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Case Reports

Ataxia Telangiectasia: Case Report of Three Affected Brothers and Review of the Literature

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Abstract Ataxia telangiectasia (AT) is a rare autosomal recessive disease resulting in progressive degeneration of multiple systems in the body. The presentation is usually in early childhood with ataxia and unrelentingly, they become chair-bound by the age of ten. Immunodeficiency and predisposition to cancer are other prominent features. In 1995, a large gene was identified on chromosome 11q22-q23, known as AT Mutant (ATM) gene and the lack of its gene product, the ATM protein, is responsible for the clinical features of AT. A Chinese family with three affected brothers is described in this case report and points of interest are discussed, also a review on this disease is presented at the end.

Key words Ataxia telangiectasia

Introduction

Ataxia telangiectasia (AT) was first described in the medical literature in the mid-1920s, but was not named as a specific disorder until 1957 by Dr. Elena Boder. The incidence is about 1 in 40,000-300,000 live births. Males and females are equally affected and there is no racial nor geographical preferences.

Case Report

History

Three brothers (NSL, NSM, NSN), aged 18, 13 & 11, were new immigrant from China and they all have history of progressive difficulty in walking since age 9.

The index case was NSM, aged 13, who was admitted through AED with history of suspected convulsions. He came to Hong Kong with his younger brother only 1 week prior to presentation. The "convulsive" movements were described by mother as almost continuous, stopped only during sleep. On admission, he had severe dystonia, in terms of back-arching (Figure 1).

An urgent EEG was arranged, the child remained alert and responsive during the whole EEG process despite the "convulsive" movements and no epileptic discharge was detected. In fact, these movements could be stopped momentarily by verbal commands. The conclusion was that

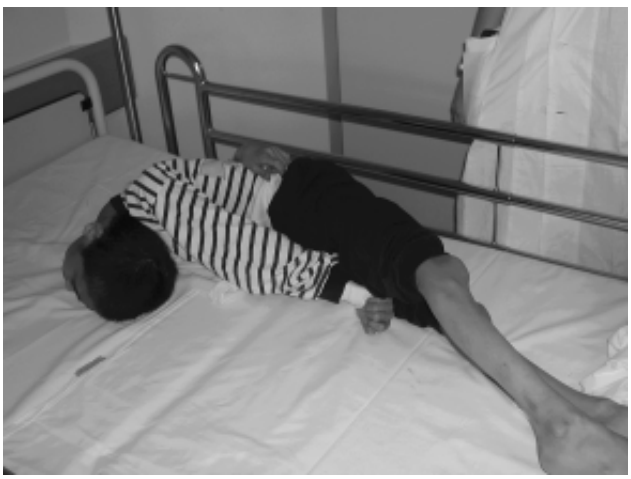

Figure 1 Posture of index case on admission.

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these are choreoathetotic movements on a background of dystonia.

Further history revealed that his eldest and younger brothers were similarly affected, so they were clinically admitted for further investigations.

Background History

Parents were Chinese and were from the same village but not closely related.

There was a healthy second brother among the four siblings (Figure 2).

Parents were healthy with no motor disability. There were no unexplained neonatal death, miscarriage or abortion in the family. No similar illness was found among the extended family.

All three were born full-term in China. Mother claimed that they were healthy with no major illness in the past. Developmental milestones were reported to be normal. They had only 1 year of formal education in China and were home-bound other times. The second son was born in Hong Kong and was brought up here by father. The eldest son, NSL, came to Hong Kong with mother in 1999.

History of Illness

Course of illness started with unsteady gait and easy falls at ~9 years of age. They then developed progressive involuntary movements of limbs, head and neck. These were followed by progressive difficulty in swallowing and speech. Within 1 to 2 years, they became chair-bound and mostly dependent for their average daily activities.

Despite these progressive disabilities, they had no major illness that required hospitalisation. Neither was there history of recurrent sinopulmonary infection.

Physical Examination

All were undernourished with growth parameters including head circumference under 3rd percentile. There were no facial dysmorphism but they tended to have a mask face.

