Freidreich's ataxia with retained reflexes: a phenotype and genotype correlation

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SUMMARY

An 18-year-old lady had presented to us with insidious onset progressive gait ataxia of 5-year duration. Her sister had similar complaints and type 1 diabetes mellitus. Examination revealed, gait ataxia, impaired tandem gait, babinski sign and severe swaying on testing for Romberg's sign. All deep tendon reflexes were exaggerated. On investigations, there was no evidence for diabetes mellitus or nutritional deficiencies. Electrocardiogram and echocardiogram were normal. Magnetic spine resonance showed marked atrophy of cervical cord with normal cerebellum. The genetic testing disclosed expanded GAA repeat length on both alleles of FXN gene. The GAA repeat length on both alleles was much less than mean length observed in Friedreich's ataxia. This case highlights how strongly the genotype influences the neurological and systemic manifestations as well as severity of disease in Friedreich's ataxia.

BACKGROUND

Friedreich's ataxia (FRDA) is the most frequent autosomal recessive ataxia characterised by involvement of nervous system, heart and pancreas. The diagnosis is based on detection of homozygous expansion of GAA repeats (normal range: 5–33) in the FXN gene (previously known as FRDA, X25) located on chromosome 19q13–21.1. The age of onset and phenotype of FRDA has been correlated with length of GAA repeats. The late onset Friedreich's ataxia (LOFA, >25 years), and very late onset Friedreich's ataxia (VLOFA, >40 years) are reported to be associated with GAA repeats of size usually less than 500 and 300 respectively, the range for the classical FRDA (onset before 25 years) being 600–1200.^{1–3} We present a case of ataxia found to be having a GAA repeat expansion much smaller than mean size in FRDA.

CASE PRESENTATION

An 18-year-old lady presented with history of progressive swaying while walking, worse in night since 5 years. Speech was normal and there was not any tremulousness of upper limbs. Also, there was no history of weakness or numbness. The family history was significant as her elder sister had similar difficulty in walking of 7-year duration and died because of poorly controlled diabetes mellitus at an age of 20 years. No other members of the kin were affected and there was no history of consanguinity in the parents.

The cognitive function was normal and her Mini Mental Status Score was 30/30. Visual acuity and fundus examination were normal. The extraocular movements including saccades, pursuits were normal, and no saccadic intrusions or nystagmus

were noticed. The tone and power were normal in all four limbs; however, there was generalised exaggeration of myotatic reflexes along with bilateral extensor plantar response. Vibration and joint position sense were intact but Romberg's was positive. Patient swayed to either side while performing tandem walk.

INVESTIGATIONS

Fasting and postprandial blood glucose levels were normal. Haemogram, renal, liver and thyroid function tests were normal. Serum vitamin B12 and folic acid levels were within normal limits. Nerve conduction study showed absent sensory nerve action potential with normal distal latency, conduction velocity and amplitude of compound muscle action potential (CMAP) in all nerves trunks. MRI showed marked atrophy of the cervical cord as compared to cerebellum which was normal (figure 1). The genetic testing using PCR disclosed expansion of GAA repeat in both alleles (254 and 298) of FXN gene.

DIFFERENTIAL DIAGNOSIS

A variety of causes of autosomal recessive ataxias need to be considered in the differential diagnosis of FRDA. These were systemically excluded here. Ataxia with vitamin E deficiency (AVED) has a phenotype quite similar to FRDA, though titubation and hyperkinesia are more common in AVED.⁴ A strong family history of ataxia and diabetes mellitus in elder sister favoured FRDA. Ataxia with oculomotor apraxia (AOA) types 1 and 2 were not considered owing to lack of apraxia of ocular movements, distal amyotrophy (severe axonal sensorimotor polyneuropathy), atrophy of cerebellum and involuntary movements.⁵ Ataxia telangiectasia has presentation very similar to AOA types 1 and 2. Muco-cutaneous markers, sino-pulmonary infections, hypogammaglobulinaemia and radiosensitivity along with predisposition to development of a variety of neoplasms are features of ataxia telangiectasia not seen in AOAs and FRDA. The other important causes of autosomal recessive spastic ataxia apart from FRDA would be autosomal recessive spastic ataxia of Charlevoix-Saguenay and Marinesco-Sjögren syndrome. Charcot-Marie-Tooth disease, an inherited polyneuropathy has gait ataxia in common with FRDA; however, in this case, CMT was improbable due to following features in this case: lack of motor weakness, retained reflexes, bilaterally extensor plantar and pure sensory neuropathy on nerve conduction study.

