

Chapter 12

Ataxia-Telangiectasia (A-T) and Related Disorders

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Ataxia Telangiectasia (A-T), Bloom Syndrome (BS), and Nijmegen Breakage Syndrome (NBS) are examples of a group of disorders called DNA breakage (or chromosomal instability) syndromes. They are characterized by chromosomal instability and breakage as well as a defect in the DNA repair mechanism. These syndromes are inherited in an autosomal recessive fashion. Affected individuals have varying degrees of delays in mental and physical development, organ system dysfunction, combined immunodeficiencies, and they are at high risk for various types of cancers.

Ataxia Telangiectasia

Clinical Features

Individuals with A-T have an unsteady, wobbly gait (ataxia), dilated corkscrew-shaped blood vessels (telangiectasia) on the white part of the eyes and sun exposed areas of the skin, immunodeficiency involving both B cells and T cells, and high rates of cancers. The neurologic symptoms worsen as individuals get older.

Some individuals with A-T are identified before they have any symptoms, because they have an abnormal newborn screen (TREC) test for Severe Combined Immunodeficiency. The first symptom of A-T is generally ataxia. When children start walking, they tend to sway, stagger, or wobble, and do not improve as they get older. They are usually unstable when sitting unsupported or standing in one place, for example, when standing in front of the sink to brush their hair or teeth. The ataxia is caused by abnormalities in the cerebellum, the part of the brain that controls balance and movement. Often these children are initially thought to have some other neurologic condition, such as cerebral palsy. When ataxia is the only symptom present, it is sometimes hard to make a diagnosis.

A-T causes a progressive decline in motor function, which may not become apparent until children are 4 to 8 years old. It is this deterioration, in addition to ataxia, which often leads to a correct diagnosis as deterioration does not occur in children with cerebral palsy. As they get older, children with A-T develop abnormalities in eye movements (delayed onset of eye movements, jerky movements, and difficulty in eye/head coordination when tracking moving objects or following a single line of print in a book). They also develop problems with fine motor control and have problems feeding and dressing themselves. Most have enough difficulty walking so that they need to use a wheel chair for at least part of the day by the time they are 10 or 12 years old. They develop an intention tremor (shaking when trying to use the hands), and difficulties with speaking (dysarthria) and swallowing (dysphagia). While this progressive deterioration occurs in all children, the rate of progression and severity vary widely from individual to individual.

Telangiectasia cause the whites of the eyes to look bloodshot. It can appear as though they have pink eye (conjunctivitis) or an allergy. Telangiectasia can also develop on sun-exposed skin such as the ears, neck, arms and legs. Most individuals with A-T

have these telangiectasia but some do not, and telangiectasia are rare in infants and very young children. This is another reason why the diagnosis of A-T is sometimes delayed.

Individuals with A-T have an increased susceptibility to infections, particularly in the lungs and/or sinuses. The reason for this susceptibility can be related to a humoral (B cell) immunodeficiency causing low immunoglobulin levels and impaired antibody responses. Approximately 2/3 of individuals with A-T have low levels or a complete absence of IgA, the immunoglobulin that protects individuals from infections on mucosal surfaces like the linings of the nose, airway, and intestines.

Individuals with A-T can also have reduced numbers of T cells, giving them a combined (B cell and T cell) immunodeficiency. They may have problems with chronic or recurrent warts or molluscum. A small number of individuals develop chronic inflammation of the skin (granulomas) that appears to be caused by a defective response to the rubella virus in the MMR vaccine. They do not usually get opportunistic infections like pneumocystis pneumonia. However, if they are treated with steroids at high doses or over a long period of time or if they need chemotherapy to treat cancer, the T cell counts may become low enough to make individuals susceptible to opportunistic infections.

The immunodeficiency in individuals with A-T generally remains stable over time but does worsen in approximately 15% of individuals. A thorough evaluation of humoral immune function is necessary in order to determine if there is a need for immunoglobulin (Ig) replacement therapy.

