International Conference on the Clinical Science of Ataxia–Telangiectasia, University of Birmingham 14–15 October 2004

Commentary

In the past few years, the biochemistry of the ataxia–telangiectasia mutated (ATM) protein and our knowledge of its cellular functions has surged ahead. The neurology of ataxia–telangiectasia (AT), including its presenting features in early childhood, as well as its progression and further ramifications in early adulthood, were discussed at the international conference on AT in Birmingham, UK.

Video clips from the Johns Hopkins Hospital, Baltimore, Maryland, USA, were used to show the wide variety of movements which can occur. Nine measurable traits were described (height for weight, scores for feeding difficulty, swallowing, eye movements, standing ability, gait, head movements, limb movements, and neuropathy) and it was shown how these were similar between affected siblings but different between families; the implication being that other genetic or environmental influences may be important for this remarkable variation. It was also suggested that there may not be a continuous decline of neurological function beyond early adulthood and that early neurological features may not necessarily be a predictor of late ones. The same scoring system is used in the Nottingham AT Clinic. Significant variation in the neurological presentation was demonstrated: patients who were compound heterozygotes for the ATM gene *5762 ins137* had a slower progressive course.

An important point emphasized, was that the neurological problems in AT are not solely due to degeneration of the cerebellum but that other discrete parts of the brain are also involved. One consequence of the cerebellar deterioration is the abnormal eye movements associated with AT.

Cerebellar metabolism has been investigated using proton magnetic resonance spectroscopy (^{1}H-MRS) and magnetic resonance imaging (MRI). Recently in Sheffield, 12 adults with AT and 12 healthy control participants underwent MRI and long-echo time ^{1}H-MRS at 3 tesla. All of the patients with AT showed marked cerebellar atrophy of the vermis and hemispheres.

The findings also suggested an increased choline signal in the cerebellum of patients with AT. This could reflect gliosis, a common feature within the AT cerebellum postmortem that may be present as a reaction to oxidative stress within cerebellar neurons.

There are several other disorders that may, initially at least, be mistaken for AT. The closest of these to AT is ataxia–telangiectasia-like disorder caused by the *hMRE11* gene. There are also other disorders including ataxia oculomotor apraxia 1 (AOA1), ataxia oculomotor apraxia 2 (AOA2) and spinocerebellar atrophy with axonal degeneration.

Mice with AT have provided some important insights into the neurodegeneration associated with loss of ATM. Following exposure to particular types of damage, brain cells in these animals were unable to die and be lost from the tissue as would normally happen. This led to the retention of damaged cells in the brain. An important role of ATM, therefore, may be to remove genetically damaged nerve cells during development to reduce neurodegeneration.

Variation in the types of mutation seen in the ATM gene affects the expression of ATM protein and this variation may relate to the clinical presentation. One of the most reliable ways of confirming the diagnosis of AT has been the elevated level of a fetal liver protein (AFP) in the serum, but the role of this AFP in the development of AT is unknown. Curiously, the level of AFP is also raised in another disorder, AOA2, which shares some of the neurological features of AT.

A very important feature of patients with AT is their predisposition to tumours, the greatest risk is for lymphoid tumours. While components of a treatment regime may have to be modified in order to take account of the increased sensitivity of AT patients to some agents, this has not prevented successful treatment of some tumours. It is important that a person with AT is not under-treated but receives an adequate dose of cytotoxic therapy aimed at curing their leukaemia or lymphoma. Radiotherapy should, of course, be completely avoided.

Another area of both interest and some mystery is the immunology of AT. Laboratory indicators suggest that all people with AT have variable degrees of immunodeficiency which does not always reflect their susceptibility to infection. For a minority, however, the immunodeficiency is more severe and they develop significant infections that can be difficult to treat and may result in a stay in hospital; approximately 10–15% need immunoglobulin replacement.

In contrast, as people with AT get older they do show a clear increase in lower respiratory tract infections. Another consequence of the neurological deterioration is the development of swallowing problems and loss of the cough reflex causing aspiration and increased susceptibility to pulmonary infections.

This conference was successful in bringing together many different clinicians from within the UK and abroad responsible for the clinical management of AT. The meeting would not have been possible without the tireless efforts of the Ataxia–Telangiectasia Society.

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