

Ataxia-Telangiectasia



Chapter 12

Ataxia-Telangiectasia (A-T) is an inherited disease that affects several body systems, including the immune system. People with A-T have an unsteady, wobbly gait (ataxia) that gets worse as they get older; dilated, corkscrew-shaped blood vessels (telangiectasia) on the whites of the eyes and on sun-exposed areas of skin; immunodeficiency involving both humoral (B-lymphocytes) and cellular (T-lymphocytes) immunity; and a high rate of cancer.

Not all features of the syndrome are present in all people with A-T, and the severity of each symptom also varies a great deal from person to person. For example, some patients with A-T may have a severe humoral immunodeficiency preventing them from making antibodies and requiring immunoglobulin replacement therapy. Others with A-T may be able to mount completely normal antibody responses to vaccines and infections, and have no evidence of immunodeficiency.

Clinical Features of Ataxia-Telangiectasia

The first presenting symptom of A-T is generally ataxia. Children with A-T usually have a delayed onset of walking and when they do, they sway, stagger and wobble. They are usually unstable when sitting unsupported or when trying to stand in one place (for example, when standing in front of a sink to brush their hair or teeth). The ataxia is caused by abnormalities in the cerebellum, a part of the brain that controls balance and movement. As toddlers, most children with A-T are thought to have a neurologic disorder such as cerebral palsy or an unspecified movement disorder. The diagnosis of A-T is often difficult to make when ataxia is the only symptom present.

A-T causes progressive decline of motor neurologic function, which may not be apparent until age 4 or 5 years. It is the deterioration that most often leads to the

correct diagnosis, as neurologic deterioration does not happen to people with cerebral palsy. With increasing age, children with A-T develop abnormalities in eye movements (delayed initiation of eye movement, jerky eye movements and difficulty with eye/head coordination when tracking moving objects or following a single line of print in a book), and fine motor control (writing or feeding themselves). They have more and more difficulty walking and usually need to use a wheelchair for at least part of the day by the age of 10-12 years. They develop an intention tremor, and difficulties with speaking (dysarthria) and swallowing (dysphagia). While the neurologic symptoms progress in all children, the rate of progression and the relative severity of each neurologic problem vary widely from individual to individual.

(Clinical Features of Ataxia-Telangiectasia continued)

Dilated and corkscrew-shaped blood vessels (telangiectasias) cause the whites of the eyes to look bloodshot or as if there is pink eye (conjunctivitis) or an allergy. Telangiectasias eventually occur in most patients with A-T but do not occur in all patients with A-T and are only rarely present in infants and very young children, another reason that the diagnosis of A-T may be delayed until school age. Telangiectasias may also be seen on sun-exposed areas of skin such as the ears, neck and extremities.

Patients with A-T have an increased susceptibility to infection. Infections most commonly affect the lungs and/or sinuses and can be caused by bacteria and viruses. Part of the explanation for these infections is immunodeficiency, particularly related to low immunoglobulin levels and problems making antibody. About two thirds of people with A-T have low levels or complete deficiency of IgA, the antibody that protects us from infections on mucosal surfaces (such as the inside of the cheek and lining of the airways, nose and intestines). Many patients have problems making antibody responses to vaccines and infections. There is a particular problem making antibody to the large sugar molecules (polysaccharides) found on the outside of some of the bacteria that are frequent causes of sinusitis, bronchitis and pneumonia. These deficient antibody responses may be associated with low levels of IgG, IgA, IgM and/or IgG subclasses.

The immunodeficiency of A-T generally remains stable over time but gets worse with age in about 15% of patients. A thorough evaluation by an immunologist is necessary for every patient with A-T to determine if there is a deficiency of humoral immunity that is severe enough to require immunoglobulin replacement or other therapy. The usual indication for immunoglobulin is a problem making antibody, not just a low level of one or more immunoglobulin classes.

