



Ataxia-telangiectasia in children

Guidance on diagnosis and clinical care

Produced by

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Nottingham City Hospital Campus
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The Ataxia-Telangiectasia Society

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Introduction

This document provides guidance to professionals on the diagnosis and treatment of ataxia-telangiectasia (A-T). A-T is a very rare complex, progressive multi-system disorder, caused by inherited mutations in a single gene. Its most visible manifestations are likely to be progressive ataxia (difficulty in co-ordinating movements), frequent infections of the throat, chest and sinuses (caused by immune deficiency) and, from the age of three or four years, telangiectasia, or red 'spider veins' in or around the eyes. The condition also carries a greatly increased risk of developing cancers, especially leukaemia and lymphoma, which nearly one in four people with the condition is likely to develop. There is also a likelihood of developing serious lung-disease as a result of the neurological and immunological deficits.

Because A-T is so rare, most paediatric departments are unlikely to see more than a tiny handful of cases over the years and other professionals no more than a single case or family. They are therefore unlikely to have any first-hand experience of treating the condition and no chance to compare cases. At the same time, A-T is a complex, multi-system condition requiring multi-disciplinary input. If the patient is to receive appropriate and co-ordinated care, it is important that each specialist has an understanding of the issues affecting the patient across the whole spectrum.

The UK Strategy for Rare Diseases, published by the Department of Health in November 2013 underlines the necessity for documents such as this. It states:

Although specialist clinical centres may provide all the essential expertise, in almost all cases most of the care is provided locally – by local hospitals, primary care teams, social care and education teams, and in the patient's home. Therefore, centres must have protocols in place to share their expertise with local services. This will require the development of shared protocols for effective communication and information sharing between the centre, local teams and the patient.¹



A-T is a condition about which there is much that is unknown or poorly understood. Our understanding is changing all the time, as is our scientific and medical knowledge and the range of medical and therapeutic interventions available to us.

This guidance offers suggestions for care for children with A-T based on the practical clinical experience and knowledge of the authors at the time of writing.

Adherence to the guidance in this document will not ensure a successful outcome in every case. It should not be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient or their carer(s), covering the diagnostic and treatment choices available.

This guidance has been developed to meet this need by specialists at the A-T Centre at Nottingham City Hospital Campus, in collaboration with the patient support organisation, the A-T Society. While primarily aimed at clinicians and other health professionals who have little first-hand experience of A-T, we expect it to be used by people with A-T and their families to help ensure that the local care that is provided to them is effective in meeting their needs.

There are currently no fully-researched and evidence-based clinical guidelines on the treatment of people with A-T published anywhere. It is our aim in future to produce such guidelines. However this is not such a document and is not to be construed as such or as a standard of care.

What this document does aim to do is to provide suggestions for care based on the experience and

current state of knowledge of doctors and therapists with considerable experience of seeing patients with A-T at what is the world's longest-established multi-disciplinary A-T clinic.

Established in 1993, the Nottingham A-T Centre, which is the paediatric centre of expertise of the NHS A-T Service, has seen and treated well over a hundred children with A-T, mostly for multiple visits. The service currently provides sessions with: a paediatric immunologist, neurologist, geneticist, respiratory physician and physiotherapist, ophthalmologist, physiotherapist, dietician, occupational therapist, social worker and psychologist. It will shortly be adding an orthopaedic surgeon to the team.

For further information, or to contact the UK A-T Service, please contact the A-T Society, see page 10.

What is ataxia-telangiectasia

The condition

Ataxia-telangiectasia (A-T), is a complex, multi-system, autosomal recessive disorder caused by mutations in the ATM (ataxia-telangiectasia mutated) gene on chromosome 11q.26. The gene codes for a protein kinase, ATM, which has been found to have a critical role in cellular responses to damaging influences and stress, particularly those resulting in double-strand DNA breaks.

Ataxia-telangiectasia (A-T), is a complex, multi-system, autosomal recessive disorder caused by mutations in the ATM (ataxia-telangiectasia mutated) gene on chromosome 11q.26

A-T is characterised by a number of clinical features. Common features include:

- Progressive neurological manifestations, including tremor, chorea, athetosis, dystonia, ataxia, dysarthria, oculomotor apraxia, and dysphagia which worsen through childhood into adult life.
- Oculocutaneous telangiectasias, which usually appear at about 3 or 4 years of age. Telangiectasias are occasionally found in the bladder or other internal organs.
- Recurrent infections, usually affecting the chest, ears and sinuses, which can lead to chronic lung damage and chronic otitis with hearing impairment.
- A wide range of immunological abnormalities, including deficiencies of immunoglobulin (particularly classes A and E), poor responsiveness

to pneumococcal polysaccharide vaccine, reduced lymphocyte numbers particularly affecting T and B cells and thymic hypoplasia, slurred speech, drooling, and dysphagia leading to low body weight.

- An increased risk of developing malignancies (22%), particularly T and B cell leukaemias and lymphomas, but also endocrine malignancies and, for women, breast cancer.
- Clinical increased radiosensitivity to therapeutic doses of ionizing radiation.
- Slow growth and/or progeric changes.
- Delayed or incomplete pubertal development.

Less common clinical manifestations include:

- Vomiting and choking, particularly in the morning.
- Non-infective granulomatous skin disease.
- Deformities of the feet and lower limbs and scoliosis.
- Incontinence of bladder and bowel.
- Diabetes mellitus, which tends to develop during adolescence or adulthood in about 25% of patients.
- Irregular menstrual cycles.

Forms of A-T

A-T in its classic form is caused by the presence of two truncating mutations, which result in either the complete absence of ATM protein, or of a mutant form with no kinase activity. In some cases, however, the presence of particular mutations, normally leaky splice site or missense mutations, does allow the production of either a reduced quantity of active ATM protein or else of a mutant protein that shows some kinase activity. In these cases patients are likely to have a milder phenotype, with symptoms developing more slowly and/or with later onset.

This 'mild-variant' A-T is particularly frequent in the UK and Ireland. It appears that approximately one case in three of A-T in the UK is of a mild-variant form (compared to an estimated one in five in other parts of the world). The main reason for this is the relatively frequent incidence of one particular leaky splice site mutation (c.5763-1050A>G) which allows the expression of a low level of normal ATM with kinase activity. This mutation may be present in one

or both alleles of up to 20% of all people with A-T with ancestry in the UK and Ireland.

Variation from the typical course of the condition, combined with heterogeneity in presentation, particularly of the neurological features of A-T, results in mild-variant A-T being sometimes under-diagnosed or misdiagnosed. It is certainly the case that in recent years, there has been an increase in the number of confirmed diagnoses of A-T being made in adults in the UK.

There are also a number of even rarer conditions closely-related to A-T, caused by mutations in genes which code for proteins which interact closely with ATM. These give rise to symptoms and signs which overlap with A-T in different ways. However given the small numbers of patients known with these conditions, and in the light of the phenotypic heterogeneity of A-T, it is not possible to be certain that the physical characteristics of these conditions have yet been accurately defined and so a diagnosis of A-T can only be confirmed by laboratory tests.

These conditions include:

- ATLD (A-T-like disorder) is caused by mutations to the MRE11 gene and produces symptoms very similar to those of A-T, especially neurological symptoms. Progression of symptoms seems to be somewhat slower than in classic A-T.
- AOA1 (ataxia-oculomotor apraxia type 1) is caused by mutations to the APTX gene which produces a protein called Aprataxin. Like A-T, it usually develops in childhood, and causes a similar range of movement and visual problems. However there are

usually no associated immunological problems and telangiectasias do not appear to develop.

- AOA2 (ataxia-oculomotor apraxia type 2) has a range of symptoms similar to those of AOA1, however it tends to develop later, typically in late adolescence or early teens. It is the result of mutations on yet another gene, the SETX gene. AOA2 seems to be a little more common than AOA1.

Incidence

In the most recent published study², the prevalence of A-T in those aged 50 years or younger was approximately 1 in 500,000, and the birth frequency 1 in 300,000. Our estimate is that in the UK and Ireland there are currently approximately 150 families with approximately 170 cases of A-T, giving a prevalence of approximately 1 in 400,000. The carrier frequency would therefore be of the order of 0.3% or approximately 1 in 300.

