Rare disease

Ataxia telangiectasia: learning from previous mistakes

Naveen Kumar, Puneet Aggarwal, Nishanth Dev, Gunjan kumar

Department of Internal Medicine, PGIMER & Dr Ram Manohar Lohia Hospital, New Delhi, India

Correspondence to Dr Puneet Aggarwal, puneetaggarwal4u@gmail.com

Summary

Ataxia telangiectasia is an early onset neurodegenerative disorder. We report a case of childhood onset ataxia and ocular telangiectasia, presenting with pulmonary infection. The patient was diagnosed as ataxia telangiectasia. The patient succumbed to death owing to late diagnosis and sepsis.

BACKGROUND

Ataxia telangiectasia (AT) is a multisystem disorder characterised by progressive cerebellar ataxia, oculocutaneous telangiectasia, susceptibility to cancer, immunodeficiency, sinopulmonary infections and sensitivity to ionising radiation. Lack of awareness about this disease leads to diagnostic delay, and patients present as adult with complications.

CASE PRESENTATION

A 15-year-old boy presented to our hospital with fever, cough with expectoration and breathlessness for 20 days. There was a history of many such episodes in the past and multiple admissions to hospitals. According to his parents, he had an unsteady gait with easy fall and slurred speech since the age of 4 years. He was a normal-term-born child, with early normal developmental milestones. At the age of 9 years, he discontinued schooling because of difficulty in walking, and by the age of 13, he was chair bound. He had abnormal choreoathetotic movements of the body, tonic posturing of limbs and redness of the angle of the eye, starting at the age of 6 years. His parents had a second-degree consanguineous marriage. His other siblings and first-degree relatives were healthy.

On physical examination, the patient had a dull expressionless face, thin build (body mass index 16.87 kg/m^2), and a stooping posture. His blood pressure was 112/76 mm Hg; pulse rate 110/min; respiratory rate 26/min; and axillary temperature 101°F . He had coarse dry hair and skin, telangiectatic vessels on the bulbar conjunctivae, and arcus juveniles (figure 1). He was in respiratory distress, with coarse crackles in both lung fields and bronchial breath sound in the right infrascapular area. Neurological examination showed mental slowness with poor responses, and dysarthric speech. Fundus examination was normal. He had ocular-motor apraxia with decreased voluntary movements of the eyes. Examination of other cranial nerves and the sensory system was normal. There was disuse atrophy of all the extremities. Deep tendon reflexes were diminished and bilateral plantar response was flexor. He had bilateral cerebellar signs: horizontal nystagmus; hypotonia; impaired control of skilled movements because of marked dysmetria;

intention tremors with past pointing. He was unable to walk owing to ataxia and weakness. There were choreoathetotic movements of the upper limbs. Cardiovascular and abdominal examinations were within normal limits.

INVESTIGATIONS

Investigations done for the patient during previous admission included contrast-enhanced CT (figure 2) which was suggestive of marked cerebellar atrophy. Initial laboratory workup revealed: haemoglobin 10.2 g/dl, white blood cell count $26\,100/\text{mm}^3$, toxic granules in the peripheral smear, normal urinalysis and blood biochemistry panel. Chest x-ray showed right middle zone and bilateral lower zone consolidation. Sputum culture grew *Klebsiella*.

Keeping a provisional diagnosis of pulmonary infection with AT, serum alpha fetoprotein (AFP) was done as screening test, which was elevated (158 IU/ml, normal 0.5–5.5 IU/ml). Immunoglobulin (Ig) profile was deranged: IgG was normal (1055.6 mg/dl; 630–1400), IgA level was reduced (35.8 mg/dl; 60–300), IgE level was reduced (0.0012 mg/dl; 0.002–0.2 mg/dl) and IgM level was raised (353.6 mg/dl; 30–148). ATM protein level was also reduced. The diagnosis of AT was made based on clinical and laboratory findings.

DIFFERENTIAL DIAGNOSIS

- Cerebellar palsy
- Friedrich's ataxia

Figure 1 Bilateral conjunctival telangiectasia with arcus juveniles.

Figure 2 CT showing marked cerebellar atrophy.

- Ataxia with oculomotor apraxia
- Ataxia telangiectasia

TREATMENT

The patient was treated with oxygen supplementation, intravenous antibiotic based on the culture reports of sputum, chest physiotherapy, and respiratory support.

OUTCOME AND FOLLOW-UP

The patient succumbed to overwhelming sepsis owing to delayed presentation to the hospital and the subsequent delay in the diagnosis.

