



CHAPTER

# 11

## Ataxia Telangiectasia

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## Definition of Ataxia Telangiectasia

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(telangiectasia) of the eyes and skin, a variable immunodeficiency involving both cellular (T-lymphocyte) and humoral (B-lymphocytes) immune responses and a predisposition to cancer.

## Clinical Presentation of Ataxia Telangiectasia

The first presenting symptom is generally ataxia, a medical term used to describe an unsteady gait. Children with Ataxia Telangiectasia (A-T) may sway when they stand or sit and they wobble or stagger when they walk. Ataxia usually results from neurologic abnormalities affecting a part of the brain (the cerebellum) that controls balance. A-T first becomes apparent when the child begins to walk, typically between 12 and 18 months of age. At this early point in time, many children are thought to have cerebral palsy or an undefined neurologic disorder. The specific diagnosis of A-T may be difficult to make when symptoms first appear. Later, neurological symptoms include abnormalities in eye movements, including rapidly alternating twitches of the eyes (nystagmus) and difficulty in initiating voluntary eye movements (oculomotor apraxia). Patients with A-T also develop difficulty using the muscles needed for speech (dysarthria) and swallowing. Often, the diagnosis of A-T is only suspected when the neurologic problems start to become progressively worse, typically at age 5-6 years.

Dilated blood vessels (telangiectasia) become apparent after the onset of the ataxia, generally between 2 and 8 years of age. Telangiectasia usually occurs on the white portion of the eye (bulbar conjunctiva) but may also be found on the ears, neck and extremities. However, telangiectasia does not develop in all people with A-T.

Another clinical feature of A-T is an increased susceptibility to infections. This symptom is a major feature in some individuals. Infections most

commonly involve the lungs and sinuses and are usually caused by bacteria or viruses. The infections are, at least in part, due to the variable immunodeficiency seen in A-T. Another factor that may contribute to lung infections is the swallowing dysfunction that results in aspiration with solid food and liquid going down the passageway to the lungs (the trachea) instead of the passageway to the stomach (the esophagus).

Patients with A-T may have defects in both their T-lymphocyte system and B-lymphocyte system. They may have reduced numbers of T-lymphocytes in their blood. These abnormalities in T-lymphocytes are usually associated with a small or immature thymus gland. The low number of T-lymphocytes generally does not increase the patient's susceptibility to infection. Most patients with A-T produce some antibody responses against foreign antigens, such as microorganisms, but some of these responses may be impaired, particularly those responses directed against the large sugar molecules (polysaccharides) found on the outside of bacteria that cause respiratory infections. These disordered antibody responses may be associated with low levels of immunoglobulins—especially deficiencies of IgA, IgE and IgG subclasses (see chapter titled *IgG Subclass Deficiency and Specific Antibody Deficiency*). Finally, patients with A-T have an increased risk for developing cancer, particularly cancers of the immune system, such as lymphoma and leukemia.

## Diagnosis of Ataxia Telangiectasia

The diagnosis of Ataxia Telangiectasia (A-T) is usually based on characteristic clinical findings and supported by laboratory tests. Once all of the clinical signs and symptoms of A-T have become obvious in an older child or young adult, the diagnosis is relatively easy. The most difficult time to diagnose A-T is during the period when neurologic symptoms are first apparent (early childhood) and the typical telangiectasia has not yet appeared. During this period, a history of recurrent infections and typical immunologic findings can be suggestive of the diagnosis. One of the most helpful laboratory tests used to assist in the diagnosis of A-T is the measurement of alpha-fetoprotein levels in the blood. This is a protein that is usually produced only during fetal development but may persist at high blood levels in some conditions (such as A-T) after birth. The

vast majority of A-T patients (>95%) have elevated levels of serum alpha-fetoprotein. When other causes of elevations of alpha-fetoprotein are eliminated, elevated alpha-fetoprotein in the blood, in association with the characteristic signs and symptoms, makes the diagnosis of A-T a virtual certainty.

