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Ataxia-Telangiectasia

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

ABBREVIATIONS

AT	Ataxia-telangiectasia
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency

Primary immunodeficiencies: Ataxia-telangiectasia (1st edition).

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INTRODUCTION

This booklet explains what ataxia-telangiectasia (AT) is, how it is diagnosed and how it is treated.

Ataxia-telangiectasia (AT), sometimes called Louis-Bar syndrome, is a human inborn error of immunity that affects between 1 in 40,000 and 1 in 100,000 live births.

The condition is characterised by poor coordination (ataxia) due to degeneration of the cerebellum, abnormal blood vessel formations (telangiectasia), immunodeficiency, radiation (sun) sensitivity and an increased risk for cancer.

AT is caused by a mutation in a gene encoding a protein that is involved in coordinating cell signalling in response to DNA damage, and it is classed as an autosomal recessive disorder. This means that two copies of the mutated gene must be present for the AT to develop.

The following sections provide an overview of the symptoms and diagnosis of AT, the genetic basis of the disease, how it is managed and how patients can live with the disease.

WHAT IS ATAXIA-TELANGIECTASIA

AT is a genetic neurodegenerative disorder that mostly appears in early childhood. The disorder is characterised by progressively impaired coordination of voluntary movements (ataxia) due to cerebellar degeneration, and some patients develop reddish lesions in the skin and mucous membranes due to abnormal blood vessel formation (telangiectasia).[1] This means that people with AT have an unsteady, wobbly gait that gets worse as they get older and dilated, corkscrew-shaped blood vessels on the whites of the eyes and on sun-exposed areas of skin. The condition varies in severity and while most cases are diagnosed during childhood, a late onset or adult onset variant is known.

People with AT may have difficulty sitting or walking, they may have distorted speech and abnormal eye movements. These symptoms often only begin to show in children aged between 12–18 months in classical forms of AT, or later around 4 to 5 years in variant forms of AT. Most of the neurological problems stop progressing around the age of 12 to 15 years in classical forms of AT. People with AT may also have difficulty with feeding and swallowing, leading to failure to thrive in some infants. It is also possible that some people with AT may develop insulin-resistant diabetes and hepatic steatosis, amongst other complications.

AT also impairs the immune system so people with AT are at increased risk of infections and an early sign of the condition may be frequent respiratory tract infections.[1] In addition, people with AT are more sensitive to radiation and have an increased risk of developing certain types of cancer, particularly ones affecting blood cells (lymphomas and leukaemia).

GENES ASSOCIATED WITH AT

AT is caused by a mutation in a gene – the *ATM* gene – on chromosome 11 encoding the ATM protein, which is involved in managing cell signalling in response to DNA damage. AT is classed as an autosomal recessive disorder, which means that two copies of the mutated gene must be present for the AT to develop. Other genes have also been associated with AT-like disorders (MRE11 gene, for example).

The identification of the gene responsible for AT has made carrier detection and prenatal diagnosis possible, but unfortunately at present the test is expensive and not widely available.
Other genes have been associated with AT-like disorders (*MRE11* gene for example).

[1] Rothblum-Ovatt C, et al. Ataxia telangiectasis; a review. Orphanet J Rare Dis 2016;11:159

DIAGNOSIS OF AT

The diagnosis of AT is made based upon a detailed history, a thorough clinical evaluation, identification of characteristic symptoms (ataxia, telangiectasia, abnormal eye movement and speech), and a variety of specialised tests including blood tests, magnetic resonance imaging (MRI), and karyotyping along with the genetic analysis of the *ATM* gene.

Neurological and other symptoms usually become apparent in early childhood. When all of the clinical signs and symptoms are observed (usually in older children and adults) the diagnosis is relatively easily but in young children the diagnosis is much harder to make as often ataxia is the only presenting symptom. 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 respiratory tract infections may be evidence of the diagnosis.

Blood tests may detect elevated levels of serum alpha-fetoprotein, which occurs in approximately 85% of cases after age 18–24 months. Blood tests may also reveal elevated liver enzymes. A MRI scan creates cross-sectional images of the brain, which can show progressive wasting (atrophy) of the cerebellum. Karyotyping is a specialised test that detects chromosomal abnormalities. Affected individuals have an increased frequency of these chromosomal abnormalities (translocation between chromosomes 7 and 14 being the most frequent finding).