Survival

While the rarity of the condition makes it difficult to evaluate, the most recent and authoritative paper³ suggests a median survival age of around 25 years. However this was calculated in a patient cohort dominated by cases of classic A-T and in the case of mild-variant A-T median survival is clearly much longer than this. While there is no published evidence, many patients with mild variant A-T are known to be living into their 40s and 50s and some even into their 60s in the UK.

Around 22% of people with A-T die of cancer. The majority of other deaths are likely to be due to lung disease⁴.

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Diagnosis

In children

An initial diagnosis of ataxia-telangiectasia is normally made on the basis of clinical evidence. The most important features are:

- Neurological symptoms, particularly progressive cerebellar ataxia. This is normally apparent from an early age, often when children first start to sit or stand and is often manifested in a wobbly gait or swaying while sitting or standing. Although the age when they start to walk is normal, they remain unsteady, as if they had only just achieved this milestone. Unlike ataxia due to cerebral palsy, the problems will worsen over time with chorea, dystonia, and tremor.
- Abnormalities of the eye movements. Movements normally become restricted and following objects becomes difficult.
- Telangiectasia in the whites of the eyes or other areas of the face and ears, though this may not occur until four or five years of age.
- Recurrent sino-pulmonary infections, although these only affect around 50% of children with A-T.

Laboratory tests may also show an elevated alpha-fetoprotein level and immunological deficiencies, particularly low levels of T cells and B cells and of one or more classes of immunoglobulin, most commonly IgA.

Differential diagnosis

In early childhood A-T can mimic cerebral palsy, especially dyskinetic types, cerebellar ataxia from a number of other causes, and developmental co-ordination disorder or developmental dyspraxia. Some cases first come to medical attention because of lung disease or because of malignancy.

Investigations

Most children in whom there is a suspicion of cerebellar ataxia, dystonia, or chorea will have an MRI brain scan, and this will be grossly normal early on in A-T. Further investigations that will point towards a diagnosis of A-T include plasma alpha fetoprotein, IgA deficiency and other immunological abnormalities, and chromosomal radiosensitivity. It is sensible at this stage to send blood in EDTA and lithium heparin for further analyses.

Laboratory confirmation

When a clinical diagnosis of A-T has been made or there is a reasonable clinical suspicion of A-T, genetic confirmation should be obtained by identifying the ATM mutations present. In the UK this is usually carried out by Professor Malcolm Taylor's laboratory at the University of Birmingham, which is designated by the NHS to do this. The laboratory will also investigate the consequences of the specific mutations present in the ATM gene.

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As part of the diagnostic process, the following tests on a lithium heparin blood sample are carried out:

- A chromosomal radiosensitivity analysis is carried out on the blood lymphocytes, as sensitivity to ionising radiation is a characteristic of A-T.
- A lymphoblastoid cell line (LCL) is made from the blood sample and a western blot carried out to look for loss of ATM protein.
- If these two tests indicate the likelihood of A-T, the whole of the patient's ATM gene is sequenced in order to identify both mutations.
- If the western blot reveals some residual ATM protein activity, as the result, for example, of a missense, or leaky splice-site mutation, an activity assay is also carried out to determine whether the ATM protein has some activity. There is a strong phenotype-genotype correlation in A-T and patients with some residual A-T kinase activity generally have a milder clinical course.

Ideally all these tests should be undertaken because, for example, some patients have no measurable increase in chromosomal

radiosensitivity, and yet the western blot shows up a greatly reduced level of ATM protein. This is because the ATM present has some activity that is effective in reducing chromosome damage. Similarly some A-T patients have normal levels of ATM protein on a western blot, but the radiosensitivity assay will indicate a lot of chromosome damage. This is because the mutant ATM protein expressed has no kinase activity. These laboratory tests are usually made available to the doctors at the specialist A-T centres, as well as to the physician requesting the confirmation.

For more information about the process or to arrange for an analysis, please contact:

A.M.R. Taylor
Professor of Cancer Genetics
School of Cancer Sciences
Vincent Drive, Edgbaston
Birmingham B15 2TT
Tel: 0121 414 4488

Referral to the National A-T Service

The National A-T Service is a partnership between:

- The Children's Centre at Nottingham City Hospital Campus
- The adult specialist centre at Papworth Hospital in Cambridgeshire
- The Ataxia-Telangiectasia Society (A-T Society)
- Professor Malcolm Taylor's laboratory at the University of Birmingham

Once a diagnosis of A-T has been made the patient should be referred to the appropriate national specialist centre for a detailed multi-disciplinary assessment. For children under 16 years of age this is the centre at the Nottingham City Hospital Campus.

It is also recommended that the patient be put in touch with the A-T Society. Their professional family support officer can provide personalised information and a wide range of support, including putting the family in touch with others living with A-T. There is no obligation to be involved with the Society and people can have as much or as little contact as they like, or none at all.

Referrals to the clinic are commonly made via the A-T Society, which provides administrative and logistical support to the centres. Their family support officer will liaise with the appropriate centre and provide help with travel and accommodation arrangements. However, if the patient or their family prefers, a referral can be made direct to the centre by their treating physician.

Contact details:

A-T Society

Kay Atkins, Family Support Officer
The A-T Society
Rothamsted
Harpenden
AL5 2JQ

Tel: 01582 760733
Email: kay@atsociety.org.uk
Website: www.atsociety.org.uk

Nottingham Children's A-T Centre

Dr Mohnish Suri, Consultant Clinical Geneticist
Clinical Genetics
Nottingham City Hospital
Hucknall Road
Nottingham
NG5 1PB

Tel: 0115 962 7728

Papworth Adult A-T Centre

Dr Nicholas Oscroft, Consultant Respiratory Physician
Papworth Hospital
Papworth Everard
Cambridge
CB23 3RE

Tel: 01480 364551

Ongoing care

Attendance at national specialist centres

It is essential that children with A-T attend the national specialist centre at Nottingham for an initial assessment by the specialist team. This will help the local team support the child with A-T and their family. As A-T generally progresses and causes more neurological, respiratory and immunological problems over the years, it is best practice to establish a local "team around the child" with a key worker and lead professional (e.g. a community nurse or physiotherapist and a community paediatrician). We recommend regular local paediatric neurology and or neurodisability follow-up and local paediatric respiratory follow-up as needed. Over time some children will benefit from a local CF-type service.

After an initial assessment at the national A-T centre, it is strongly recommended that the child continues to make regular visits to the centre. The frequency of these visits varies between the centres.

Following each visit a letter detailing the findings and any recommendations from each specialty will be sent to the referring physician, the local team and the family. Where it is felt necessary for urgent treatment to take place, the clinic will also prescribe or make referrals as necessary.

Nottingham

The A-T Specialist Centre in Nottingham was established in 1993 and is the longest-running A-T clinic in the world.

Clinics are held over two days (Thursday & Friday), six times a year. At each clinic, six children are seen on an outpatient basis.

Over the course of two half days (two mornings or two afternoons) the children see a paediatric team comprising:

- Geneticist
- Neurologist
- Speech & language therapist
- Genetic counsellor
- Ophthalmologist
- Dietician
- Respiratory physician
- Occupational therapist
- Psychologist
- Immunologist
- Physiotherapist
- Respiratory nurse and physiotherapist

Bloods are also taken for a detailed immunological analysis and other investigations as indicated. Patients are usually recalled to the clinic every two or three years. If there is an urgent need for a patient to attend the clinic, this can normally be arranged.

Papworth

From about 16 or 17 years of age, patients are referred to the A-T Specialist Centre for Adults at Papworth Hospital, which has particular expertise in the treatment of lung conditions.

Patients are seen over two days (Monday and Tuesday morning) but stay overnight in the hospital in private rooms. Only one or two patients are seen each week.

It is essential that children with A-T attend the national specialist centre at Nottingham for an initial assessment by the specialist team. This will help the local team support the child with A-T and their family.