Other diagnostic tests include:

1. Detection of the protein (ATM) made by the A-T gene using a western blot
2. Measurement of cellular damage (cell death or chromosomal breakage) after exposure of cells to x-rays in the laboratory
3. Sequencing (reading the spelling) of the A-T gene (ATM)

## Inheritance of Ataxia Telangiectasia

Ataxia Telangiectasia is inherited as an autosomal recessive disorder (see chapter titled *Inheritance*). The gene responsible for A-T has been identified and is found on the long arm of chromosome 11 at 11q22-23. It controls the production of a phosphatidylinositol-3-kinase-like enzyme

involved in cellular responses to stress, DNA damage and cell cycle control. The identification of the specific gene responsible for A-T has made carrier detection and prenatal diagnosis possible, though it can be done only in a few specialized laboratories and is very expensive.

## General Treatment for Ataxia Telangiectasia

There is no cure for any of the problems in Ataxia Telangiectasia (A-T), and treatment is largely supportive. Patients of all ages should be encouraged to participate in as many activities as possible. Children should be able to attend school on a regular basis, but most will eventually need full-time classroom aides. Progressive eye movement abnormalities make reading difficult, but listening skills do not deteriorate. As a result, it is helpful to introduce books-on-tape at a young age to foster development of listening skills. Computers are also helpful learning aides that can be easily adapted to the specific needs of an individual who has problems with eye and hand coordination. Physical and occupational therapists should be included in the treatment team to

prevent the development of stiffness in muscles and to maintain functional mobility.

A prompt diagnosis should be sought for all suspected infections and specific therapy instituted. For patients who have normal levels of serum immunoglobulins and normal antibody responses to vaccines, immunization with influenza (flu) and pneumococcal vaccines may be helpful. For patients with total IgG, or IgG subclass deficiencies, and/or patients who have problems making normal antibody responses to vaccines, immunoglobulin replacement therapy may be indicated. In an effort to decrease exposure to the flu, all household members should receive the flu vaccine every fall.

## General Treatment for Ataxia Telangiectasia continued

Special attention should be paid to the lungs. A-T patients have difficulty taking deep breaths and coughing to clear mucus from the airways. They may benefit from daily chest physiotherapy or use of a therapy vest. If chronic lung disease develops, a lung specialist should be consulted about the use of intermittent antibiotic prophylaxis, inhaled medicines to decrease airway inflammation or constriction and the need for supplemental oxygen while sleeping. Many A-T patients develop problems with chewing and swallowing. Those who aspirate (have food and liquids entering their windpipe and lungs) may improve when thin liquids

are eliminated from their diet. In some individuals, a tube from the stomach to the outside of the abdomen (gastrostomy tube) may be necessary to eliminate the need for swallowing large volumes of liquids and to decrease the risk of aspiration.

Diagnostic X-rays should be limited because of the theoretical risk that the X-rays may cause chromosomal damage. In general, X-rays should only be done if the result will influence therapy and there is no other way to obtain the information that the X-ray will provide.

## Specific Therapy for Ataxia Telangiectasia

Specific therapy for the neurologic problems of A-T is not possible at the present time. The use of thymic transplants, thymic hormones and bone marrow transplantation has not led to improvement. Similarly, there is no evidence that

any specific supplemental nutritional therapy is beneficial. However, now that the gene has been identified and the gene's normal function is being studied, hopefully new and specific therapy may become available.

## Expectations for the Ataxia Telangiectasia Patient

In general, Ataxia Telangiectasia (A-T) follows a progressive course. It must be stressed that the course of the disease can be quite variable and it is difficult to predict the course in any given individual. Even within families, where the specific genetic defect is the same, there can be great variability in the type and severity of different neurologic problems and immunodeficiency. The course of the disease in most patients is characterized by progressive neurologic deterioration. Many patients are confined to a wheelchair in their teens. Infections of the lungs (bronchitis or pneumonia) and sinuses (sinusitis)

are common and may damage the lungs even if treated promptly. Malignancies or cancers are also more common in patients with A-T. They can be treated but require modifications of standard chemotherapy protocols. For example, A-T patients should never receive radiation therapy for cancer.

It should be emphasized, that although the above course is the most typical, the course of A-T varies considerably from patient to patient. Some patients have been able to attend college and live independently, and some have lived into the fifth decade of life.