Most patients with A-T have reduced numbers of T- and B-lymphocytes, an abnormality that can be easily measured by a blood test. They may have problems with warts and a skin infection called molluscum, but they do not usually get opportunistic infections. However, if they are treated with steroids (such as prednisone) at high doses or for long periods of time, or if they need chemotherapy to treat cancer, the T-lymphocyte counts may become low enough that they become susceptible to opportunistic infections such as pneumocystis pneumonia.

Immunodeficiency is not the only explanation for lung infections in patients with A-T. Problems with swallowing (dysphagia) can cause aspiration. This occurs when solid foods or liquids go down the windpipe (trachea) and into the lungs instead of going down the esophagus into the stomach. Patients with A-T also have an ineffective cough, so they have difficulty clearing aspirated material and mucus from the airways. Chronic lung infections are sometimes managed by using prophylactic (preventive) antibiotics, and wearing special vibrating vests several times a day to help clear mucus. A gastrostomy tube may be inserted to provide calories directly into the stomach, providing nutrition and decreasing the amount of food and liquid that needs to be taken by mouth.

Patients with A-T are at an increased risk for developing all types of cancers, but particularly cancers of the immune system (lymphomas or leukemias). Cancer occurs in about 1/4 of all patients with A-T. It can occur at any age, and the risk cannot be predicted by the severity of immunodeficiency or any other feature of the disease.

Diagnosis of Ataxia-Telangiectasia

The diagnosis of A-T is usually based on common clinical features (ataxia, telangiectasia, abnormal eye movement and speech) and supported by laboratory tests (see list at right). When all of the clinical signs and symptoms are observed (usually in older children and adults), the diagnosis is made relatively easily. In young children, the diagnosis is much harder to make. Often the only presenting symptom is ataxia. Telangiectasias do not usually occur until after the age of 5 years, and do not occur at all in some patients. Eye movements are almost always normal in young patients. A history of recurrent upper and lower respiratory tract infections may be another clue to the diagnosis.

One of the most important lab tests used in the diagnosis of A-T is the measurement of the alpha

fetoprotein level in the blood, as about 95% of patients with A-T have elevated levels of alpha fetoprotein after age 18-24 months. Other confirmatory laboratory tests include:

- Elevated level of the blood protein CA125
- Increased cell death or chromosomal breakage after exposure of blood cells to x-rays in the laboratory
- Absence of the ATM protein on a Western blot
- Abnormal DNA sequence (mutation) of the A-T gene (ATM)

Inheritance of Ataxia-Telangiectasia

A-T is inherited as an autosomal recessive disorder. (See chapter titled "Inheritance.") The ATM gene is found on the long arm of chromosome 11. This gene controls the production of the ATM protein, an essential enzyme involved in cellular responses to DNA damage and other forms of stress in every cell of the body. For example, if there is a break in the double strand structure of the DNA, ATM signals the cell to stop

growing and dividing (cell cycle arrest), and ATM signals the DNA repair machinery of the cell to start working. The identification of the gene responsible for A-T has made carrier detection and prenatal diagnosis possible. Unfortunately, the sequencing test required to identify the mutation in the ATM gene is expensive and available in only a few laboratories.

General Treatment of Ataxia-Telangiectasia

There is no cure for any of the problems associated with A-T. Treatment is supportive but should be proactive. There are many parts of this disease, and a team approach, including the patient and family, primary care provider, immunologist, pulmonologist and neurologist is essential. A nutritionist as well as physical, occupational

and speech therapists, will have important contributions to make for specific problems that patients encounter. An example of the utility of the team approach is to monitor for and manage swallowing problems. Dysphagia and tremor can make meals last a long time and be very fatiguing, can interfere with nutritional

(General Treatment of Ataxia-Telangiectasia continued)

intake, and can lead to aspiration. Once recognized, early placement of a gastrostomy tube (G-tube, a tube that goes through the skin of the abdomen directly into the stomach) can provide supplemental nutrition that allows growth, improves stamina and decreases the risk of lung damage from aspiration.