During their time at the centre, patients see a team comprising:

- Respiratory consultant
- Physiotherapist
- Clinical immunologist
- Speech and language therapist
- Neurologist
- Social worker
- Occupational therapist
- Dietician

Patients are offered blood tests, a respiratory assessment, an immunological assessment, videofluoroscopy, and sometimes a chest CT scan, brain MRI, and nerve conduction/EMG studies. Patients usually attend the clinic about once a year.

Local care

It is vital to establish appropriate local care, to ensure that the child is monitored and their needs met between visits to the specialist centre. We recognise that resources and organisation of healthcare will vary from area to area but this section outlines our general recommendations.

Paragraph 5.8 of the UK Strategy for Rare Diseases states that every patient “should have an overall care plan to manage co-ordination of care between health and social services” and we strongly endorse this. Ideally a formal arrangement should be established, with regular “team around the child” meetings, involving representatives from health, education and social care. We also recommend that each child has a local named key worker, and a local named lead professional, as set out in paragraph

5.9 of the UK Strategy for Rare Diseases.^{5,6}

Patients will need support at different stages of the disease from a range of different health professionals, but generally need a local community paediatrician, a local paediatric neurodisability specialist or paediatric neurologist and a local paediatric respiratory specialist, and their teams. The A-T clinic will then be able to liaise with the local team more effectively.

Detailed guidance is to be found in the individual sections following this; however, we strongly recommend the following form part of the care package:

Respiratory care: A respiratory review at least every three months, and more frequently if the child is unstable.

Neurology: A paediatric neurodisability review at least every 6 months, and more frequently if the child is unstable.

A local paediatric neurology review at least every year, or more often if support is needed by the neurodisability paediatrician.

Immunology: In those children where recurrent infections are related to immune deficiency, local immunologist input is recommended. This is essential for children who may need to commence immunoglobulin replacement therapy.

SLT and diet: Regular assessments by a speech and language team, and also dietetic review.

Physiotherapy: Regular assessment and review.

Paragraph 5.8 of the UK Strategy for Rare Diseases states that every patient “should have an overall care plan to manage coordination of care between health and social services”.

A diagnosis of A-T is normally confirmed by the following laboratory tests:

- Chromosomal radiosensitivity test on peripheral blood lymphocytes
- Western blot on lymphoblastoid cell line to look at ATM protein expression and its kinase activity
- ATM gene mutation analysis
- If the previous tests show no abnormalities, expression of hMRE11 protein and aprataxin will be examined, to check for A-T-like disorder and AOA1

The results of these tests should be discussed with patients and/or their families and, in particular, what the implications may be for the severity of the A-T, for example, whether or not there is any evidence of ATM kinase activity or particular mutations known to be associated with a milder phenotype. However it should be made plain that at the current state of knowledge, and given the known variation between individuals, even with the same mutations, no detailed prognostic advice can be given.

It is advisable to ask about parental consanguinity and details of any other relatives with neurological problems or cancer. This should be done by drawing a three-generation family tree.

Parents should be given information about the autosomal recessive inheritance pattern of A-T and offered genetic counselling.

They should be given information about the availability of prenatal testing for A-T in any future pregnancy and also the availability of pre-implantation genetic diagnosis for A-T, as an option to prenatal testing for parents who would not contemplate termination of pregnancy. In the event that parents may wish to consider either of these options, arrangements should be made to test parents for the two ATM mutations identified in the affected child to confirm their carrier status.

Where relevant, there should be discussion of the possibility of unaffected siblings and siblings of parents being A-T carriers, and the concomitant risk of A-T in their offspring. Where relevant, advice should also be given about how carrier testing for these individuals can be arranged - by GP referral to their Regional Clinical Genetics Service.

Parents should be given information about medical problems that can be seen in individuals with A-T in particular of the increased risk of cancers. Other topics that may be covered, if not being addressed by another specialist, include neurological problems, sino-pulmonary infections, problems with growth and development, problems with feeding, sleep apnoea, sun-sensitivity and scoliosis. Guidance should be given on any warning signs to be looked out for, particularly for leukaemia and lymphoma.

When teenage girls are seen, in particular at the time of transition to adult services, the elevated risk of breast cancer in adult women with A-T should be discussed. Information should be provided about the current guidance on breast cancer surveillance

Information should also be provided about the increased risk of breast cancer for the mother of a child with A-T.

in women with A-T which, at the time of writing, envisages an annual MRI scan from the age 25 years onwards.

Information should also be provided about the increased risk of breast cancer for the mother of a child with A-T and for any other female carriers of the A-T mutation in the family. There should also be information about the current guidelines for breast cancer surveillance in A-T carriers. At the time of writing, this involves a mammogram being carried out every 18 months from the age of 40 until the age of 50 years, when they will be offered three-yearly mammograms as part of the NHS Breast Screening Programme. Details of this can be found on the website of the NHS Breast Cancer Screening Programme (<http://www.cancerscreening.nhs.uk/breastscreen/higher-risk.html>) in the *Imaging protocols* document.

Respiratory management

Dr Jayesh Bhatt, Consultant Respiratory Paediatrician

Introduction

There are no large adequately-powered randomised controlled trials of any respiratory treatments in ataxia-telangiectasia so all recommendations are based on combinations of extrapolation from other diseases and expert opinion.

The major respiratory complications of A-T are:

- acute and chronic respiratory tract infection, with the risk of bronchiectasis, related to immunodeficiency and poor secretion clearance
- aspiration syndromes, related to inco-ordinated swallowing, which can lead to bronchiectasis
- scoliosis, especially in adolescence
- respiratory muscle weakness
- (much more rarely) interstitial lung disease (ILD)
- restrictive and obstructive lung disease may develop after chemotherapy treatment for cancers

Given the complexity of the respiratory complications of A-T, it is strongly recommended that all children are cared for by a respiratory paediatrician in the local tertiary regional centre.

Patterns of respiratory care

Given the complexity of the respiratory complications of A-T, it is strongly recommended that all children are cared for by a respiratory paediatrician in the local tertiary regional centre.

In suitable circumstances, a shared care system may be operated with a local district general hospital, along the lines of the CF model. We recommend a respiratory review at least every three months, and more frequently if the child is unstable. The components of the review should include:

- Assessment by an experienced paediatrician
- Assessment of airway clearance techniques by a physiotherapist with a special respiratory interest
- Culture of sputum or cough swab including for *Pseudomonas aeruginosa*
- Availability of spirometry for those children able to perform the technique. Stringent follow-up lung function monitoring should be adhered to in survivors of cancer
- Pulse oximetry
- Specialist radiology – given the risk of malignancy, the need for X-rays should be carefully considered, and the dose of radiation minimised with the aid of an experienced paediatric radiologist. If deemed necessary to guide management, X-rays should be performed, but only after consultation with a specialist.

In addition, access to regular assessments by a speech and language team, and also dietetic review to ensure optimal nutrition, is essential. It is assumed that the child will have access to all basic forms of support, including paediatric psychology, occupational therapy, social work and play therapy, and all relevant professionals to ensure optimal access to services including school.

Management of respiratory disease

General high quality respiratory care is essential including avoidance of environmental tobacco smoke and full immunisation, including annual influenza immunisation.

Infection: There is no data to recommend, or otherwise, prophylactic antibiotics, but most children are recommended prophylactic azithromycin by the immunologists. There are no data on the microbiology of A-T lung disease but experience in one of the biggest clinics (Nottingham) suggests that H influenzae, M catarrhalis, Strep pneumoniae, Staph aureus and occasionally *Pseudomonas* are the main pathogens when the culture is positive.

