Friedreich Ataxia

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Abstract

Friedreich ataxia is an autosomal recessive disorder, due to expansion of trinucleotide repeat in Frataxin gene which presents with ataxic gait, absent tendon reflexes, extensor plantar response and positive Romberg test. We present a child who came with complaints of progressive ataxia of gait since the age of 10 years and was diagnosed to have Friedreich ataxia. They have associated cardiomyopathy and endocrine abnormality like diabetes and hypothyroidism.

Keywords: Areflexia; Friedreich Ataxia; Extensor Plantar Response; Romberg's Sign; Trinucleotide Repeat.

Introduction

Friedreich ataxia (FA) an autosomal recessive disorder is the commonest of the inherited ataxias, affecting approximately 1–2 per 100,000 population1. It is due to homozygous expansion of a guanine adenine adenine (GAA) trinucleotide repeat in intron 1 of the Frataxin gene on chromosome 9. The usual presentation is progressive ataxia absent knee and ankle jerks and dysarthria. The natural history of this disease is one of relentless progression. The patient usually becomes wheelchair bound within 10-15 years of onset. Only a few reports have documented the onset of the disease during childhood and also due to rarity of the case, we are presenting a 11 year old child who presented with progressive ataxia of gait since the age of 10 years and on evaluation was diagnosed to have FA. Though FA presents with predominant neurological manifestations, they have associations with cardiomyopathy and endocrine abnormality, hence long term follow up is imperative.

Case Report

A Eleven year old girl born of s e c o n d d e g r e e consanguineous marriage presented with history of swaying while walking for past two years. There was associated difficulty in squatting and climbing down stairs. There was no history of tripping while walking, wasting of muscles tingling or paraesthesia in the lower limbs. Over one year it slowly progressed to gait instability. She did not have any feeding difficulties. There were no abnormalities in hearing or vision. There was no significant past or family history except for pes cavus in father. Examination revealed high arched palate, abnormal dermatoglyphnames forics, saddle gap in the feet, pes cavus (Fig 1) and kyphoscoliosis. Vitals were normal. She had microcephaly with subnormal intelligence. Cranial nerves and fundus were normal. She had wide based gait with ataxia and positive Romberg's sign. Child had dysmetria, dysdiadochokinesia and horizontal nystagmus. There was lower limb areflexia and extensor plantar response. There were no dysarthria, involuntary movements, calf muscle hypertrophy or fasciculations. Her sensory system was normal. MRI showed normal brain parenchyma and thinning of the cervical segment of the spinal cord (Figure 2). Nerveconductionvelocities were normal. Electrocardiogram showed biventricular hypertrophy. There were no conduction

blocks. Echocardiography thyroid profile and blood sugar were within normal limits. In view of cerebellar ataxia with bilateral pyramidal signs, loss of deep tendon reflexes, kyphoscoliosis and pes cavus a diagnosis of FA was made. Physiotherapy was initiated. She requires long term follow up for cardiomyopathy and diabetes mellitus.

Fig. 1: Pes cavus

Fig. 2: Thinning of cervical segment of spinal cord

Discussion

FA affects central and peripheral nervous systems, heart, skeleton and endocrine pancreas. The estimated carrier frequency ranges from 1:50 to 1:100 in people of European, North African, Middle Eastern and Indian origin. The point prevalence is 3 per one lakh population [1]. FA is typically a disease of young adults with no gender predilection. The varied initial diagnosis and the delay in reaching a final diagnosis reflect the lack of knowledge and published reports on FA in children. A family history

of Friedreich's ataxia may lead to early diagnosis. Mean age of earliest symptom in the vast majority. Within five years of symptom onset, most individuals with FA exhibit scanning dysarthria, lower extremity weakness, and diminished or absent joint position and vibration sense. Involvement of peripheral sensory and motor neurons results in a mixed axonal neuropathy [2]. Muscle weakness is most prominent in hip extensors and abductors. Spasticity in the lower limb is common and can be significant, affecting foot plantar flexors and inverters to a greater extent than dorsiflexors and everters.

Neurologic manifestations result from progressive degeneration of the dorsal root ganglia, posterior columns, corticospinal tracts, the dorsal spinocerebellar tracts of the spinal cord, and cerebellum.Optic nerve atrophy, often asymptomatic, occurs in approximately 25% of individuals with FA. Cognition is generally not impaired in FA but motor and mental reaction times can be significantly slowed. Complex oculomotor disturbances are characteristic and include abnormal saccades and square wave jerks. Despite normal pure-tone audiometry, patients with FA may have problems with speech perception which is suitably termed as "auditory neuropathy/dyssynchrony". There is also evidence of vestibular dysfunction.