Immunodeficiency is not the only reason for susceptibility to infection. Individuals with A-T often have neurologic problems with swallowing (dysphagia), which can cause aspiration (solid food or liquids go down the trachea and into the lungs instead of into the esophagus and stomach). They also have an ineffective cough so that they have difficulty clearing mucus and aspirated material from the airways. The ineffective clearance can lead to chronic lung infections. The use of a vibrating vest or a cough assist device several times a day may be useful to shake mucus loose and make secretions easier to cough up. Sometimes infections related to aspiration can only be prevented by bypassing the mouth and esophagus and putting calories and nutrients directly in to the stomach through a gastrostomy tube (G-tube), thereby decreasing the amount of food and liquid taken by mouth.

Individuals with A-T are at an increased risk for developing cancers. For individuals under the age of 20 years, most cancers are lymphomas or leukemias. For individuals over the age of 20 years, there is also a considerable problem with solid organ cancers including the breasts, esophagus, colon, liver, and intestines. Treatment of the cancer must be modified to account for sensitivity to radiation and certain types of chemotherapy. Cancer occurs in approximately 25% of individuals with A-T.

Diagnosis

The diagnosis of A-T is based on detection of the features of the syndrome and supported by the following laboratory tests:

- Elevated alpha fetoprotein in the blood
- Mutation (abnormal DNA sequencing) in the A-T gene (ATM)
- Increased cell death or chromosomal breakage after the exposure of blood cells to x-rays in the laboratory
- Absence of the ATM protein on Western blot

Inheritance

A-T is an autosomal recessive disorder, which means that two copies of the abnormal gene (one from each parent) are required to cause the condition. The ATM gene controls the production of the ATM protein, an essential enzyme involved in cellular responses to DNA damage and other forms of cellular stress. For example, if there is a break in the double strand structure of the DNA, ATM signals the cell to stop growing and dividing, and then signals the DNA repair machinery to start working. The identification of this gene has made carrier testing and prenatal diagnosis possible.

Treatment

There is no cure for A-T or any of the specific features of the syndrome. Treatment is supportive. A team of care providers, including the affected individual, family members, primary care providers, immunologists, pulmonologists, neurologists, nutritionists, and ancillary therapy providers, is key in managing the disease. Other providers such as geneticists and oncologists may also be part of the team.

Treatment should be proactive as well as supportive. While the timing of the progression of the disease is unpredictable, the progression of the disease is not. For example, feeding problems will inevitably develop as dysphagia, and tremors can make

meals take a long time and become very fatiguing. Nutrition can be compromised and aspiration can occur. Early placement of a G-tube can supply nutrition that will allow growth, improve stamina, and decrease the risk of aspiration associated problems.

Infection management is another important part of treatment. Preventing infection is the first step. Prevention includes handwashing and avoiding individuals who are ill. Unless they are receiving Ig replacement therapy, individuals with A-T should receive all standard immunizations, including an annual influenza vaccine and a pneumococcal vaccine every 5-10 years. The MMR vaccine should be avoided because of the risk of developing cutaneous granulomas. Close contacts and family members should also receive all recommended immunizations, including an annual influenza vaccine.

Respiratory problems can be serious for individuals with A-T. They often have problems taking deep breaths and effectively coughing. They may benefit from a regular program of chest physiotherapy and daily use of a therapy vest. The key is to establish a pulmonary care regimen before serious, irreversible lung problems develop. If chronic lung disease develops, individuals may benefit from antibiotic prophylaxis to prevent infection and inhaled corticosteroids to decrease inflammation. Supplemental oxygen may also be beneficial.

Diagnostic A-T is a disorder of DNA breakage, and thus, there is a theoretical risk of chromosomal damage from radiation. Certain types of imaging tests pose a threat to individuals for chromosomal damage. For example, X-rays should be limited in individuals with A-T. It is generally accepted that x-rays should be done only if the results will have an impact on diagnosis and treatment. It is also important to limit the amount of radiation delivered in a routine CT scan by limiting the number of images taken. Individuals with A-T can have diagnostic MRIs and ultrasound exams, without problems since their imaging procedures are different than X-rays and CT scans. Consultation with a radiologist will help determine the best way to get imaging if it is necessary.

Expectations

Unfortunately, there is not a cure for A-T, and there are no specific therapies for the neurologic problems associated with the disease. The key to treatment is to anticipate that problems will occur and progress, and to deal with them proactively. For example, putting in a G-tube and getting at

least part of needed calories and nutrients via G-tube feedings can prevent problems associated with malnourishment and decrease the risk of lung problems caused by aspiration. Diagnosing and treating an associated antibody disorder and instituting a regimen for airway clearance and other pulmonary care can help with infection prevention. Using a wheelchair when ambulation becomes difficult can help prevent exhaustion and other related difficulties. Addressing issues proactively will improve the quality and length of lives for individuals with A-T.