We recommend additional antibiotics under the following circumstances:

- Any increase in respiratory symptoms, especially chronic productive cough, irrespective of whether there are any abnormalities heard with the stethoscope. Culture of respiratory secretions should be performed, and airway clearance techniques reviewed. Blind treatment with oral antibiotics should be commenced, guided by previous cultures. If there are no previous results which are helpful, then blind treatment with co-amoxycylav or another antibiotic which covers H Influenzae, M Catarrhalis, Strep pneumoniae and Staph aureus should be given. We recommend the use of high doses (formulary 'serious infection' dose) for 2-4 weeks continuing until the child has returned to baseline for at least 7 days especially when the family feels that the child is more or less returned to baseline. Antibiotics can be changed depending on the culture results.
- Any positive culture should be treated with 2-4 weeks of an appropriate oral antibiotic as above, even if the child is asymptomatic
- If the response to oral antibiotics is inadequate, or if the child is very unwell, admission for intravenous antibiotics and intensive airway clearance is mandated. Choice of intravenous antibiotics will depend on cultures or best guess. Isolation of Ps aeruginosa should be treated with a CF-protocol eradication regime, for example three weeks oral ciprofloxacin and three months nebulised colistin.
- In a child with a chronic productive cough despite trials of antibiotics, especially if culture negative, consideration should be given to induced sputum sample or fibreoptic bronchoscopy (FOB) and bronchoalveolar lavage (BAL) to obtain material for culture. Opportunistic infections are rare in A-T but, if suspected, early FOB and BAL is mandated
- Children with A-T are also prone to sinusitis and otitis media, and these should also be treated with prolonged courses of antibiotics.

Reversible airflow obstruction: Documentation of an acute response to bronchodilators is not uncommon and, of course, A-T does not protect a child from also developing asthma. There is no

evidence that prescribing inhaled corticosteroids (ICS) to children with A-T and reversible airflow obstruction, but no risk factors for asthma, is beneficial. It is suggested that if a trial of ICS is contemplated, it should be for a finite period with definite end-points, before the child is committed to long-term therapy. It should be noted that there is increasing evidence that ICS may increase the risk of airway infection in other contexts, and hence there is a reason for caution for long-term use.

Aspiration: Suspicion should be aroused if there are symptoms such as cough during eating, or failure to swallow saliva. The expertise of an experienced speech and language therapist should be sought. If the child has an unsafe swallow, gastrostomy or jejunostomy feeding is advised. Again a videofluoroscopy with limited radiation exposure should be required if there is suspicion of silent aspiration. Enteral feeding is also mandated if the child, while not actually having an unsafe swallow, takes such a long time to eat that nutrition is not maintained.

Interstitial lung disease: This is rare, but should be suspected if the child has a persistent dry cough, breathlessness, persistent crackles in the absence of respiratory infection, or oxygen desaturation. The evidence base for an investigation pathway is even scantier, but since the treatment is with high dose oral corticosteroids, most would advocate obtaining a tissue diagnosis. This would involve a limited low dose CT scan followed by video-assisted thoracoscopic surgery (VATS) or open lung biopsy. Such evidence as exists suggests that early treatment with oral corticosteroids is most beneficial, so diagnosis and treatment should be aggressively pursued at an early stage.

PSG: Indications for cardiorespiratory polysomnography should be considered if there is a clinical suspicion of sleep-related breathing abnormalities, rapid or progressive decline in lung function or developing scoliosis.

Respiratory muscle training and or cough augmentation: No current evidence supports this routine but should be considered in an individual child if there is a weak or disco-ordinate cough.

Neurology management

Dr William Whitehouse Consultant Paediatric Neurologist
Dr Gabriel Chow, Consultant Paediatric Neurologist

Frequent neurological problems in children with A-T

Walking: Generally children learn to walk at the usual age (about 10-18 months of age), but remain a bit unsteady, like normal children who have only just learned to walk, then become more wobbly (ataxic) over 2-3 years with frequent falls, then actually cannot get about as well as they used to from 5-6 years. Often, in typical A-T, they will benefit from access to a wheelchair from 8-10 years of age. Keeping ambulant, at least indoors, for example, with a wheeled frame with handles that supports the child from behind, will be enjoyed by the child and, together with a standing frame, help prevent scoliosis. In non-ambulant children and young people scoliosis is probably more common than previously realised and requires assessment by a spinal team, and sometimes surgery.

Talking: Early language development is normal, but by school entry most children with typical A-T will have a quiet voice, with indistinct words, which gradually become harder for strangers to understand. The voice can sound nasal. It is hard for them to sustain long sounds. Delay in initiating speech can be frustrating and children and young people with A-T should be given extra time in conversation, to reply before you repeat the question. Limitation and delay in facial expression and voluntary movements will impair their non-verbal communication too, although many children have sustained and engaging social smiles, appropriately reflecting their mood, when not feeling exhausted. Later electronic communication aids can be very useful, but the young person will require expert assessment if a suitable device is to be found, given the other motor impairments and movement disorder.

Writing and fine motor skills: These become slower and more wobbly through primary school and access to and support with computers, such as large keyboards and switching on the accessibility settings in Windows, can be a great help.

Eye movements: become more difficult through primary school, with slowness in changing the direction of gaze, delay in initiating movements, having to use head thrusts to change gaze (oculomotor apraxia), and difficulty keeping their place when reading. Using a ruler or straight edge can help, as can using larger font on coloured paper.

Extra movements and stiffness: These can cause problems through the school years with jerks, tremors and stiff postures when children least want them. Such movements can severely impair vision, even though the eyes and visual brain are normal. Spasms can be painful, and disrupt sleep. Muscle strength: This is good in childhood and early adulthood, although people with A-T do develop a mild and slowly progressive neuropathy, which mainly affects sensory nerve fibres. Fatigue is a common problem, movements

Feeding becomes increasingly difficult through the school years. It gets harder for the young people to feed themselves because of jerks and stiffness and ataxia, and swallowing can become unco-ordinated, slow and uncomfortable.

require more mental effort to initiate and sustain, for example, speaking, writing, doing anything physical. Also sleep can be disturbed by painful postures and spasms. It is sensible to pace oneself, but it can be so frustrating that some young people will feel like giving up. Medical advice to optimise night time sleep can be important.

Feeding: This becomes increasingly difficult through the school years. It gets harder for the young people to feed themselves because of jerks and stiffness and ataxia, and swallowing can become unco-ordinated, slow and uncomfortable,

with food and especially fluids being aspirated. This is helped by gastrostomy, which should be considered sooner rather than later, to avoid malnutrition and associated compounded immunocompromise. Some also develop gastro-oesophageal reflux, further increasing the risk of aspiration and of oesophagitis and anaemia. Gastro-oesophageal reflux can be made worse by nasogastric or gastrostomy feeding, so should be considered prior to gastrostomy, as a fundoplication may be appropriate.

Early language development is normal, but by school entry most children with typical A-T will have a quiet voice, with indistinct words, which gradually become harder for strangers to understand.

Learning and cognitive function: Although cognition seems unaffected in childhood, communication, reading and mobility are severely affected as the child gets older, impacting significantly on education, exercise, and all social and leisure activities. Assessing cognitive function is very difficult in older children and young people with A-T.

Mood and mental health: Adolescence can be a difficult time for young people but especially when they have a physically disabling condition like A-T to deal with.

Medical drug treatment

We hope in the future to have specific A-T treatments directed at enhancing or replacing ATM. Some specific treatments to slow the disease progression are being trialled, for example various steroid regimes and amantidine sulphate, but their place in treatment is not yet established. Other medication will be useful from time to time for particular symptoms as part of the child's care, for example muscle relaxants such as baclofen, diazepam, tizanidine, dantrolene are sometimes helpful for stiffness and spasms. Carbidopa and other "Parkinson's" drugs may also be helpful for specific symptoms. A trial of the use of a topical hyoscine patch or part of a patch depending on age could be prescribed to reduce drooling. This is changed every three days.

The role of deep brain stimulation (DBS) in selected patients with A-T has not yet been explored.

