mutations expensive and labor intensive with the use of currently available methods. On the other hand 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 (7). Further research is done on curing splicing mutations.

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Table 1

ESID criteria of AT syndrome

| 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: |
| Possible | Male or female patient with progressive cerebellar ataxia and at least one of the following four findings: |

References