

# The clinical variability of Ataxia Telangiectasia – an update



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## Summary

- Ataxia telangiectasia belongs to the group of DNA repair disorders and presents with a progressive neurodegenerative disorder
- Affected individuals can exhibit radiosensitivity, immunological abnormalities, respiratory problems and an increased malignancy risk
- The clinical phenotype of ataxia telangiectasia is variable and includes individuals with only mild neurological signs and late onset. In these patients, the condition is likely to be sometimes misdiagnosed or not recognised.
- It is important to be aware of this diagnosis, as patients require specific surveillance for malignancy and management by a multidisciplinary team.

## Introduction

Ataxia Telangiectasia (AT) is an autosomal recessive hereditary multisystem disorder with an estimated prevalence of 1:400,000 in the UK.<sup>1,2</sup>

The disease is caused by mutations in the ataxia telangiectasia mutated gene (ATM, 11q22.3), which encodes a protein kinase that has an important role in DNA repair.<sup>3</sup> Affected individuals with classical AT typically present in childhood with a progressive neurodegenerative disorder that is associated with immune defects and a predisposition to malignancy. Life expectancy in classical AT is significantly reduced and affected individuals often die from respiratory complications or malignancy. It is increasingly recognized that a less severe form of the disease (variant AT) can be seen in adults, which is likely to be sometimes misdiagnosed.

In this review, we will provide a brief overview on clinical features, diagnosis and current management guidelines of classical and variant ataxia telangiectasia, as well as discussing genetics and pathophysiology of the condition.

## Overview of subtypes and clinical features

Ataxia Telangiectasia shows significant genotype-phenotype correlation. Mutations in classical AT cause complete absence of ATM kinase activity, which relates to a severe phenotype with onset in early childhood. In contrast, individuals with variant ataxia telangiectasia have mutations that leave some residual ATM kinase activity. This corresponds to a much milder clinical phenotype, characterised by late onset and often predomi-

nantly neurological involvement, rather than associated systemic complications.<sup>4,5</sup>

## Classical ataxia telangiectasia

Children with classical AT usually show no abnormalities in the first months and often sit and walk at the normal age. However, clumsiness, unsteadiness or abnormal eye-movements can already be apparent at that age and gradually progress during childhood. Most children with classical AT are wheelchair bound by the time they enter secondary school and present with a progressive cerebellar syndrome, that is frequently accompanied by extrapyramidal signs (dystonia, chorea), a peripheral neuropathy and myoclonus.

The eye movement disorder with prominent oculomotor dyspraxia is a distinguishing feature of the disease, particularly if accompanied by oculo-cutaneous telangiectasia which typically develop before the age of ten (Figure 1).

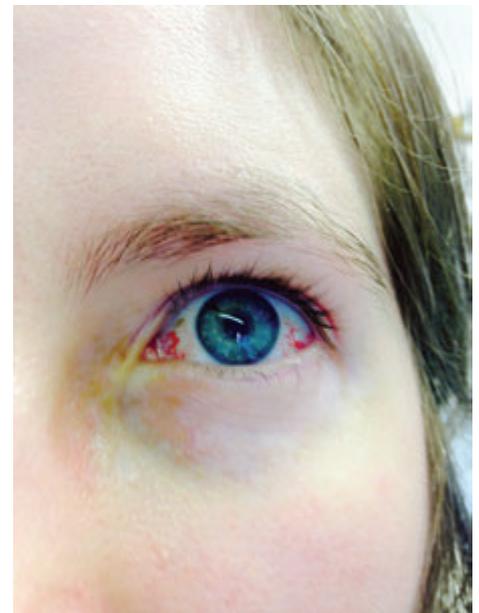


Figure 1. Ocular telangiectasia in a 21-year-old woman with classical ataxia telangiectasia.

Variable immunological abnormalities are common, including immunoglobulin deficiency, reduced numbers of lymphocyte subsets and poor vaccine response. Furthermore, many individuals with classical AT have a range of respiratory complications, caused by a combination of neurological problems (in particular poor swallow and respiratory muscle weakness), immune defects (leading to respiratory tract infections and risk of