Patterns of neurology care

A-T patients have complex neurological difficulties but the pace of deterioration is not usually sudden, although losing particular abilities, such as writing or walking can be devastating to the child, young person and their family. It is strongly recommended that all children are cared for by a local multidisciplinary multiagency neurodisability team with the help and support, specialist advice and regular review from a local paediatric neurologist in a tertiary, regional centre. In suitable circumstances, a shared care system may be operated with a local district general hospital paediatrician as service configurations vary from place to place. However, a team around the child with education and social care as well as medical support will be needed. There should be a lead professional, such as a local consultant in paediatric neurodisability, generally based in the community, or a hospital-based neurodisability paediatrician. There should be a local key worker, who will work closely with the lead professional and help co-ordinate care and services week by week. We recommend a paediatric neurodisability review at least every six months, and more frequently if the child is unstable. We recommend a local paediatric neurology review at least every year or more often as support is needed by the neurodisability paediatrician, with multidisciplinary review at the national A-T clinic every 2-3 years.

The components of the local paediatric neurodisability team should include:

- an experienced paediatric neurologist or consultant in paediatric neurodisability
- an experienced paediatric ophthalmology team
- an experienced paediatric physiotherapist
- an experienced paediatric occupational therapist
- an experienced paediatric speech & language therapist
- an experienced paediatric dietician
- an experienced paediatric orthotics and seating service
- access to paediatric communication technology assessment

In suitable circumstances, a shared care system may be operated with a local district general hospital paediatrician as service configurations vary from place to place. However, a team around the child with education and social care as well as medical support will be needed.

Co-ordination with the GP, local respiratory paediatric advice, paediatric immunology, and clinical genetics, and other medical and psychological support as needed, education and social care will need to be managed locally. This can be a significant challenge, which will be facilitated by the team around the child model with a key worker and lead professional.

Management of neurological impairments

Neurology care for these children demands a multidisciplinary approach. The physical neurological needs of the child are discussed, and practical help is advised for any difficulties encountered in the home or school situation. The ophthalmological needs may be addressed by the use of different materials to help with reading.

The ability to eat and swallow effectively is monitored. If this is faltering, discussion about dietary adjuncts or alternative methods of feeding, including gastrostomy will be discussed at an early stage.

If mobility is an issue, suggestions are made regarding equipment available - splints, walkers, wheelchairs, ramps, aids for washing and access.

The neurological assessment

A standard neurological assessment has been undertaken at the Nottingham A-T clinic for many years, based on local practice and a quantitative scale developed in Baltimore⁷.

More recently an international consortium has been developing the A-T Neurological Examination Scale Toolkit (A-T NEST), which allows a more detailed and nuanced assessment.

Immunological management

Dr Elizabeth McDermott, Consultant Immunologist

Dr Graham Davies, Consultant Paediatric Immunologist • Dr Lucy Cliffe, Consultant Paediatrician

Immunological manifestations in A-T

Immunological abnormalities observed in A-T include deficiencies of immunoglobulin classes A and E and occasionally immunoglobulin G: IgG subclass 2 and 4 deficiency, with a tendency to high IgM levels. Occasionally a picture of hyper IgM syndrome has been described. There is poor responsiveness to pneumococcal polysaccharide vaccine but fairly good responses to conjugate pneumococcal vaccine. Reduced lymphocyte numbers affecting T and B cells but not NK cells is also seen. Amongst T cells, the naïve CD4 CD45 RA population seems to be most depressed and T cells bearing gamma delta T cell receptors may be increased. Spectratyping of T cell receptor repertoires show some abnormal skewing of different V beta families in some individuals. Studies of functional T cell responses have shown very variable results with reduced T cell proliferative responses in some individuals.

The immune features mentioned above are heterogeneous, showing a wide spectrum of abnormalities. Those with mutations allowing some residual ATM kinase activity do have less severe immune abnormalities. Interestingly, the immune abnormalities do not always correlate well with the clinical susceptibility to infection. Follow-up studies show that the immune deficiency is static in most cases and does not deteriorate over time.

Clinical manifestations of immunodeficiency

Infections

Recurrent infections are the commonest manifestation of immunodeficiency in A-T. These usually affect the chest, ears and sinuses and can lead to chronic lung damage and chronic otitis with hearing impairment. Invasive bacterial disease, such as sepsis, bone and joint infection or meningitis, is unusual. The lung disease in A-T which, apart from

malignancy, is one of the commonest causes of early death has multiple causes. Inability to protect the airway as the neurological disease progresses, poor cough response because of muscle weakness and inco-ordination and the tendency in some patients to develop scoliosis in adolescence can all contribute. Inflammatory problems including bronchiolitis obliterans and chronic interstitial lung disease have been described in A-T.

Herpes viruses may be a problem in A-T. Herpes simplex infections were reported in 7 of 100 patients in one series although not apparently severe, while 5/44 patients with chicken pox had disease severe enough to require hospitalisation. Cytomegalovirus infections have not been reported as being problematic and neither have Epstein-Barr virus (EBV) infections. In contrast to what occurs in some other immunodeficiencies, the predisposition to lymphoid malignancy in A-T does not seem to be caused by susceptibility to EBV disease. A-T patients often suffer severe and persistent warts suggesting poor handling of papilloma viruses. Interestingly, Pneumocystis jiroveci pneumonia is very rare.

Autoimmunity

In common with other immunodeficiency states associated with poor T cell immunity, autoimmune phenomena may occur. Vitiligo is the most common. Autoimmune haemolytic anaemia has been described as a problem in the small number of A-T patients with a very severe immunodeficiency. Non-infective granulomatous skin disease is a particularly difficult condition to treat. The cause of this is uncertain. Searches for triggering microbes are usually negative.

Malignancy

The lifetime risk of developing a malignancy in this condition is around 22% in the UK. T and B cell leukaemias and lymphomas can occur but the former are more common. Carcinomas and brain tumours also occur.

Recurrent infections are the commonest manifestation of immunodeficiency in A-T. These usually affect the chest, ears and sinuses.

Management

Management of patients with this rare multi-system disorder is best overseen by a specialist clinic serving a critical number of patients to enable the generation of experience and expertise and staffed by a multidisciplinary team. If this is not available, all patients should be reviewed by an immunologist to assess the infection history and perform basic immunological investigations. The minimum would include lymphocyte subsets, immunoglobulins and functional antibodies.

Management of infection susceptibility

The aim is to reduce the risk of infection in each individual, so improving quality of life and reducing the risk of long-term organ damage.

A number of small studies have suggested that the pneumococcal conjugate vaccine is able to generate protective antibody responses in A-T patients, but to a lower titre than in normal controls.

Immunisation

Pneumococcal vaccine: Several studies have shown that antibody responses to pneumococcal polysaccharide vaccine are defective in A-T. Whilst there are no bacteriological studies to confirm the role of pneumococcus as a significant pathogen in this group of patients, it is recognised as a significant pathogen in other immunodeficiency states. It is therefore reasonable to assume that such defective responses contribute to the susceptibility to sino-pulmonary infections.

A number of small studies have suggested that the pneumococcal conjugate vaccine is able to generate protective antibody responses in

A-T patients, but to a lower titre than in normal controls. It is therefore reasonable to administer conjugate pneumococcal vaccine to all A-T patients regardless of their age, even though the currently used 13-valent vaccine is only licensed for children up to the age of 5 years. The practice of administering a subsequent dose of polysaccharide vaccine to boost responses to those serotypes in the conjugate vaccine, and to potentially produce some response to other serotypes, has been called into question because of concern over the potential development of B cell hyporesponsiveness (to those serotypes not included in the conjugate vaccine) after repeated doses of polysaccharide vaccine. Certainly use of multiple doses of the polysaccharide vaccine is not advised. The advent of newer conjugate vaccines with an extended number of serotypes will provide better protection and reduce the possibility of serotype replacement which has been described in vaccinated children developing otitis media.

Influenza vaccination: Annual influenza vaccination is recommended for all A-T patients since influenza may be particularly problematic not only for those with immunodeficiency but also in those with neurological disease. We also recommend giving influenza vaccine to A-T sufferers who are on immunoglobulin replacement therapy. The rationale for this is that administered immunoglobulin will not contain antibodies against new antigenic variants of influenza. Furthermore, even those A-T patients on immunoglobulin are likely to have some retained ability to mount an antibody response.