Cardiovascular, respiratory and gastrointestinal systems showed no abnormality. Neurological examination showed major abnormalities. Walking was impossible without support. Pes cavus was noted on all three. The tone was quite variable, alternating between normal and rigid. The index case was quite extreme in his tone variability, he was sometimes as rigid as a board (Figure 3). They had a lot of choreoathetotic movements especially during excitement and again the index case being the worst. Power was quite normal despite a lot of muscle wasting. Reflexes could not be elicited even with reinforcement. Cranial nerves were grossly intact. Fundi were normal. There was no truncal ataxia but other cerebellar signs, including finger-nose test amd dysdiadochokinesia, were positive. They also had scanning speech. No nystagmus was detected. Ocular apraxia could be demonstrated. There were some dilated scleral vessels (Figure 4) but none on cheek nor ears.

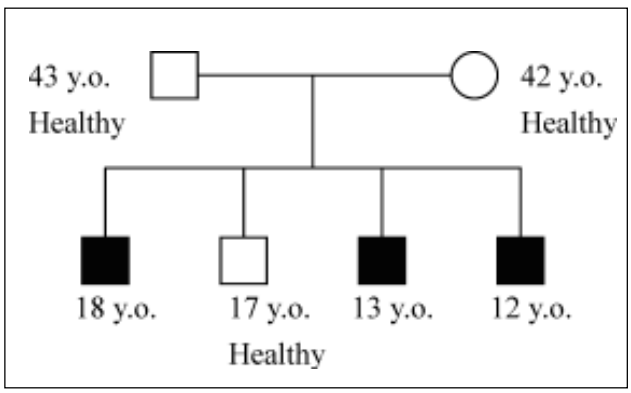

Figure 2 Family tree.

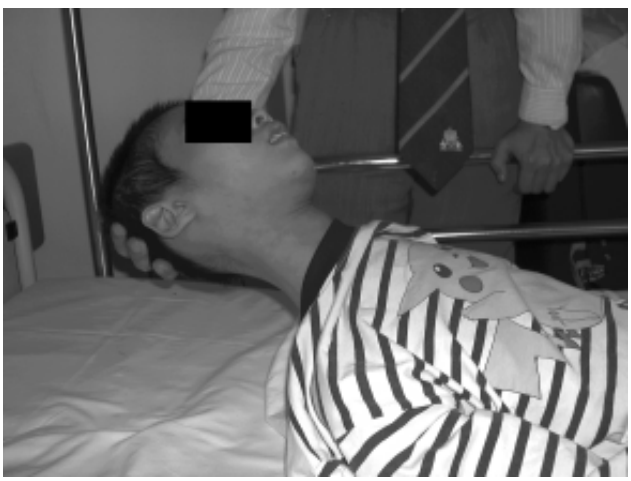

Figure 3 The index case can be as rigid as a board and be lifted up like this.

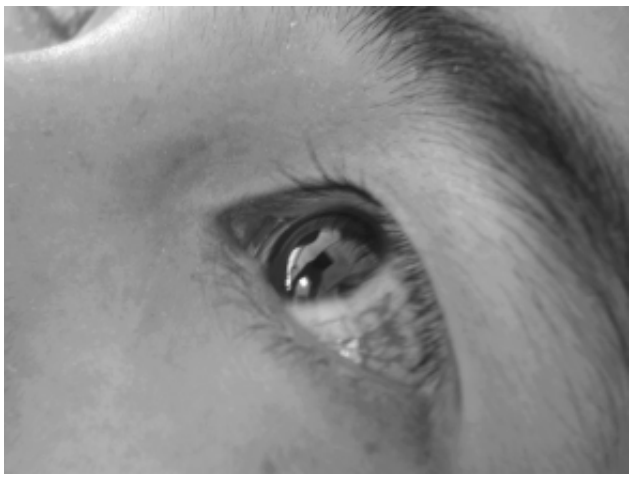

Figure 4 Scleral telangiectasia.

Major Abnormalities

- Choreoathetosis
- Dystonia
- Cerebellar sign
- Telangiectasia

Investigations

Alpha foeto-protein (AFP) and carcinoembryonic antigen (CEA), which are markers of AT, were checked. AFP in these 3 brothers were grossly elevated, ranging from 290- 470 IU/ml (normal <5.8). Their CEA were normal. Serum secretory IgA, IgG2, IgG1 and IgE were found to be normal. Cerebral CT were done and showed Dandy-Walker complex abnormalities in the 2 younger brothers.

