Case Report

A homozygous nonsense mutation of ATM gene in a Chinese family with five ataxia telangiectasia children: lesson for prenatal diagnosis

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Abstract: Ataxia-telangiectasia (AT) is a hereditary neurodegenerative disease. We presented a Chinese family with healthy non-consanguineous parents and all-five children presenting with unsteady gait. Genetic analysis of two living siblings showed an ATM homozygous nonsense mutation (c.6100C>T) that has not been reported in Chinese patients, while both parents were compound heterozygous. Limited expertise and lack of diagnosis may lead to the neglect of disease and bring a great tragedy to the family. Prenatal diagnosis may be desirable to identify fetuses at risk of AT when the nature and location of ATM mutation in a family have been identified.

Keywords: Ataxia-telangiectasia (AT), ataxia-telangiectasia mutated (ATM), c.6100C>T, Chinese family, prenatal diagnosis

Introduction

Ataxia telangiectasia (AT) is a rare human autosomal recessive disease in children characterized mainly by progressive cerebellar ataxia, immunodeficiency, and oculocutaneous telangiectasia [1]. The estimated prevalence of AT has been reported to vary from 1 in 40,000 to 1 in 300,000 live births [2]. The disease is caused by biallelic mutations of ataxia-telangiectasia mutated (ATM) gene that located on chromosome 11 q22-23 [3]. More than 700 ATM gene mutations have been reported in AT patients (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=ATM), most are frameshift or nonsense mutations. No evidence for the existence of hotspot mutations is available up to now. AT is the most common cause of progressive ataxia in childhood. It was suggested to be a more common variety of hereditary ataxias in Chinese children [4]. Several cases have been reported in China [5-7]. However, establishment of AT diagnosis is most difficult in very young children. Identification of ATM mutations present in a family may provide insights into the prenatal diagnosis of the disease [8]. In this report, we presented a Chinese family with healthy non-consanguineous parents and all five children presenting with unsteady gait in their early childhood, of which three have died at their early ages. Genetic analysis of two living patients showed an ATM homozygous nonsense mutation (c.6100C>T) that has not been reported in Chinese patients.

Case report

This study was approved by the Institutional Review Board of the Children's Hospital of Hebei Province and informed consent was obtained from all the family members. The proband, the fifth child in his family, was a 7-year-old boy presented to our hospital with the chief complaints of gait disturbance for 6 years, cough for more than 10 days, and hemoptysis for 2 days. The other four children were all reported to have a history of gait disturbance. The first child was a boy who died of pneumonia at the age of 1 year. The second, third and fourth children were girls, all of them have complaints of gait disturbance, recurrent respirato-
Prenatal diagnosis for AT

Figure 1. Bilateral ocular telangiectasias of the proband. A. Right eye; B. Left eye.

Figure 2. Chest CT scanning showed bilateral bronchopneumonia with lower lobe bronchiectasis (A), while no abnormalities in the thymus was found (B).

The proband had normal births and development until the age of 14 months, when he developed gait instability and bilateral conjunctiva telangiectasia (Figure 1). No cutaneous telangiectasia and slurred speech was observed. Laboratory testing revealed positive alpha fetoprotein (AFP) test, low levels of immunoglobulin A (IgA, 0.05g/L) and immunoglobulin G (IgG, 0.03 g/L), as well as lymphopenia (3.98*10^9/L, CD3+: 69.3%; CD4+: 24.7%; CD8+: 28.0%; CD19+: 1.9%; NK: 23.4%). No abnormality in the chromosome examination was found. The chest CT scanning showed bilateral bronchopneumonia with both lower lobe bronchiectasis, while concurrent of infection could not be excluded. No thymic abnormalities were found (Figure 2). Brain magnetic resonance imaging (MRI) showed bilateral cerebellar atrophy and sinusitis (Figure 3). Genetic analysis of the ATM gene in proband and his only living sister identified a homozygous nonsense mutation located in exon 42 (c.6100C>T, p.(Arg2034*)), while both the parents were found to be compound heterozygous for the (c.6100C>T, p.(Arg2034*)).

