Early-Onset Friedreich's Ataxia With Oculomotor Apraxia

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Abstract- Friedreich's ataxia (FRDA) is a rare autosomal recessive spinocerebellar ataxia which in the majority of cases is associated with a GAA-trinucleotide repeat expansion in the first intron of Frataxin gene located on chromosome 9. The clinical features include progressive gait and limb ataxia, cerebellar dysarthria, neuropathy, optic atrophy, and loss of vibration and proprioception. Ataxia with ocular motor apraxia type 1 (AOA1) is another autosomal recessive cerebellar ataxia which is associated with oculomotor apraxia, hypoalbuminaemia, and hypercholesterolemia. Here we describe two siblings (13- and 10-year-old) display overlapping clinical features of both early-onset FRDA and AOA1. Almost all of laboratory test (including urinary analysis/culture, biochemistry, peripheral blood smear, C-reactive protein level, erythrocyte sedimentation rate-1h) results were within the normal range for both patients. Due to the normal laboratory test results; we concluded that the diagnosis was more likely to be FRDA than AOA1. Therefore, neurologists should bear in mind that clinical presentations of FRDA may vary widely from the classical phenotype of gait and limb ataxia to atypical manifestations such as oculomotor apraxia.

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Introduction

Friedreich's Ataxia (FRDA) is the most prevalent hereditary type of ataxias with a prevalence of 1/50,000 in general population (1). It belongs to a big family of rare neurodegenerative disorders which are known as autosomal recessive spinocerebellar ataxias. FRDA is linked to a GAA-trinucleotide repeat expansion in the first intron of Frataxin (*FXN*) gene located on chromosome 9; however, in a small percentage of patients this expansion is heterozygous and accompanied with some missense mutations of *FXN* (2).

The age of onset of FRDA is usually around puberty, but several cases with unusual age at onset have been reported in the literature. More interestingly, the age of onset of FRDA has shown to be negatively correlated with the GAA and CAG repeat length within the *FXN* and *POLG* (mitochondrial DNA polymerase) genes, respectively (3-6).

The most common presenting symptoms are progressive gait and limb ataxia, cerebellar dysarthria, neuropathy, distal wasting, sensorineural deafness, optic atrophy, absent reflexes, and loss of vibration and proprioception (7). Also, scoliosis has been suggested as the secondary criteria for the clinical diagnosis of FRDA (7), given the presence of scoliosis in almost all of FRDA patients. Metabolic disorders such as diabetes are also quiet common among FRDA patients, as nearly all of them have a decreased insulin response to arginine and about 10% become diabetic (8,9). Cardiac involvements are largely responsible for mortality and morbidity of FRDA patients, owing to that they were causes of death in 60% of these patients (10). However, it should be noted that the neurological status has not been proved to predict electrocardiogram abnormalities (11). There was a substantially increased GAA length in FRDA patients who had also diabetes or cardiomyopathy (3,6). Profound vision deficit is rare, even though B. Diehl and colleagues (2010) have recently reported a case of this impairment and episodic

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complete blindness in company with marked optic atrophy (12). Ataxic dysarthria is displayed in FRDA in different patterns, representing the involvement of corticospinal and corticobulbar tracts beyond the cerebellum. Meanwhile, cognitive impairments have been recently indicated to be present mildly in FRDA patients (13).

Here we present two sisters with early onset FRDA and oculomotor apraxia who were children of a cousin marriage and were referred to Children's Medical Center for neurological assessments.

Case Reports

Case 1

The first patient was referred to the neurology clinic when she was 13-year-old. She had a negative family history for any neurological disorders. Her parents had noticed balance control problems when she was 5-year-old. Clinical examination showed unsteady walking with balance and coordination difficulties, dysarthria, and bad handwriting. However visual, auditory and mental conditions were normal. Other differential diagnoses such as Ataxia Telangiectasia (AT) and Wilson diseases were ruled out using blood test and physical examination. Brain MRI showed a significant cerebellar atrophy. She did not have any history of convulsions, headache, behavioral disorders, infantile jaundice and loss of consciousness. We noticed a declared oculomotor apraxia, downward pescavus and normal muscle tone and sensation tests were normal. Babinski reflex was also normal. The result of the finger to nose coordination test was abnormal. She had difficulty with tandem walking.

Deep tendon reflex and respiratory rate were reduced. Outcomes of electromyography (EMG) and nerve conduction velocity (NCV) tests revealed peripheral axonal neuropathy. Visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) were done by physicians and showed normal patterns. Echocardiography showed normal heart structure and function. We requested complete laboratory tests set include: urinary analysis/culture, biochemistry, peripheral blood smear (PBS), C-reactive protein level (CRP quantitative), erythrocyte sedimentation rate-1h (ESR-1h). All of them were within the normal range, except for the plateletcrit (PCT) parameter which was slightly increased and both of the mean corpuscular hemoglobin (MCH) and meant corpuscular hemoglobin concentration (MCHC) were slightly low.

Case 2

This patient was 10-year-old when she was referred to the clinic. The parents noticed similar symptoms to her older sister, except to pattern of her balance and coordination problems that was somewhat different. She was unable to maintain balance while sitting. There was no evidence of visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP). Because of asthma, she had been confined to bed for eight days at birth. ECG was normal (i.e. no noticeable active pulmonary lesion, normal heart dimensions, lack of any mediastinal lesion, normal pulmonary vessels relative patient age, and free embryonic sinuses). Blood tests revealed a slightly increased number of neutrophil, monocyte and red blood cell (RBC), and PCT while MCH and MCHC were slightly decreased.

Discussion

FRDA is the most prevalent hereditary type of ataxia, which presents with a variety of clinical signs and/ or symptoms. However, the most common ones include gait and limb ataxia, dysarthria, and loss of lower-limb reflexes (6). On the other hand, AOA is characterized by cerebellar neuropathy and peripheral neuropathy. So far two main types of AOA have been described in the literature. AOA type 1 (AOA1) has an early age at onset (i.e. childhood) and is associated with hypercholesteromia and hypoalbuminemia, while AOA type 2 (AOA2)'s onset occurs in adulthood and is associated with high level of creatinine phosphokinase and alpha fetoprotein (14,15).

Here we described two siblings with the concurrence of early onset FRDA and oculomotor apraxia. However, initially, it appeared that AOA1 was more probable than FRDA, as AOA1 is typically diagnosed in young children (mean age at onset=6.8±4.8), while the mean age of onset for FRDA patients is around 10.52 years. Overlapping clinical features between AOA1 and FRDA necessitate laboratory tests and genetic studies for GAA-trinucleotide repeat expansion and Aprataxin gene which are mainly considered to be responsible for FRDA and AOA1, respectively. Due to the normal laboratory test results and given that AOA1 is associated with hypercholesterolemia; the diagnosis was more likely to be FRDA rather than AOA1. The genetic investigation was required to be reassured of this diagnosis, but it could not be done due to the unavailability of the patients' blood sample.

In conclusion, learning points of these two cases can

be emphasized as follows. First, those neurologists should bear in mind that clinical presentations of FRDA may vary widely from the classical phenotype of gait and limb ataxia to atypical manifestations such as oculomotor apraxia. Second, that laboratory test results might provide us with valuable information for differential diagnosis between FRDA and AOA, particularly when genetic analysis cannot be performed. Third, that genetic analysis is presently acknowledged as the most powerful tool for differential diagnosis between inherited ataxias.

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