Children with A-T can and should attend school, although most will need assistive devices and full-time aides to assist with activities of daily living while the children are at school. Some academic difficulties are to be expected as progressively impaired eye movements make reading difficult. Delayed initiation of speech and problems with writing or using a computer may make it seem that there is cognitive impairment. However, cognitive function and hearing are not impaired in individuals with A-T. Early introduction and use of adaptive devices and technologies will help to mitigate some of the challenges children with A-T face at school. These children should always have an Individualized Education Program (IEP) and school personnel should be an integral part of the care team.

A-T is a progressive disease, but the timetable of progression is not the same for all individuals. It cannot be predicted in an individual. There is great variability between affected individuals, even individuals within the same family. The key is to assemble a care team knowledgeable about the disease, tuned in to potential problems, and dealing proactively with them. For example:

- A chronic cough may indicate a lung or sinus infection or demonstrate the need for a more effective airways clearance regimen.
- Choking when eating or drinking may indicate aspiration.
- Failure to grow or a child falling off their growth curve may indicate insufficient caloric intake.
- Daily fevers, pallor, and fatigue may indicate a malignancy.
- Infections that recur or fail to resolve when treated appropriately may indicate an immunodeficiency.

Even if problems are addressed proactively and promptly, the reality is that there will still be neurologic deterioration. It is important to note that as research and knowledge about A-T increases, so does the hope for changing the course of the disease. In the recent past, children with A-T seldom lived to adulthood. Currently there are individuals with A-T who are college students and able to live independently. Some individuals are living into their 50's. The goal of ongoing research is to make this the norm for individuals with A-T, rather than the exception.

Bloom Syndrome

Bloom Syndrome (BS) is a chromosomal damage syndrome, with some of the same features as A-T. The disease is caused by a mutation in the BLM gene that encodes a protein important in repairing malfunctioning DNS strands during DNA replication. BS is characterized by short stature, learning disability, dermatologic problems, immunodeficiency, obstructive lung disease, infertility, and increased risk of all types of cancers. As with all syndromes, not every affected individual has all of these characteristics, so there is great variability and degree of severity among individuals.

Individuals with BS often have high-pitched voices, narrow facial features, and long arms and legs. They tend to have normal muscle development but reduced amounts of subcutaneous fat tissue. The dermatologic problems associated with BS include significant sun sensitivity and poikiloderma, a skin condition characterized by areas of abnormal pigmentation and telangiectasias. The diagnosis of BS is made when individuals present with characteristic features of the syndrome and is confirmed with genetic testing.

The potential for cancer is the greatest concern for individuals with BS. Often individuals have multiple malignancies. Leukemia is the most common cancer in individuals less than 20 years and solid organ tumors are more common in individuals older than 20 years. Colon cancer can present at any age, as can skin cancers.

As with A-T, proactive care is key to improve the quality of life. Affected individuals should have all routine cancer screenings including colonoscopy and skin surveillance. In this population, symptoms, such as fatigue, night sweats, bruising, and swollen glands, should be assumed to be signs of malignancy until they are proven otherwise.

Nijmegen Breakage Syndrome

Nijmegen Breakage Syndrome (NBS) is a chromosomal instability condition. Affected individuals generally have small heads (microcephaly), a combined B and T cell immunodeficiency, and predisposition for cancers. Individuals with NBS often have mild growth retardation and cognitive disability. They have a propensity for infections, particularly sinopulmonary infections, because of the combined immunodeficiency. Individuals with NBS require the same types of care as do those with other DNA breakage syndromes. Health maintenance and cancer surveillance are critically important, as is aggressive management of infection and related problems.

Summary

DNA breakage syndromes are a rare group of disorders characterized by radiation sensitivity, and varying degrees of immunodeficiency as well as cognitive and/or physical developmental problems. All share an increased risk for malignancies. While there is no cure for these illnesses, symptoms can be alleviated by proactive medical management and surveillance by a knowledgeable healthcare team. Early diagnosis is important to allow for optimal management of the affected child, as well as genetic counselling for the parents and extended family members.

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