TREATMENT

Idebenone was started at a dose of 450 mg twice a day for its antioxidant properties. For gait ataxia,

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Figure 1 MRI cervical spinal cord: T2-weighted sagittal sequence showing normal cerebellum (arrow) with markedly atrophic cervical cord (arrowhead).

physiotherapy—Frenkel's exercise—was initiated. Blood glucose is monitored regularly.

OUTCOME AND FOLLOW-UP

At 4 months, there was no significant change in the gait difficulty.

DISCUSSION

The onset of disease in our case was in adolescence as progressive gait ataxia. There was evidence of pyramidal involvement along with retained reflexes and posterior column dysfunction. The optic nerve, skeletal system, heart and pancreas were not affected. The nerve conduction study revealed a pure sensory neuropathy with CMAPs normal in every aspect. Significant cervical cord atrophy was noticed on MRI though the cerebellum was normal.

In the majority of patients of FRDA, the phenotype, including severity of neurological impairment and systemic involvement, is strongly influenced by the genotype. The age of onset is inversely proportional to the degree of expansion in GAA repeats as mentioned earlier. Hypertrophic cardiomyopathy (HCM) is reported in two-thirds of FRDA patients. Isnard *et al*⁶ found that HCM was present in 81% of patients with GAA repeat length in excess of 770 as compared to only in 14% of patients with fewer than 770 GAA repeats. Diabetes mellitus is reported in only 30% of case and it is correlated more with age of onset than the GAA expansion size.⁷ Scoliosis is seen in two-thirds of FRDA-affected individuals and in 100% cases when evaluated radiologically.⁸ Optic nerve atrophy occurs in 25% of cases which is symptomatic in only 13%. Incidence of sensorineural deafness is limited to only 13% patients and this was not observed in our case too.⁹

FARR refers to subset of FRDA with retained reflexes. In a study of 101 patients by Coppola *et al* 90 had FRDA and 11 (~11%) had FARR. The mean age of onset of FARR (26.6

± 11.4 years) was observed to be much later than FRDA (14.2 ± 6.9 years). The incidence of skeletal abnormalities, hypertrophic cardiomyopathy, pes cavus and vibration sense impairment was lower in FARR as compared to FRDA. The mean size of the smaller allele was significantly less (408 ± 252 vs 719 ± 184 GAA triplets) in all FARR patients.¹⁰

The presentation in the given case is quite similar to FARR as there was no skeletal deformity and cardiac involvement, and the vibration sense was intact. The size of GAA triplet was also compatible with FARR. However, the age of onset was rather earlier than that expected in FARR.

Although no clear recommendations on treatment of FRDA exist, therapeutic approaches acting at different stages of pathogenesis have been tried. These include reduction in oxidative stress using idebenone, gene replacement therapy and agents like erythropoietin and histone deacetylase (HDAC) inhibitors which increase the frataxin level. In order to evaluate the effect of idebenone on the neurological function in FRDA M. Thomas *et al* conducted a 12 month open label study which was extension of a 6-month, randomised, double-blind and placebo-controlled study. It was concluded that idebenone, at a dose of 1350/2250 mg, stabilised the neurological function and improved the fine motor skills and speech.¹¹ The studies evaluating efficacy of idebenone in treatment of cardiomyopathy has shown variable results and a recently performed study did not provide evidence for beneficial effect of idebenone on left ventricular hypertrophy after 6-month therapy with idebenone.¹² A randomised controlled trial failed to show to any significant benefit of erythropoietin in neurological disability.¹³ The GAA expansion leads to silencing of FRDA gene expansion by causing hypoacetylation of H3 and H4 histones and trimethylation histone H3 at Lys9 explaining the heterochromatin-mediated gene repression. The HDAC inhibitors switch on the repressed FXN genes by increasing acetylation.¹⁴

In our case, there was no change in the disability status after 4 months, the effect of idebenone needs to be further observed.

CONCLUSION

The phenotype and genotype of disease observed in this case are quite similar to that described in FARR. The persistence of reflexes, absence of hypertrophic cardiomyopathy and a rather slow progression of disability correlate well with the size of GAA triplet expansion.

Learning points

- ▶ The core diagnostic features of Friedreich's ataxia (FRDA) are early onset gait ataxia along with absent lower limb reflexes, extensor plantar response and a pure sensory neuropathy with relatively normal motor conduction velocity. In around 11% of individuals homozygous for the trinucleotide GAA expansion, the reflexes are preserved till late which is labelled as FARR.
- ▶ FARR is similar to FRDA but differs on account of a later age of onset, lower incidence of skeletal abnormalities, hypertrophic cardiomyopathy, pes cavus and vibration sense impairment. The mean size of GAA repeat expansion is smaller than in FRDA.
- ▶ The smaller size of trinucleotide expansion correlates with a relatively less severe disease and lesser systemic complications.

Competing interests None.

Patient consent Obtained.

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