Varicella zoster vaccine: Severe varicella infection in patients with A-T can occur but most patients contracting the infection have a mild illness. Nevertheless, there is the risk of severe infection and varicella encephalitis which, as it most commonly affects the cerebellum, will exacerbate the neurological condition. VZV vaccine is therefore recommended in all cases that have not already contracted the natural disease. The exception would be those rare cases with very profound T cell lymphopaenia (CD3 count of <500) in whom there would be concerns of vaccine-associated disease.

Other live viral vaccines: Unless there is a family history, most children with A-T have usually received live viral vaccines before their diagnosis. We are not aware of any reports of adverse effects of measles, mumps, and rubella (MMR) vaccine. This vaccine is

an important vaccine to give since measles infection may be more likely to lead to secondary bacterial pneumonia in this group of patients. MMR should therefore be administered to all patients with the exception of those with profound lymphopaenia, as for VZV vaccine. The new live nasal influenza vaccine is likely to be safe in most children with A-T, except those with quite severe immune deficiency. It would be safer however, to use the injectable vaccine in any child where the immune system status has not been formally evaluated.

Yellow fever vaccine should not be used in any patients with A-T.

Other vaccines: Antibody levels against *Haemophilus influenzae* type b (Hib) and Tetanus toxoid have been reported as being protective in most patients with A-T following immunisation. The normal protocol should therefore be followed.

Human papilloma virus (HPV) vaccine is a non-live vaccine which on theoretical grounds should be particularly important for girls with A-T in view of the apparent problem in the handling of those papilloma viruses causing cutaneous warts and the general predisposition to malignant disease including carcinomas.

BCG vaccine should not be used routinely but can be used in those patients with a very high risk of TB contact unless there is profound T cell lymphopaenia.

Antibiotics

Prophylactic antibiotics probably help reduce the burden of respiratory tract infections in A-T. The use of cotrimoxazole prophylaxis has been superseded in the UK by azithromycin. This may be useful not only through its antimicrobial properties but through an anti-inflammatory effect. Though there are no formal trials of this drug in A-T, studies in cystic fibrosis patients colonised with *Pseudomonas aeruginosa* showed a beneficial effect on lung function which was not directly due to its antimicrobial properties. The long tissue half-life of azithromycin means that only intermittent administration is required (three doses per week or per fortnight depending on severity of clinical problems). There would of course be concern

about relying on this agent where the prevalence of macrolide resistance amongst pneumococcal isolates in the community is high. Alternatives to macrolides would be cotrimoxazole or a single daily dose of cefixime.

Immunoglobulin

The decision to commence immunoglobulin in A-T is generally taken on clinical grounds because of recurrent infections usually associated with a low IgG level. About 15% of individuals with A-T will require Immunoglobulin replacement. Standard dosages are used but since A-T patients are very unlikely to be completely IgG deficient, and endogenous production is likely to continue, monitoring of trough IgG levels is less useful in determining dosages than in other antibody-deficient patients. Subcutaneous administration has shown to be both efficacious and acceptable to patients on replacement therapy.

Management of other immunological complications

The treatment of granulomatous disease can be very difficult in A-T. Whilst such granulomas are nearly always non-infective, the possibility of their being driven by infection such as mycobacterium needs to be covered with appropriate antibiotics, particularly as the mainstay of treatment will be immunosuppression. Systemic steroid therapy is usually required and the dose may need to be escalated. There is little experience with the use of biologics for this problem to date.

Follow-up of individuals

Although the immune abnormalities in A-T seem to be fairly stable with time in the majority of cases, it is important to regularly review patients to assess their infection history. If infections have become an increasing problem, it is important to assess general aspects as well as immunity, such as swallowing, calorie intake or lung pathology.

This section is based upon the *Update on the management of the immunodeficiency in ataxia-telangiectasia* in Expert Review of Clinical Immunology 2009⁸.

Use of X-rays

Dr Mohnish Suri, Consultant Clinical Geneticist

Patients with classic and variant forms of A-T are unusually sensitive to ionizing radiation, including X-rays and radiation that is used in the treatment of cancers (radiotherapy). The available evidence for the radiosensitivity in patients with A-T is based on observations of patients who have received radiotherapy for the treatment of cancers before the diagnosis of A-T was made and from studying the effects of gamma irradiation on fibroblasts and cultured lymphocytes from patients with A-T. Exposure of A-T children to therapeutic doses of ionizing radiation has resulted in the death of patients.

Increased radiosensitivity forms the basis for one of the tests used for the diagnosis of A-T (the chromosomal radiosensitivity test). However, there is no data available regarding the adverse effects of

diagnostic X-rays or CT scans in patients with A-T. In the absence of available data/evidence a pragmatic approach is recommended for the use of diagnostic X-rays and CT scans in patients with A-T. According to this approach, a single X-ray can be performed for diagnostic purposes such as diagnosis of a chest infection or scoliosis. However, repeated X-rays should be avoided. Similarly, a single low-dose CT scan can be used where it is essential for diagnostic purposes, such as the diagnosis of bronchiectasis or infiltrative lung disease. Where possible, the smallest radiation dose should be used, for example for a CT chest scan, or an alternative modality such as a MRI scan should be considered, which may provide similar information to a CT scan but without the attendant risks of radiation exposure.

Cancer risk

Professor Malcolm Taylor, University of Birmingham

The cancer predisposition in A-T is well documented with the majority of tumours being of lymphoid origin in childhood.

Overall cancer risk

In a recent study⁹ of 296 consecutive genetically confirmed cases of A-T from the British Isles and the Netherlands, 66 patients were identified with a tumour, 47 of lymphoid origin and 19 non-lymphoid. This gives an overall cancer risk of 66/296 or 22%. The non-lymphoid tumours include brain tumours, hepatocellular carcinoma, endocrine tumours, breast cancer and myeloid leukaemia.

Cancer risk in classic A-T

In 187 classic A-T patients (as defined by absence of ATM kinase activity in their cells) 51 tumours (40 lymphoid and 11 non-lymphoid) were identified. This gives a risk of 51/187 or 27%.

The development of childhood tumours (lymphoid and brain) in A-T patients is associated almost exclusively with absence of ATM kinase activity. Importantly, expression of some residual ATM kinase activity had a strong protective effect against tumour development in A-T children.

Breast cancer

Surviving female A-T patients also showed a substantially increased risk of breast cancer with the cumulative risk at age 50 years being 45%. By definition the majority of these patients had a milder form of ataxia-telangiectasia and survived longer.

A-T patients carrying the c.7271T>G mutation may be at particular risk of breast cancer. The same mutation was also identified in a second A-T family where breast cancer occurred in carriers of the mutation. The authors computed a relative risk of developing breast cancer of 12.7 associated with carrying this ATM mutation, compared with a relative risk of 74.1 in homozygotes.¹⁰ This is consistent with the increased risk of breast cancer also observed in female carriers of ATM mutations, with the risk being larger in women under the age of 50.¹¹

Major causes of increased mortality in A-T, therefore, are lymphoid malignancies in children, and non-lymphoid malignancies in adult A-T patients. It is important that ATM mutation analysis is available to patients.

Treatment of cancer

Dr Michael B. Kastan, Executive Director, Duke Cancer Institute

Dr John Sandlund, Medical Director, Leukemia/ Lymphoma Clinic, St Jude Children's Research Hospital

There has to date been mixed success in treating cancers in A-T. Many A-T patients seem to have an increased vulnerability to toxicity and/ or may be vulnerable to relapses or new malignancies. The rarity of A-T and the fact that cancers are usually treated locally have slowed the accumulation of clinical expertise on the treatment of cancer so that only now is some sort of consensus starting to emerge, with the authors of the section below at the forefront in bringing this together.

There is currently no one centre of expertise in the UK. It is recommended that clinicians treating a child with A-T for cancer for the first time talk to colleagues who have had recent experience of doing so. The A-T Society will be able to put you in touch with colleagues with appropriate experience either in the UK or abroad.