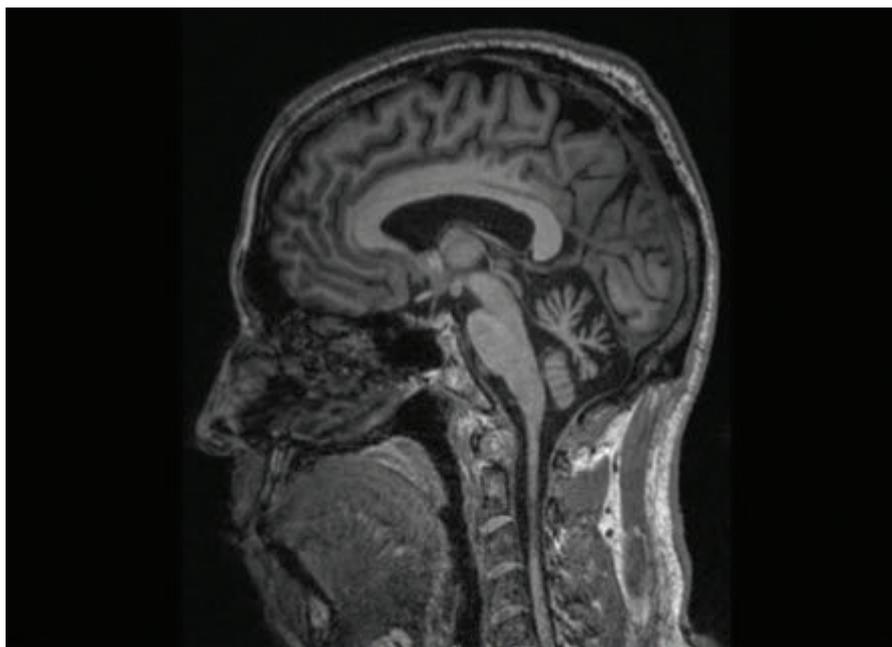


Figure 2a. Sagittal T1 weighted MRI (40 year-old man with variant ataxia telangiectasia), showing cerebellar atrophy.

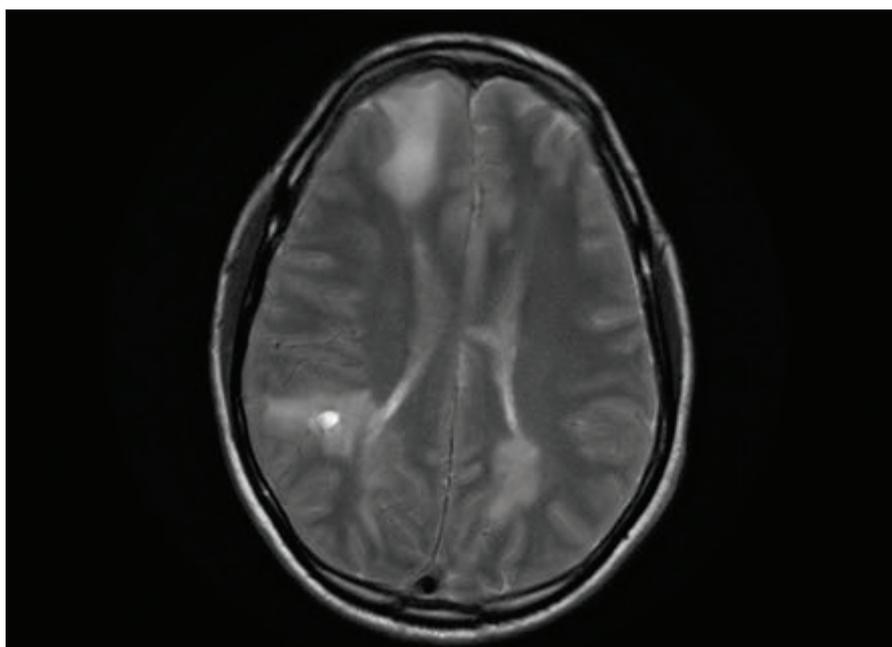


Figure 2b. Axial T2 weighted MRI (27 year-old man with classical ataxia telangiectasia), showing bi-bilateral areas of white matter high signal with a cyst-like lesion.

bronchiectasis) and other potential complications (i.e. pulmonary complications from chemotherapy, interstitial lung disease, etc). Classical AT is associated with a predisposition to cancer (in particular lymphoid and brain tumours) with an estimated malignancy risk of 25-30%. Together, the combination of systemic complications and progressive neurological decline lead to a severe phenotype and reduced life expectancy with a reported median survival age of 25 years.<sup>6</sup> The cause of death in classical AT is related to respiratory complications in the majority of individuals, but about a fifth die from malignancy.

#### **Variant ataxia telangiectasia**

The presence of some residual ATM kinase activity relates to a less severe phenotype with later onset, often only in adulthood. Individuals typically present with progressive neurological symptoms, most commonly extrapyramidal (dystonia, tremor, chorea) or cerebellar symptoms.<sup>7</sup> These symptoms relate to the abnormal brain regions that are also implicated in functional imaging and pathological studies.<sup>8</sup> Features of a peripheral neuropathy or amyotrophy are not invariably present; likewise, eye movements can be normal although some have slow saccades, nystagmus, broken pursuit or oculomotor

apraxia. Conjunctival or peripheral telangiectasia can be absent and many individuals with variant AT have no evidence of immune defects or respiratory complications. Furthermore, the increased radio-sensitivity is not as large and the spectrum of malignancies that these patients are susceptible to is different to the classical form.<sup>9</sup>

The phenotype of variant AT can be very mild, for example some individuals only have a dystonic tremor or a mild ataxia neuropathy. It therefore seems likely that the condition is sometimes not recognised or misdiagnosed.