DISCUSSION

AT, also known as Boder-Sedgwick syndrome, is a predominantly cerebellar form of spinocerebellar degeneration. It is a multisystem disorder with varied manifestations, which can be classified among immunodeficiency diseases, disorder with abnormal radiosensitivity, neurocutaneous syndromes, chromosomal instability/DNA repair defects syndromes, cancer-prone genetic disorders, and progeroid syndromes.

It was first described by Syllaba and Henner in 1926.¹ The syndrome was later named after Louis Bar, who first described it in detail, in a Belgian child. The term ataxia telangiectasia was coined by Boder *et al*² in 1958, who recognised its familial incidence and the autosomal recessive mode of inheritance.

The responsible gene is *Ataxia telangiectasia mutated (ATM) gene*, which has been mapped to chromosome 11q22-23. It recognises and corrects errors during DNA duplication by activating the cellular checkpoints protecting against any damage, and destroys the cells when it can not be corrected. Without it, exposure to ionising radiation (x-ray, but not to ultraviolet rays) and certain radiomimetic chemical results in chromatid break.

AT is a rare disease with a prevalence of about 1 in 100 000 population.^{3 4} Men and women are equally affected and there are no racial or regional preferences. However, it is more common among ethnic groups with a high frequency of consanguinity. Parents of our patient also had history of consanguineous marriage.

The median age of death is approximately 20 years, usually because of respiratory failure (50%), cancer (15%) or a combination of both (remaining cases).

These patients are hypersensitive to ionising radiation and radiomimetic drugs, and need treatment modifications.

The hallmark neurological manifestation is ataxia. It starts in infancy, but it becomes apparent when the child begins to walk. Affected children have a peculiar 'little clowns' gait, which is highly suggestive of AT. Ataxia is truncal early in the course of the disease, affecting sitting, standing and gait. The normal development of motor system between ages 2 and 5 years masks the progression of ataxia. At this stage, it is often wrongly diagnosed as cerebral palsy, acute infectious ataxia, or ataxia with oculomotor apraxia. After the age of 5 years, ataxia rapidly progresses, involving peripheral coordination. Patients often require a wheelchair by the age of 10 or 11 years.

Patients have other cerebellar signs like dyssynergia, intention tremor of the extremities, progressive dysarthria and muscular hypotonia. As the child matures, other features, such as choreoathetosis (most prominent extrapyramidal feature, mask ataxia if severe), myoclonic jerks of the trunk and extremities, progressive dystonia of the fingers, may appear. Patients have characteristic dull mask-like facies, stooping postural attitudes and slow initiation and performance of voluntary activity. Early mental development is normal, but slows after 10–12 years. If patient survive till adult, he can have progressive distal muscular atrophy and fasciculation with relative preservation of proximal strength; involvement of dorsal column of the spinal cord with gradual loss of vibration and position sense, and axonal peripheral polyneuropathy.

Oculocutaneous telangiectasia usually appears at the age of 3–7 years. Conjunctival telangiectasias are first noted in the interpalpebral bulbar conjunctiva away from the limbus. Eventually, it becomes generalised and simulates conjunctivitis. Cutaneous telangiectasias are seen on the ears, palate, bridge of the nose, later extends to the neck, the dorsum of the hands and feet. Progeric changes such as atrophic and sclerotic skin giving mask-like appearance, grey hair and loss of subcutaneous fat, occur in 90% of patients. Other skin manifestations are: seborrhoeic dermatitis, atopic dermatitis, café au lait spots and vitiligo.

Abnormal eye movements are universal finding in children with AT. The most common abnormalities are nystagmus, impaired voluntary ocular motility (voluntary gaze apraxia, disorders of smooth pursuit and limitation of upward gaze). Oculomotor apraxia may precede appearance of the telangiectasias.

Our patient also had typical feature of progressive neurological manifestation in form of ataxia, oculomotor apraxia, cerebellar signs with progressive muscle atrophy and ocular telangiectasia.

Immunodeficiency affects approximately 70% of AT patients. Typically, levels of IgA, IgE and IgG (particularly IgG 2 and 4) are reduced and IgM is increased because of failure of switch process from IgM to other immunoglobulin. In addition, all patients have a small or absent thymus, and function of both helper and cytotoxic T cell are reduced. Immunodeficiencies lead to recurrent infections in our patient also.