Scoliosis and pes cavus are extremely common in FA (60–79%) and is clearly progressive. Diabetes mellitus occurs in 8–32% of FA patients. Progressive systolic dysfunction is common. Cardiomyopathy was the immediate or contributory cause of death in 83.3%. 3 Subjective symptoms of exertional dyspnea, palpitations and anginal pain may be present in moderately advanced disease. Arrhythmias and congestive heart failure are the most common cause of mortality. Mural thrombi in the left ventricle are common and some patients with FA have embolic strokes.

The gene for FA was mapped to chromosome 9ql [3] in 1988 by Chamberlain and colleagues. An inverse relation was found between the size of the smaller and both age at onset and time until confinement to a wheelchair. The association of cardiomyopathy with large expansion is important for prognosis [4]. The incidence and progression of cardiomyopathy is directly proportional to the length GAA expansion. Genetic confirmation requires demonstration of triple repeat sequences of GAA on chromosome [9].

According to Harding's criteria an age of onset before 25 years, progressive ataxia, absent deep tendon reflexes and dysarthria are considered to be essential criteria. Scoliosis, pyramidal weakness in

lower limbs, absent tendon reflexes in arms, impairment of vibration and joint position sense and cardiomyopathy are additional criteria [5] Nystagmus, optic atrophy, deafness, distal amyotrophy, pes cavus and diabetes mellitus are other criteria found in less than 50% cases Abnormalities in nerve conduction studies are severely slowed or absent sensory conduction with normal motor conduction velocity, motor nerve conduction velocity of greater than 40 m/s with reduced or absent sensory nerve action potential and absent H reflex. ECG is abnormal in the vast majority with T wave inversion, left axis deviation, and repolarization. Echocardiographic evaluation may reveal left ventricular hypertrophy that is more commonly asymmetric than concentric [6].

Conclusion

Clinical differentiation of various causes of progressive ataxia can be difficult .Pathologic examination of patients with progressive ataxia enables identification of three broad categories of diseases according to the site of the gross and histologic abnormalities These three categories are the spinocerebellar forms, of which Friedreich's ataxia is the most common; the corticocerebellar atrophies; and the cerebellar-brainstem atrophies.

Histopathologic features of Friedreich's ataxia include neuronal loss in the spinal ganglia and Clarke's column and loss of myelinated fibers, with compensatory gliosis of the fasciculus gracilis and cuneatus in the posterior columns and of the spinocerebellar and pyramidal tracts in the lateral columns of the spinal cord . Spinal cord thinning is reported almost invariably in pathologic descriptions of the disease. MR imaging can show selective loss of bulk in the cerebellum and brainstem in corticocerebellar and cerebellar-brainstem atrophies hich are associated with brainstem and cerebellar white matter signal changes in olivopontocerebellar atrophy.Atrophy of the upper portion of the cervical spinal cord has been emphasized in prior MR studies of patients with Friedreich's ataxia , but intramedullary signal abnormalities were not mentioned.

MR imaging could be used to depict the changes in the white matter tracts that are known to occur in the cervical spinal cord of patients with Friedreich's ataxia. Detection of such changes could increase information provided by MR imaging in patients with Friedreich's ataxia and be helpful for differential diagnosis in patients with progressive ataxia of uncertain clinical type. Loss of myelinated fibers and gliosis in the posterior and lateral columns of the spinal cord are histopathologic hallmarks of Friedreich's ataxia. These are accompanied by atrophy of the upper portion of the spinal cord. MR imaging can be used to detect signal changes in the white matter tracts of the cervical spinal cord in patients with Friedreich's ataxia.The anteroposterior diameter of the spinal cord is decreased in patients with Friedreich's ataxia in the upper cervical spinal cord. Abnormal signal in the posterior or lateral columns of the spinal cord is observed on sagittal and/or axial images in patients with Friedreich's ataxia and is not observed in other patients with corticocerebellar atrophies; and the cerebellar-brainstem atrophies. MR images of the cervical spinal cord in patients with Friedreich's ataxia show thinning and intramedullary signal changes in the cervical portion of the spinal cord, consistent with degeneration of posterior and lateral white matter tracts. These MR findings might be helpful for differential diagnosis in patients with progressive ataxia of uncertain clinical type.

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