The following guidance on the treatment has previously been circulated privately by the authors, and included in a recently published paper.¹²

Suggested management and supportive care guidelines for children with A-T and cancer

Approximately 10-30% of A-T patients will develop a malignancy during their lifetime. The vast majority of these cancers are of lymphoid origin. There is no consensus regarding the optimal strategy for treating children with A-T who develop hematopoietic malignancies. Historically, many of these children have been treated with therapy that is much less intensive than the conventional

approach for non-A-T patients with similar malignancies during the corresponding treatment era. Although these less intensive approaches may have stemmed from perceptions that these children would not tolerate intensive therapy, there is in fact no data to suggest that these children cannot tolerate intensive therapy. However, it is clear that children with A-T require a modification in certain components of intensive therapy.

Suggested chemotherapy administration guidelines:

- Children with A-T have a hypersensitivity to ionizing radiation. Therefore, this modality should be avoided in the management plan if possible. Similarly, radiomimetic drugs such as bleomycin should also be avoided.
- Children with A-T are less able to compensate for the muscle weakness induced by vincristine because of their underlying ataxia. In this regard, weekly vincristine may not be tolerated very well. Thus, at the earliest sign of weakness, vincristine should be discontinued or delivered at a reduced dosage. Vinblastine, which is associated with less neurotoxicity than vincristine, may be a safer drug to use.
- Children with A-T appear to be at higher risk for cyclophosphamide and/or ifosfamide related hemorrhagic cystitis. This complication may develop months after the drug is delivered. Therefore, it is important that patients receive vigorous hydration and mesna when these drugs are administered, regardless of the dose intensity.

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- Children with A-T may have more methotrexate induced gastrointestinal tract toxicity than non-A-T patients. Therefore, efforts to optimize drug excretion (i.e. aggressive hydration, appropriate alkalinisation of the urine, and avoidance of concurrent delivery of other nephrotoxic agents), close monitoring of methotrexate levels and aggressive leucovorin rescue need to be incorporated into the treatment plan.
 - The potential increased risk for hypersensitivity associated with the use of topoisomerase inhibitors, such as etoposide and adriamycin in A-T patients, has prompted some investigators to empirically use a 3/4 strength dosing strategy with these agents, except in the case of a poor initial treatment response, where full dosage is used.
- Suggested supportive care guidelines:**
- Placement of a double lumen Hickman catheter: this facilitates the delivery of chemotherapy, antibiotics and parenteral nutrition as needed.
 - Nutritional consultation and follow-up: children with A-T may have more difficulty maintaining acceptable weight while receiving chemotherapy.
 - Baseline pre-chemotherapy neurology consult and brain MRI.
 - Blood cultures and early institution of broad spectrum antibiotics for fever with neutropenia, fever without neutropenia, or ill appearance (even if subtle change).
 - Diagnostic X-rays are generally avoided in A-T patients, however, they should be considered if necessary to deliver appropriate medical care. In some situations, modalities such as MRI or US may be used instead of X-rays.
 - Prophylactic septria.
 - Zantac or protonics.
 - IVIG may be considered in some cases, for example unusual viral infections such as adenovirus.

There is currently no one centre of expertise in the UK. It is recommended that clinicians treating a child with A-T for cancer for the first time talk to colleagues who have had recent experience of doing so. The A-T Society will be able to put you in touch with colleagues with appropriate experience either in the UK or abroad.

General anaesthesia

Dr Jon Davies, Consultant Anaesthetist

There has been scanty evidence to date on the risks posed by this very rare condition and precautions have advised ensuring a full evaluation of the various bodily systems prior to anaesthesia:

- neurological, in particular assessing cerebellar and bulbar function
- respiratory and cardiovascular in light of chronic lung disease and also the effects of increased pulmonary vascular resistance on cardiac function
- haematological, looking for malignancies resulting in pancytopenia and necessitating transfusion of blood and platelets pre-operatively

Patients are at increased risk of aspiration due to the neurological sequelae of the disease, and some may require post-operative ventilation/ventilatory support. They are also thought to be at risk of glucose intolerance and peri-operative serum glucose can be elevated. In view of the likelihood of immunodeficiency, good aseptic technique throughout the peri-operative period is obligatory. It is also wise to be judicious in the use of muscle relaxants in the presence of progressive neurological disease. Use of succinylcholine may cause hyperkalaemia in patients with significant neuropathy and muscle weakness.

A recent article by a group from The John Hopkins Hospital, Baltimore¹³ reviewed records on 21 patients with A-T, undergoing 34 episodes of general anaesthesia for a total of 41 procedures over a 15 year period (1995-2009). This is thought to be the largest published series to date. They found that patients can be anaesthetised with a risk comparable to that for other medically complex paediatric patients.

In their series all patients were seen in a multidisciplinary care centre, including respiratory, neurology and immunology specialists, allowing for disease-specific peri-operative optimisation and post-operative follow-up. There were no complications of anaesthesia during the peri-operative period, and no unexpected admissions to the paediatric intensive care unit (PICU). A quarter of the patients who went through the normal recovery unit required supplemental oxygen, usually via nasal cannulae, for up to 24 hours post-operatively. In view of the complicated patient population, all patients were anaesthetised

within an in-patient hospital setting, even though a fifth were able to go home on the same day of surgery. All patients, including those admitted to PICU, survived.

It is thought that unrecognised respiratory issues are likely to cause the most problems during the peri-operative period, and that critical care facilities should be available for stabilisation and optimisation. This is especially true for emergent/urgent procedures. Despite a high rate of pulmonary comorbidities in their patients, they found stable ventilator courses intra-operatively (as measured by end tidal CO₂, exhaled tidal volumes, fraction of inspired O₂, pulse oximetry, peak inflating pressures and respiratory rate). They

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attributed this to their strategy of managing their patients with pulmonary optimisation techniques including consultant evaluation, pulmonary function testing, treatment and follow-up.

See also:

Syndromes: Rapid Recognition and Perioperative Implications by Bruno Bissonette, Igor Luginbuehl, Bruno Marciniak and Bernard J Dalens. McGraw-Hill Medical. 2006

Anesthesia For Genetic, Metabolic & Dysmorphic Syndromes of Childhood by Victor C Baum & Jennifer E O'Flaherty. Lippincott Williams & Wilkins. 2007

Dietary management

Annette Brown, Speech and Language Therapist

Issues for dietary management in A-T

The co-ordination and other neurological problems that develop over time in A-T can compromise the nutrition and hydration of people with A-T in a number of ways. These problems with eating drinking and swallowing are known as 'dysphagia'.

Issues affecting people with A-T include:

- Difficulty in getting food to or into the mouth
- Reduced control of food in the mouth and/or drooling

The aim of dietetic intervention is to promote health and well-being by meeting nutritional needs and preventing or reducing the impact of complications such as infection, lack of energy and lack of coordination. Adequate nutrition is also essential to ensure appropriate growth.

- Difficulties in chewing and length of time required to form a bolus
- Difficulties in clearing the mouth and swallowing
- Food or liquid entering the lungs (aspiration) which may or may not cause coughing or choking
- Reflux of food or liquid from the stomach to the oesophagus

These factors can be exacerbated by symptoms such as fatigue and recurrent infections. They can reduce the intake and enjoyment of food and fluid, with the result that children with A-T often lose interest in eating. Poor nutritional intake leads to weight loss and under-nutrition, which in turn increases fatigue and vulnerability to infection and other illnesses.

Addressing these issues can require the support of both a speech and language therapist (SLT), who can help address the physical challenges to eating and drinking, and a dietician, who can help ensure that the child receives adequate nutrition.

Support from a speech and language therapist

It is important that parents, teachers and other carers of children with A-T keep a close eye on their ability to eat and drink. This should be backed up by regular reviews with SLT services. This should happen as a minimum annually, but it is advisable to make it more frequent, particularly when the symptoms of A-T are changing.

Many deaths from A-T occur as a result of lung disease. It is likely that dysphagia contributes to this, both directly through particles of food, drink and saliva getting into the lungs and indirectly in that poor nutrition can reduce the ability of the body to protect itself from or fight off infections. An SLT will be able to advise on strategies to make eating easier and reduce the risk of choking or aspiration. However these will vary from child to child according to how they are affected by A-T, the food or drink they eat and their own approach to this.