All suspected infections should be properly evaluated and treated. Infection prevention efforts are important. This includes hand washing and making sure that those people with whom the patient comes in contact do not have acute respiratory tract infections. All household members should receive an influenza vaccination every fall. Patients with A-T who do not need immunoglobulin should receive all standard immunizations, as well as yearly influenza vaccine and a pneumococcal (pneumonia) vaccine every five to ten years.

Respiratory problems can be serious for patients with A-T. Often they have problems taking deep breaths and effectively coughing to clear mucus from their airways. They may benefit from daily chest physiotherapy and/or the use of a therapy vest. A regular program of respiratory care should be established before serious, irreversible lung problems develop. If chronic lung disease develops, patients may benefit from antibiotic prophylaxis, inhaled corticosteroids to decrease airway inflammation, and/or supplemental oxygen therapy. Patients who are having problems with aspiration (food and liquids going down the trachea into the lungs) may improve when thin liquids are eliminated from the diet.

On occasion, it is safest for most food and liquid to be delivered directly into the stomach with a G-tube instead of being swallowed.

Diagnostic x-rays should be limited as A-T is a chromosomal breakage disorder, and there is the theoretical risk that x-rays could cause chromosomal damage. In general, x-rays should be performed only if the results will influence treatment and management, and the information cannot be obtained in any other manner.

Children with A-T should be able to attend school, but most of them will eventually require full time aides to assist with activities of daily living while at school. Academic difficulties occur because progressively impaired eye movements make reading difficult and because the delay in initiation of speech and impaired ability to write or use a computer limit the ability of patients with A-T to demonstrate what they have learned. Cognitive function and hearing is not impaired. It is often helpful to introduce books-on-tape at an early age to foster the development of listening skills, which will become increasingly important as visual problems progress. Computers can also be particularly helpful as they can be adapted to the particular needs of people who have problems with eye and hand coordination. Counseling for the patient and the family is almost always helpful.

Specific Therapy for Ataxia-Telangiectasia

There is neither a cure for A-T nor is there a specific therapy for the neurological problems associated with the disease. Nobody has yet shown in a convincing way that physical therapy or specific nutritional supplements (as opposed to general good nutrition) have helped, though there are many proponents of these approaches.

Management of immunodeficiency and general nutrition, prevention of pneumonia, and providing some exercise will improve the quality and length of life. Neither bone marrow transplantation nor injection of neural stem cells into the brain is considered safe at this time.

Expectations for Patients with Ataxia-Telangiectasia

A-T is a progressive disease, but the timetable for this progression is not predictable in an individual patient. Not all patients with A-T are the same. Even within the same family, where the specific genetic defect is the same, there is great variability in the severity and types of problems experienced by each affected person. Being aware of potential problems may affect progression. For example:

- A chronic cough may indicate a lung or sinus infection
- Choking when drinking may indicate aspiration
- Failure to grow or a child falling off of their growth curve may indicate nutritional issues
- Infections that recur or do not get better when appropriate antibiotics are used may indicate an immunodeficiency

These and other concerns should be communicated to the healthcare team as soon as possible, rather than assuming that they are an inevitable part of the disease and that nothing can be done about them. The earlier a problem is addressed, the greater the chance for successful management of that problem.

Even if complications are promptly addressed, the reality is that there will be neurological deterioration. It is realistic to assume that all patients with A-T will, eventually, be unable to ambulate safely and will require a wheel chair and other adaptive devices. Usually, this occurs by the time the patient is a teenager. Similarly, some degree of lung disease can be expected, even if lung infections are aggressively and promptly treated. If cancer is diagnosed, it can be treated but modification of the treatment regimen may be necessary. For example, patients with A-T should never be treated with radiation therapy because of the potential of the radiation causing chromosomal breakage.

It is important to remember that as research and knowledge about A-T increase so does the hope for changing the course of the disease. In the past, children with A-T seldom lived to adulthood. At present, a few patients with A-T are part-time students at community colleges and have been able to live independently. Some have lived into their fifties. The goal of ongoing research is to make this the norm for patients with A-T, rather than the exception.