Whilst neurophysiology in variant AT can be normal, many patients have evidence of a sensory-motor neuropathy or amyotrophy and need to be managed accordingly. MRI brain scans in adults with variant AT often show cerebellar atrophy but white matter abnormalities, intracerebral telangiectasia and fluid collection (probably from 'leaky' capillaries) can also occur (Figure 2).<sup>10</sup> The frequency of these changes is unknown and we currently arrange baseline MRI scans in all adult patients with AT.

There are currently no epidemiological studies on life expectancy and clinical course of variant AT although there is likely to be significant variability within the group, possibly relating to specific mutations. However, several individuals over the age of 50 (some of whom are still relatively independent) have been reported in French, Dutch and American cohorts, which corresponds to our experience in the UK.

#### **Genetics, pathophysiology, diagnosis (MT)**

Patients with typical classical A-T all show biallelic mutation of the *ATM* gene that results in total loss of ATM kinase activity, irrespective of whether any ATM protein is expressed. In some classical patients mutant ATM protein without activity is expressed. The key is absence of ATM kinase activity. In contrast, milder forms of A-T are associated, in all cases, with expression of some ATM protein with some activity. In these circumstances the origin of protein is from ATM missense mutations, producing mutant protein but with residual activity, or leaky splice site mutations producing a low level of normal ATM with activity of course.<sup>11</sup>

Interestingly, therefore, different milder patients will express different ATM proteins. In the UK a significant proportion of milder A-T patients express normal ATM from the same leaky splice site mutation; these patients might be expected to have some uniformity of neurological presentation, and possibly different from other milder patients with mutant proteins. Indeed, there is some scope for several distinguishable neurological phenotypes in milder patients with different mutant proteins each with some residual activity. These different phenotypes may be dependent on the level of protein expressed, the range of targets of the different ATM proteins etc. These relationships are not

understood at present and there is interesting work to be done here.

The diagnosis of classical A-T usually occurs at the age of 2-4 years, because of early onset unequivocal signs. Approximately half of all A-T patients in the UK are adults and a good proportion of these have a milder phenotype. Significant numbers were diagnosed as adults although the age of onset is less clear and may be in either childhood or adulthood. The diagnosis of atypical and milder A-T may occur at any age, with the oldest patient diagnosed in the UK being 64y. With one exception so far, all milder A-T patients will express some ATM that has reduced activity compared with normal. Therefore any potential A-T patient of any age can have the diagnosis confirmed by analysing the activity of their ATM. This is done by carrying out the assay in a lymphoblastoid cell line made from the patient's blood. In those patients with reduced activity, the subsequent identification of *ATM* mutations will inevitably show the presence of sequence changes consistent with the expression of mutant protein. Interestingly, an increased level of serum AFP is a good marker for classical A-T and may also be associated with milder A-T although whether this is true for all milder A-T is not known and perhaps should not be relied on as an indicator for all A-T.

Finally, there is a milder and much rarer form of A-T (ATLD) caused by mutation, not of the *ATM* gene, but of *MRE11*.<sup>12</sup> The same *ATM* kinase assay described above, will also identify these patients, because they also have defective *ATM* kinase activity. The reason for this is because full *ATM* kinase activity is dependent on the *Mre11* protein.

### Management

All individuals with a diagnosis of classical or variant AT should be managed by a multidisciplinary team with experience in the condition. The team should include a respiratory physician, immunologist, geneticist, neurologist and various therapists who will co-ordinate care with local services. In the UK, patients are assessed annually or bi-annually in the National ataxia telangiectasia clinics for children (Nottingham) or adults (Papworth Hospital) (Figure 3). Guidelines for the management of children with AT have recently been published by the ataxia telangiectasia society together with the Nottingham team.<sup>2</sup>

It is recommended that adults with variant AT also undergo a multidisciplinary assessment, as some will have immune defects or respiratory complications. Furthermore, all adults with AT should receive genetic counselling including guidance on the increased risk of cancers. Women with AT should have annual breast MRI from age 25, heterozygote carriers (whose malignancy risk is also increased<sup>13</sup>) should be offered 18-monthly mammograms from the age of 40 years until the age of 50, after which they receive three-yearly mammograms as part of the National Breast Screening programme. Individuals with AT often have increased radiosensitivity and it is important to limit X-ray exposure and be aware of increased toxicity from chemotherapeutic agents.

Unfortunately, disease-modifying agents for ataxia telangiectasia have as yet not been identified and neurological management of adults is therefore is symptomatic. Drug treatments including levodopa, amantadine, trihexiphenidyl, baclofen or clonazepam are useful in some patients, particularly those with predominant extrapyramidal presentations. Furthermore selected patients may be suitable for deep brain stimulation.

Figure 3

#### Contact Details for National Ataxia Telangiectasia Clinics in the UK.

Nottingham Children's AT Centre  
Dr Mohnish Suri, Consultant Clinical Geneticist,  
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T: +44 (0)115 9627728.

Papworth Adult A-T Centre  
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