Genetic Services were referred but initially chromosomal studies failed to detect any abnormality. Repeated examination showed evidence of spontaneous chromosomal breakages in 2 out of 50 cells:

- One has marker chromosome (a portion of chromosome deleted from an unidentified chromosome).
- Another has an insertion of a segment of chromosome 7 into chromosome 14.

This percentage of spontaneous chromosomal breakage was not as high as in typical cases of AT.

Summary of Clinical Characteristics

	NSL	NSM	MSN
Age at presentation	18	13	11
Age of disease onset	9	9	9
Current status			
Mobility	Need assistance	Chair-bound	Need assistance
Feeding	Self	Assistance	Mild assistance
Dysarthria	Mild	Severe	Moderate
Investigations			
AFP (< 5.8 i.u./ml)	468	291	350
CEA (< 5.0 ng/ml)	1.3	4.7	1.6
IgG (6.94-16.18 g/l)	8.03	9.92	7.89
IgM (0.6-2.63 g/l)	2.39	2.31	3.56
IgA (0.68-3.78 g/l)	2.26	4.12	3.75

Discussions

There are several interesting points to note on these cases.

First of all, the very prominent dystonia and choreoathetosis had made us a bit hesitated to label them Ataxia Telangiectasia initially. In fact we were thinking of familial causes of involuntary movement disorders but none really suit their clinical pictures. After literature review (refer to later section for full review), up to 25% cases of AT have marked choreoathetosis which can be so prominent as to overshadow their ataxia. Also dystonia can be a feature.[1]

Secondly, it is interesting that the only unaffected sibling happened to be reared in Hong Kong. We, therefore, suspected if poisoning could be a cause. However, detailed questioning revealed that there was no similarly affected child in the same village and they drank from water-pipes rather then wells. Life-style review did not find any suspicious information.

Furthermore, the onset of symptoms appeared much later than typical cases. It is possible that the mother's history is not totally reliable as she later claimed that these boys tended to fall easily in early childhood. However, the disease progression may be masked by the normal development of their motor skills together with the fact that they were mostly homebound. Another postulation is that if the gene product,

ATM protein, is still present, the presentation would be milder with later disease onset.

Finally, these cases have all the clinical features of AT, however, chromosomal studies in Hong Kong failed to demonstrate the high rate of spontaneous chromosomal breakages. Some centers would expose these lymphocytes to certain dose of irradiation before checking for chromosomal breakage. Sun et al[2] had studied the colony survival assay (CSA) after irradiated the blood with 1.0 Gy and defined a diagnostic CSA range in AT patients as <21%. Nevertheless, these services are not available in Hong Kong.

Review on Ataxia Telangiectasia

Genetics

AT is an autosomal recessive disease. In 1995, a large gene was identified on chromosome 11q22-q23, known as AT Mutant (ATM) gene. Numerous (>270) unique mutations have been described. The gene product, ATM protein, has multifunctions. This protein has strong similarities to phosphoinositol-3 kinases, which appear to participate in a number of important cellular responses, including insulin-dependent glucose transport and a variety of growth factor responses. Defects in this function will result in increased rate of apoptotic cell death, radiosensitivity, and the premature death of neuronal cells, especially cerebellar Purkinje cells. Another region of the ATM protein is similar to one found in several yeast proteins involved in DNA repair and perturbations in the cell cycle after irradiation,[3,4] thus resulting in increased susceptibility to cancer and radiosensitivity. According to Dr. Boder, ATM gene has become a focus of international research, because it exhibits features that are of major concern in medicine today including cancer susceptibility, immunodeficiency, progressive neurological deterioration and premature aging. It is hoped that AT may reveal the links between them.

However, at present, neither the ATM gene nor the ATM protein can be checked readily.