Discussion

AT is a progressive disorder characterized by early-onset cerebellar ataxia, oculocutaneous
Prenatal diagnosis for AT
telangiectasia, and immune defects. The onset of the disease generally occurs between the age of 1 and 2 years with abnormal head movements, loss of balance, slurred speech, and abnormal eye movements [9]. The clinical course is variable. Telangiectasias appearing in the ocular, face and ears at 3-5 years of age, are often neglected, or even remain absent in variant AT [10]. The serum AFP level has been evaluated to help the diagnosis of the infants with ataxia symptoms [11], and elevated AFP level was reported in AT patient. Other associated features include T- and B-cell abnormalities with IgA and IgG deficiencies [10, 12], and a predisposition to malignancy [13]. The high incidence of sinopulmonary infections has also been described [14].

Our study here described a Chinese family with all five children presenting with gait disturbance from health non-consanguineous parents, of which three had died at their early ages. The diagnosis was elucidated by the typical clinical presentation of gait instability and bilateral conjunctiva telangiectasia. Blood tests showed positive AFP test, reduced levels of serum IgA and IgG, and lymphopenia in the fifth child (proband), the findings consistent with AT. No cutaneous telangiectasia and chromosome breaks were noted in our patient, partially consistent with the results reported by Jeong et al. [2], which indicated the bilaterally ocular telangiectasia with no cutaneous telangiectasia. However, there was no slurred speech in the proband of our study. Whereas, the bilateral bronchopneumonia was evident on CT scan with both lower lobe bronchiectasis, and brain MRI showed cerebellar atrophy and sinusitis, further confirmed the diagnosis of AT.

AT is well known to be associated with mutations in the ATM gene, expressed ubiquitously and encoding a serine/threonine protein kinase involved in monitoring and maintaining DNA integrity, cell cycle regulation, and coordinate cell-signaling pathways [15]. Mutations in ATM gene generally resulted in the absence of full-length, functional protein product [16]. People with heterozygous mutation of ATM gene are generally asymptomatic, but are at an increased risk of radiation sensitivity [6] and with a high incidence of several types of cancer [17]. By contrast, homozygous mutations result in the AT phenotype. More than 700 different, mostly truncating ATM gene mutations have been reported in AT patients. In this study, the genetic analysis of the proband and his only living sister identified an ATM gene nonsense mutation in exon 42 (c.6100C>T, p.(Arg2034*))). The c.6100C>T mutation at codon 2034 was firstly described by Telatar et al. in two unrelated American families, and most patients who are not consanguineous were reported to be compound heterozygotes [18]. It was later identified in cell line of AT patients [19] and in patient with radiation sensitive breast cancer [20], whereas the mutation was reported to be located in different exons. Recently, Sharon et al. have also reported a family case of AT with c.6100C>T nonsense mutation located in 44 exon (p.R2043X) [11]. In our case, mutation was found to be located in exon 42, and it may be because of the difference in gene annotation between studies. However, despite of these, to

**Figure 3.** MRI of brain shows cerebellar atrophy (A) and MRI of sinus showing sinusitis (B).
Prenatal diagnosis for AT

the best of our acknowledgement all the ATM mutations identified in Chinese were no homozygous mutation like this [7].

To summary, our study showed a family case of AT with all five children affected, limited expertise and lack of diagnosis may lead to the neglect of the disease, thus bring a great tragedy to the family. Genetic analysis showed an ATM homozygous nonsense mutation (c.6100C>T, p.(Arg2034*)) in the two living children, and both the parents were found to be compound heterozygous for the c.6100C>T, p.(Arg2034*). Limited expertise and lack of diagnosis may lead to the neglect of disease and bring a great tragedy to the family. Prenatal diagnosis may therefore be desirable to identify fetuses at risk of AT when the nature and the location of ATM mutation presented in a family have been identified.

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Disclosure of conflict of interest

None.

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Prenatal diagnosis for AT


