A patient with evolving bronchiectasis

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A 7-year-old girl was referred with a history of recurrent chest and upper respiratory tract infections since infancy. She had a chronic productive cough without features of asthma (e.g. worsening at night or with activity) and marked nasal symptoms (blocked nose, rhinorrhoea). Further history revealed no specific allergies although there was a vague history of atopy. The girl's mother had chronic sinusitis. The patient's stools were normal in consistency and frequency. Another major complaint pertained to her 'slowness'. Her mother noted that she was sometimes off balance.

The patient had been diagnosed with 'immune deficiency' based on subnormal immunoglobulin levels and had been started on monthly immunoglobulin replacement therapy. However, she had not had other organ infections.

Examination revealed a tired-looking girl with no active respiratory distress. Lack of facial expression, without facial weakness as such, was a prominent observation. Her oxygen saturation was 92% in room air. She had clubbing but no lymphadenopathy. She was not dysmorphic and had no stigmata of a hyper-immunoglobulin E (IgE) syndrome (eczema, coarse facial features). She had early telangiectasia on her skin (over both thighs) and bulbar conjunctivae. Her ear, nose and throat (ENT) examination revealed allergic shiners and middle ear fluid. She also had marked nasal turbinate enlargement. There was no halitosis. She had a herpes labialis. Her chest revealed a Harrison's sulcus (left more than right). Crepitations (coarse) were heard in both mid-zones. She had no active wheezing. Her heart was clinically normal and she was not in cardiac failure. Neurological examination revealed cerebellar signs including very mild ataxia (mainly revealed by her inability to perform tandem walking), past-pointing and dysarthria. Performance of fine alternating movements appeared clumsy. All her deep tendon reflexes were brisk bilaterally. She was drooling but seemed able to swallow normally. She appeared mentally slow.

Total and subclass immunoglobulin levels were normal at the time of her most recent visit but she had received immunoglobulin replacement that week. Chest radiographs showed bilateral mid-lobe bronchiectatic changes with tram-track signs. An earlier computed tomography (CT) scan revealed bronchiectasis. Magnetic resonance imaging (MRI) scans of the brain revealed mild cerebellar atrophy. A highly elevated alpha-fetoprotein (AFP) level (103 µg/l) was noted.

In summary, the patient had a congenital immune deficiency with bronchiectasis and new neurological signs. The differential diagnosis was: (*i*) ataxia telangiectasia (AT); (*ii*) AT-like disorder without telangiectasia; (*iii*) common variable agammaglobulinaemia; (*iv*) gastro-oesophageal reflux/cricopharyngeal inco-ordination; and (*v*) primary ciliary dyskinesia.

A diagnosis of AT was confirmed by the elevated AFP level.

No specific therapy was prescribed for this patient. Immunoglobulin replacement, chest physiotherapy and antibiotics as needed have been continued. Some of the experimental therapeutic strategies outlined below are being considered.

Discussion

AT has been reported previously from South Africa,[1-3] but it remains a rare condition.

AT is regarded as one of the neurocutaneous disorders and it links pathology in the respiratory and central nervous system (CNS). It results from a mutation in the AT-mutated (ATM) gene. This is an autosomal-recessive neurodegenerative disorder with immune deficiency, neurodegenerative lesions and malignancy potential. It is now classified as one of the chromosomal instability syndromes (Table I).

TABLE I. CHROMOSOMAL INSTABILITY SYNDROMES[6]

Ataxia telangiectasia
Nijmegen breakage syndrome
Bloom syndrome
Fanconi anaemia
Immunodeficiency, centromeric region instability, facial anomalies syndrome
Xeroderma pigmentosum
Cockayne's syndrome
Trichothiodystrophy
Rothmund-Thomson syndrome

The protein coded by this gene forms part of the protein kinase family. It is a large protein containing 3 056 amino acids with different functional domains. Activity of this protein is increased after ionising radiation and double strand breakage (DSB).[4] In 2005, Löbrig and Jeggo[5] eloquently reviewed the co-operation between the repair and checkpoint function of ATM function. A primary sensor namely the Mre11-Rad50-Nbs1 (MRN) complex senses the DSB and that leads to activation of the ATM gene. A variety of ATM-dependent substrates will then take part in multiple steps via cell cycle checkpoint arrest and repair.

DNA double-stranded breaks (DSBs) initiate a molecular response to repair DNA or activate apotosis.[7] Repair occurs via non-homologous end-joining (NHEJ) or homologous recombination (HR). These distinct pathways operate at different stages of CNS development. HR is critical for proliferating cells while NHEJ is critical for differentiating cells.

In this condition immune dysfunction has a variable age of onset. There may be abnormal thymic function as well as lymph node follicular dysgenesis. The predisposition to infections varies among patients, from unnoticed to serious and frequent episodes of severe infection. It is interesting to note that upper respiratory tract infection is rarely progressive, but lower tract infections increase with age and could be partially ascribed to the progressive abnormalities of chewing and swallowing with an increased risk for aspiration. Opportunistic infections, specifically *Candida,* mucosal and cutaneous infections are also rare compared with in other immune-suppressed patients.[8] Common warts, however, have been noted more commonly in patients with AT, but none of the patients who received live viral vaccines had any complications.[8]

The CNS manifestations vary widely and 10 different traits have been described. The interesting phenomenon is that ataxia telangiectasia varies among families, but is stable within a specific family. Ataxia telangiectasia is possibly due to other genetic or environmental influences.[9] By the age of 2 - 3 years ataxia may be visible, wherafter the telangiectasia usually follows ataxia in development.[10] Ataxia telangiectasia can be diagnosed in the absence of telangiectasia. The diagnostic criteria used at Johns Hopkins Children's Centre are set out in Table II.

Cabana *et al.*[11] recommend strongly that toddlers and children with undiagnosed and progressive ataxia should have their AFP levels tested. This is important in the optimal treatment of the immunodeficiency as well as in the early identification of individuals potentially at risk for malignancies.[11]

Treatment options are listed in Table III, but most of these are nonspecific or experimental.

Life expectancy is generally 19 - 25 years.[15] Life expectancy does not correlate with level of neurological impairment.

TABLE II. DIAGNOSTIC CRITERIA FOR AT[11]

Neurological features
Ataxia that starts in the first 2 - 3 years of life
Oculomotor signs and dysarthria round about schoolgoing age
Movement disorders, progressive ataxias, hypomimia of the face, unco-ordinated swallowing and peripheral neuropathy
One or more of the following
Ophthalmic telangiectasia
Raised α-fetoprotein (AFP) after 1 year of age
Chromosomal breakage, spontaneous or induced

TABLE III. TREATMENT OPTIONS – ATAXIA TELANGIECTASIA

Immune deficiency
Regular immunoglobulin replacement therapy 200 - 400 mg/kg/month
Bronchiectasis
Physiotherapy
Bronchodilators
Antibiotics as per indication
CNS damage – treatments are experimental[12-14]
Corticosteroids
Iron chelators
Gabapentin

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