Heterozygotes

~0.5 to 1.5 percent of the population are carriers of AT. These people with only one defective copy of the gene may also have an increased risk of certain cancers. It was estimated that up to 8 percent of all cases of breast cancer are AT carriers. They are also found to be hypersensitive to ionising radiation and radiomimetic drugs, thus they may not tolerate certain antineoplastic regimens. Identification of such heterozygotes in cancer patients before treatment can allow the use of more appropriate therapeutic regimens. The mother of these 3 brothers is an obligate carrier and is known to have increased risk of breast cancer. However, the benefit of frequent screening mammograms must be balanced against the risk of radiosensitivity. The current opinion is to have the routine screening for breasts cancers appropriate for that general population.

The carrier status of the unaffected brother is estimated to be 50% but definitive test to identify this would be very helpful in counselling.

Clinical Features of Ataxia Telangiectasia

Ataxia

Gait ataxia marks the beginning of this progressive disease, onset is ~2 years of age. The typical description is they walk like a "little clown". Besides their gait, their abilities to write and to speak are also affected. Even reading eventually becomes impossible as eye movements become difficult to control (ocular apraxia).

Telangiectasia

These are dilated vessels usually found at corners of eyes, or on the surface of the ears and cheeks exposed to sunlight. They often are not seen till after 6-year-old. So far, the mechanism of developing telangiectasia is still unknown.

Immunodeficiency

It affects ~70% of AT patients. Deficient levels of IgA and IgE are found and render them prone to sinopulmonary infections.

Predisposition to Cancer

Cancer is 1,000 times more frequent in AT than in the general population. Lymphoma and leukaemia are particularly common. Ironically, they are extremely sensitive to radiation, which means that AT patients cannot tolerate radiotherapy as well.

It is fascinating that these patients tend to have elevated AFP & CEA, both of which are tumour markers. These two substances are produced normally during fetal development but the production is inhibited after birth. It is possible that this inhibition is one of the roles of the ATM protein. Some interesting questions would be whether the levels of these markers relate to their proneness to cancer, and whether changes in their levels can be used for early cancer detection during follow-up. Further large-scale studies would be needed to answer these questions.

Other Possible Symptoms

- Mask face
- Absence or dysplasia of thymus gland
- Choreoathetosis
- Dystonia
- Slowed growth
- Proneness to insulin-resistant diabetes in adolescence
- Progeric changes in hair and skin and progeric vascular changes

Diagnosis

AT is still a clinical diagnosis but with advancement in genetic services, more reliance on genetic diagnosis is possible.

There is no widely accepted diagnostic criteria. But in my literature review, I found 2 sets of diagnostic criteria from 2 articles both done at the Ataxia-Telangiectasia Clinical Center at the Johns Hopkins Medical Institutions and I will quote as follows.

Diagnosis I [5]

Ataxia or significant motor incoordination with raised alpha fetoprotein (AFP) (>2x) +3 of the following 4 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) immunoglobulin deficiencies

Patients with less than three of these characteristics were required to have the diagnosis confirmed by the finding of radiation-induced chromosomal breaks in lymphocytes.

Siblings of known patients with AT who are older than 1 year of age and had ataxia only needed to have an elevated AFP.

Diagnosis II [6]

Presence of characteristic neurologic features (gait ataxia, oculomotor dysfunction, dysarthria, and a movement disorder) and at least one of the following:

1) oculocutaneous telangiectasia
2) elevated levels of alpha-fetoprotein in serum
3) spontaneous or X irradiation-induced chromosomal breakage

Our cases fulfill either one of these 2 diagnostic criteria.

Common Errors in the Diagnosis

AT is a rare disease and many paediatricians have never seen such a case, making the recognition difficult. Usually these cases would be misdiagnosed at early age before the appearance of telangiectasia. The steady motor deterioration may be compensated for by the normal development of motor skills between the age of 2 and 5 years, which may mask the progression of ataxia so that an impression of improvement is often reported.

Treatments

There is as yet no specific therapy. The hope lies in gene therapy. Nevertheless, intensive rehabilitation involving multiple disciplines may delay their clinical deterioration and hopefully improve their quality of life. Prompt treatment of infection especially in cases with immuno-deficiency is particularly important. Some even advocate the use of IVIG in severe infections.

Prognosis

Nowadays, this disease remains incurable and unrelenting. They are usually wheelchair-bound by the age of ten. They usually die from respiratory failure or cancer by their teens or early twenties. Only a few AT patients were reported to live into their forties.

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