Patients of AT are at higher risk of cancer, lifetime cancer risk being 10–38%. In children, more than 85% of neoplasms are acute lymphocytic leukaemia or lymphomas. In adults with AT, solid tumours (stomach cancer, breast cancer, medulloblastoma, basal-cell carcinoma, ovarian dysgerminoma, leiomyoma and thyroid cancer) are more frequent.

Patients are predisposed to respiratory tract infections due to immunodeficiency and defect in chewing and swallowing due to progressive neurological impairment. Repeated infections are present in 48–81% of patients. Recurrent pneumonia results in bronchiectasis and advanced lung disease, ultimately leading to death in 50% of patients.

Approximately 75% of patients with AT may have growth retardation and endocrine disorders, especially ovarian agenesis, testicular hypoplasia and insulin-resistant diabetes. The short-and-thin stature of the patients is similar to other DNA homeostasis disorders, such as Bloom's syndrome and Fanconi's anaemia.

Ataxia-Telangiectasia Clinical Center, Johns Hopkins Medical Institutions proposed a criteria⁵ for diagnosis of AT.

A case is diagnosed when a patient with ataxia or significant motor incoordination has a raised AFP ($>2\times$), along with three of the following four characteristic clinical features:

1. Incoordination of head and eyes in lateral gaze deflection
2. Ocular telangiectasia
3. Gait ataxia associated with an inappropriately narrow-base
4. Lymphopenia (especially of CD4) and immunoglobulin deficiencies (mainly of IgA and IgG subclasses)

In patients having less than three of these features, radiation-induced chromosomal breaks in lymphocytes have to be demonstrated to confirm the diagnosis. In siblings of patients with AT, who are >1 year of age and have ataxia, a raised AFP confirms the diagnosis.

Our patient fulfilled the criteria and hence a diagnosis of AT was made.

The diagnosis is usually suspected clinically by identification of both ataxia and oculocutaneous telangiectasia.

Serum AFP level is increased in 90–95% of patients (generally not beyond 300–400 ng/ml), and is the first screening test in suspected cases. A raised CEA level supports the diagnosis. Radiosensitivity can be demonstrated by colony-survival assay. Sufferers often have immunological abnormalities: dysgammaglobulinaemia (decreased IgA, IgG2, IgG4 and IgE, increased IgM); abnormal cellular immunity (low lymphocyte count, low T-lymphocyte proliferation in the presence of mitogens and poor response to skin tests to antigens). ATM protein can be measured by immunoblotting, which can be either reduced, or dysfunctional. Cytogenetic and molecular testing confirms the diagnosis. MRI may show signs of cerebellar atrophy.

Currently there is no cure, or any treatment to slow the progression of the disease. Therapy for AT is supportive: antibiotics for infection, physiotherapy for bronchiectasis and contractures. γ -globulin injections may be given to help supplement a weakened immune system. Patients should be aggressively screened for malignancy, especially after the first decade of life and good respiratory care should be provided at an early stage.

However, even though our patient had typical presentation of AT, diagnosis was not made till the age of 15 years because of unawareness of the disease, and patient was exposed to ionising radiation in form of contrast-enhanced CT. The present case is an illustration of the fatal nature of the disease in its late stage. With heightened awareness among clinicians, AT can be diagnosed at an early stage and morbidity and mortality can be reduced.

Learning points

- Ataxia telangiectasia should be suspected in a patient of progressive neurological impairment in form of ataxia associated with telangiectasia.
- No radiation exposure should be given to a patient of ataxia telangiectasia as it predisposes to cancer.
- Recurrent sinopulmonary infections are common in ataxia telangiectasia.
- High clinical suspicion and early diagnosis are back bone to reduced mortality and morbidity.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Syllaba L, Henner K. Contribution a l'indépendance de l'athetose double idiopathique et congenitale. *Rev Neurol (Paris)* 1926;1:541–62.
2. Boder E, Sedgwick RP. Ataxia-telangiectasia a familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. *Pediatrics* 1958;21:526–54.
3. Su Y, Swift M. Mortality rates among carriers of ataxia-telangiectasia mutant alleles. *Ann Intern Med* 2000;133:770–8.
4. Swift M, Morrell D, Cromartie E, et al. The incidence and gene frequency of ataxia-telangiectasia in the United States. *Am J Hum Genet* 1986;39:573–83.
5. Lefton-Greif MA, Crawford TO, Winkelstein JA, et al. Oropharyngeal dysphagia and aspiration in patients with ataxia telangiectasia. *J Pediatr* 2000;136:225–31.

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