If aspiration is suspected, it may be appropriate to undertake video fluoroscopy to assess the situation. However, as this involves radiation, and A-T is associated with sensitivity to radiation, this should only be undertaken if it is important to clarify the situation.

Support from a dietician

The aim of dietetic intervention is to promote health and well-being by meeting nutritional needs and preventing or reducing the impact of complications such as infection, lack of energy and lack of co-ordination. Adequate nutrition is also essential to ensure appropriate growth.

Dietary management of children with A-T is similar to the management in other degenerative conditions. At the National A-T Centre, a registered dietician is a member of the multi-disciplinary team, working closely with medical staff and other allied health professionals including speech and language therapist. Locally, a registered dietician with paediatric experience will be able to provide local advice and support.

Appointments at the National A-T Centre are an opportunity to review nutritional status and identify changes which might affect nutrition. At each visit, an assessment is carried out including estimation of nutritional intake and review of weight, height and growth.

Dietary advice for the child and their family is based on individual circumstances. It may be particularly helpful at times of change, for instance a change of school, which can impact significantly on nutrition and fluid intake. The dietician will produce a written summary of recommendations after the visit and will co-ordinate and liaise with dietetic colleagues at the child's local centre where required.

Dietetic interventions tend to fall into one of three levels:

- General advice for children whose appetite is good and who are growing as expected.
- Advice for the child and family should encourage optimal nutrition and adequate hydration, encouraging a variety of foods based on the main food groups identified in the Eat Well Plate¹⁴ adapted to age and cultural requirements.
- Nutritional support for children experiencing difficulty with eating and drinking.
- Regular monitoring of weight and height is important to identify concerns at an early stage, preventing weight loss and under-nutrition where possible. Small frequent meals and snacks using nutrient-rich foods such as full-fat dairy products and food fortification should be encouraged. Oral nutritional supplements and other prescribable products available from the GP may benefit nutritional intake if they are taken. If there is a risk of aspiration, a SLT will advise on modification of texture, liaising with the dietitian about how this will affect intake of food and fluid.

- Enteral feeding using a gastrostomy or jejunostomy tube to supplement or replace oral intake.

Enteral feeding enables nutrition and hydration requirements to be met while reducing the risk of aspiration and associated infections. When efforts to maintain weight and fluid intake by mouth do not provide enough nutrition, the placing of a tube should be discussed with the family. Most parents are understandably reluctant to consider a feeding tube or gastrostomy, however discussion with another family with first-hand experience of the benefits can help.

The potential risks and benefits of the procedure should be discussed carefully giving every opportunity for the family and child to air their views and concerns. It should be made clear that having a gastrostomy is not an 'all-or-nothing' choice and that most people are able to continue to eat normally. However, a feeding tube can relieve a lot of pressure from trying to eat enough and thus make mealtimes more relaxed and enjoyable. It is essential that a child who is enterally tube-fed is in regular contact with their local dietetic team for advice and support, including adapting feeding regimens to changing nutritional requirements.

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Physiotherapy management

Janet Corderoy, Physiotherapist

The key aims of physiotherapy for children with ataxia-telangiectasia are to optimise and maintain functional activity. Physiotherapists will work with children and their families, involving them in all aspects of decision making with specific regard to physical activities, provision of equipment and advice offered in educational settings. They will liaise with the multidisciplinary team in health, education and social care to provide resources and the environment needed for each child. The aim is to assist the child to reach their potential and maintain their gross motor skills at an appropriate level. There should be ongoing assessment and review because of the changing nature of the condition, with the following points being considered:

Postural management

From an early age a 24-hour postural management system should be the goal. Optimising posture will be beneficial in maintaining functional ability, sitting and standing balance and respiratory function. It should include a discussion about night-time positioning and the provision of appropriate equipment to maintain a symmetrical posture with spinal integrity in all positions.

Orthotics

Orthotics should be considered where muscle imbalance or tonal change are causing muscle shortening or limit functional activity. Weight bearing, i.e. walking and standing, can assist in maintaining muscle length in the lower limbs. Resting splints worn at night time may be needed to maintain muscle length and foot position. Splinting may be introduced during the day to maintain safe and functional mobility. Review and assessment by an orthotist, in discussion with the physiotherapist, may be required for more complex splinting requirements.

Muscle strength and activity

All forms of activity are useful and are to be encouraged. This can include specific core strengthening exercises and all sports. Technology can assist with movement games, particularly when these can often be played while sitting. The focus will be on fun and this can be a valuable opportunity for social interaction for children and families.

Respiratory management

Where necessary, assessment and advice should be given to ensure management of secretions and early recognition of chest infections. Secretion clearance techniques may include breathing exercises, manual techniques or other adjuncts and can be play-based, for example blow-football. Regular activity and exercise will also form a significant part of optimising respiratory function.

Fatigue

Children will tire quickly which can affect their learning, physical exercise and social activities. They need appropriate rest times during the day which can involve actual sleep or quiet play.

Education

Advice can be offered around adaption of the PE curriculum as needed, access visits arranged to review the environment and advice given on use of equipment and/ or a specific exercise programme in school.

Social

It is important to encourage social activities that are not just school-based for a child's ongoing physical and emotional well being. This is often an invaluable opportunity to encourage sporting activities.

As children near the age of transition from paediatric to adult services, it is vital to identify the multidisciplinary input they will need. Local service provision may vary enormously from area to area and adult services may have waiting times to access services. Early referral to adult services should ensure the transition is as seamless as possible.

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Pubertal development

Children with classic A-T are at risk of pubertal delay or failure of onset of puberty manifesting as delayed or absent development of second sexual characteristics and amenorrhoea or irregular periods in girls. This can be also associated with absence or reduction of the pubertal growth spurt resulting in short stature in adult life. Pubertal delay and failure can be associated with increased FSH levels. Adult women with classic A-T are also at increased risk of premature ovarian failure resulting in premature menopause.

Pubertal delay and reduction of the pubertal growth spurt are only seen infrequently in children with variant A-T.

Data on pubertal development and progress in A-T is limited and it is recommended that pubertal development is assessed and monitored in all children with A-T. Children who demonstrate pubertal delay or pubertal failure should be investigated by a paediatric endocrinologist, with investigations that would be recommended in any child with pubertal delay or failure, to determine the cause of this problem.

Scoliosis

Although there are anecdotal reports about scoliosis developing in patients with A-T, there is currently no data available in the medical literature about the prevalence of scoliosis in patients with A-T, its age at onset, rate of progression or factors that contribute to it. Similarly, very little information is available regarding the outcome of surgery for scoliosis in patients with A-T.

All patients attending the National Paediatric A-T Clinic are assessed for scoliosis. A preliminary audit of this data has shown that 17% of children with A-T have scoliosis. The age at diagnosis ranged from 18 months to 14 years and the severity varied from mild to severe. Most of the patients with scoliosis had classic A-T, but it was also seen in a patient with variant A-T.

Based on this audit, it is recommended that all children with A-T are assessed and monitored for scoliosis. If scoliosis is identified, a referral to the

regional spinal service is recommended for further investigation to determine its severity and for its management. Parents should also be advised about the correct posture for their child in a wheelchair and during sleep by a paediatric physiotherapist and occupational therapist. A single X-ray to evaluate the severity of scoliosis can be performed but repeated spinal X-rays should be avoided. The possibility of follow-up spinal MRI scans can be considered.

Surgery for severe or progressive scoliosis should be undertaken in a tertiary care facility with a paediatric intensive care unit following pre-operative assessment by a respiratory paediatrician and immunologist jointly with a paediatric anaesthetist. Restrictive lung function is a major risk factor for adverse outcome after the start of mechanical ventilation in adolescent A-T patients. Surgery in A-T patients, where mechanical ventilation may be required, needs careful consideration.

A-T is a condition about which there is much that is unknown or poorly understood.

Our understanding is changing all the time, as is our scientific and medical knowledge and the range of medical and therapeutic interventions available to us.

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It can be downloaded from our website www.atsociety.org.uk, where you will find much more information on A-T and the support available in the UK.

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