For families in which the mutated ATM gene is known to occur, diagnosis can be achieved antenatally (before birth) at different stages of pregnancy by genetic analysis (and as early as 12 weeks of amenorrhoea) and after a genetic counselling consultation has been performed.

WHAT TREATMENT IS SUGGESTED FOR AT?

There are currently no known treatments that can slow, stop, or reverse the neurological degeneration associated with AT. Physical, occupational and speech therapies are very helpful. A dietician may monitor for and manage swallowing problems. Dysphagia and tremor can make meals last a long time and be very fatiguing, can interfere with nutritional intake, and can lead to aspiration. A dietician may help by recommending dietary modifications to ensure proper nutrition is achieved through high calorie foods or food supplements, or the early placement of a gastrostomy 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.

Treatment is symptomatic and supportive. Genetic counselling may be of benefit to persons with AT and their families. Other manifestations of the condition can be managed as outlined below and patients are best managed through a multidisciplinary approach with input from immunologists, pulmonologists, dieticians, oncologists, endocrinologists and physiotherapists.[2]

IMMUNOGLOBULIN REPLACEMENT THERAPY

People with AT who also have an overt immunodeficiency may benefit from mainstay antibacterial prophylaxis and, if not efficient enough in preventing infections, immunoglobulin replacement therapy. It is considered that half of the patients with AT harbour a malfunction immune system that requires such therapies.

Vaccinations should be kept up to date including pneumococci and influenza and antibacterial prophylaxis may be considered for those with a history of repeated or intractable bacterial infections. Please refer to Vaccines guidelines (esp. live attenuated vaccines).

PULMONARY MANIFESTATIONS

Patients with AT often have problems taking deep breaths and effectively coughing to clear mucus from their airways. Patients may benefit from chest physiotherapy. More than 25% of people with AT will develop chronic lung disease. Early recognition and treatment of symptoms, including antibacterial therapy, is essential to prevent the progressive lung damage.[3] Vaccination against common respiratory pathogens should also be considered. If chronic lung disease develops, patients may also benefit from inhaled corticosteroids to decrease airway inflammation and/or supplemental oxygen therapy. Approximately 10% of the patients may experience one or more episodes of spontaneous pneumothorax. Restrictive lung disease caused by scoliosis and weak respiratory muscles can be seen as well.

SKIN GRANULOMAS

This complication is not frequent but needs attention from patients and caregivers as it can be severe and require specific therapies (such as corticosteroids and/or anti-tumour necrosis factor agents) after careful evaluation by trained dermatologist and pathologist.

CANCER

People with AT have around a 25% lifetime risk of developing cancer. These are most often lymphomas or leukaemia in people under 20 years of age and a high suspicion should be maintained especially when potential symptoms emerge such as unexplained fever or persistent swollen lymph nodes. Malignancies in patients over 25 years of age are usually carcinomas.

EXPECTATIONS FOR PATIENTS WITH AT

AT is a progressive disease, but progression is not predictable and varies considerably from patient to patient, as do the severity and types of problems experienced. Being aware of potential problems may affect progression and the earlier a problem is addressed, the greater the chance for successful management of that problem.

Children with AT 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 can occur because progressively impaired eye movements make reading difficult and because of the delay in initiation of speech and impaired ability to write or use a computer. Cognitive function and hearing are not impaired. Audio books can help develop listening skills, which will become increasingly important as visual problems progress. Computers can be helpful as they can be adapted to the needs of people who have problems with hand–eye coordination.

It is realistic to assume that all patients with AT will, eventually, be unable to ambulate safely and will require a wheelchair 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.

The life expectancy of people with AT is increasing as understanding of the condition and treatments for the associated complications improve. Over the past 20 years, the expected lifespan of individuals with AT has increased considerably with most individuals now living into their 40s and 50s.

[2] Van Os NJH, et al. Ataxia-telangiectasia: recommendations for multidisciplinary treatments. Dev Med child Neurol 2017;59:680-9

[3] Bhatt JM, et al. ERS statement on the multidisciplinary respiratory management of ataxia telangiectasis. Eur Respir Rev 2015;24:565-81

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

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