FRIEDREICH ATAXIA (FA) ASSOCIATED WITH DIABETES MELLITUS TYPE 1 AND HYPERTHROPHIC CARDIOMYOPATHY

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Abstract

Progressive signs of ataxia in a eight years old girl prompted neurological investigation. The girl had unstable gait with incoordination of limb movements, impairment of position and vibratory senses, dysarthria, pes cavus, positive Babinski sign and scoliosis. At the age of fourteen the girl was referred in a comatose condition, in a severe diabetic ketoacidosis. Ataxia and hypoactive knee and ankle jerks prompted the analysis of the frataxin gene (FXN; 606829). The most common molecular abnormality: GAA trinucleotide repeat expansion in intron 1 was found with + 300 GAA repeats (1490bp) (normal individuals have 5 to 30 GAA repeat expansions, whereas affected individuals have from 70 to more than 1,000 GAA triplets). Electrocardiogram showed diffuse T wave inversion with sinus bradycardia, while ultrasound revealed concentric, symmetric hypertrophy of left ventricle leading to the diagnosis of hyperthrophic cardiomyopathy. At the age of 14 years, the patient was bound to the wheel-chair, unable to walk. Her brother started to show ataxia at the age of 8 years, and subsequent analysis showed hyperthrophic cardiomyopathy, too. His mutational analysis revealed the same frataxin abnormality, with + 300 GAA repeats. So far, no signs of diabetes occurred. The parents are heterozygous with FXN of 9 -10 GAA (490 bp). Both children received a beta blocker, while the girl's diabetes mellitus was treated by insulin preparations. This is a report of two siblings with Fridreich ataxia and hyperthrophic cardiomyopathy. In addition, the girl developed type 1 diabetes mellitus.

KEY WORDS: Friedreich ataxia, diabetes mellitus type 1, hyperthrophic cardiomyopathy, siblings.

Introduction

Friedreich ataxia (FA) is an autosomal recessive neurodegenerative disease which involves both the central and the peripheral nervous system. FA is usually manifested before adolescence with incoordination of limb movements, impairment of position and vibratory senses, dysarthria, nystagmus, diminished or absent tendon reflexes, Babinski sign, scoliosis, pes cavus, and hammer toe are also frequent findings. A significant proportion of patients (two thirds to nearly all affected homozygotes) develop cardiomyopathy. About 10% of them develop diabetes mellitus, while ~20% have glucose intolerance (1). The mean life span of FA patients is ~35 years. Frequently reported causes of death are cardiomyopathy and diabetic complications (1). Friedreich ataxia is caused by mutations in frataxin gene (mapped on chromosome 9q13). The product of the gene is soluble mitochondrial protein with 210 amino acids and crystal structure called frataxin. 98% of the patients have an expansion of GAA trinucleotide repeast located within the first intron of the FXN gene, the other 2% are due to point mutations in the FXN gene (2, 3). So far, 17 mutations had been described (3). Normal individuals have 5 to 30 GAA repeat expansions, whereas affected individuals have 70 to more than 1,000 GAA triplets (4). Longer expanded repeats cause more profound frataxin deficiency and are associated with earlier onset and severe for of FA (5, 6).

Case report

History: The proband was born after uneventful pregnancy and delivery to healthy and young parents. Progressive signs of ataxia were noted before the age of twelve years. **Physical examination**: Hypoactive knee and ankle jerks, unstable gait with incoordination of limb movements, impairment of position and vibratory senses, dysarthria, dysmetria, intentional tremor, pes cavus, Babinski sign and scoliosis were observed. Her brother started to show ataxia at the age of 8 years. **Diagnosis**: Multiple cardiac investigations were done initially and during the follow-up. Since her first referral the electrocardiogram showed diffuse T wave inversion with sinus bradycardia, while cardiac ultrasound revealed concentric, symmetric hypertrophy of left ventricle leading to the diagnosis of hypertrophic cardiomyopathy. Progressive EKG and ultrasound worsening was also noted. The same hypertrophic cardiomyopathy was diagnosed in the brother. At the age of fourteen years she was referred in deep coma. The complete signs of severe diabetic ketoacidosis were present: hyperventilation of Kussmaul type (32/min), peripheral cyanosis, severe dehydratation. Blood and urine analyses showed high levels of glucose (51,5 mmol/ dm3) and severe acidosis (pH 6,8, HCO_3 8,5 mmol/dm3, BE-20,7). The history of diabetes mellitus started 10 days ago with typical signs of polyuria and polydypsia. The glycosilated hemoglobin level was increased, 14%. Intensive treatment normalized and eliminated the signs of diabetic ketoacidosis. She is so far treated with a conservative insulin treatment with premixed and fast acting insulins. **Molecular analysis**: The most common molecular abnormality of GAA trinucleotide repeats expansion in the intron 1 was found in both the proband and her brother. The number of repeats in the siblings was: + 300 GAA (1490bp) (healthy individuals have 5 to 30 GAA repeat expansions, affected individuals between 70 and more than 1,000). The parents were heterozygous with FXN of 9 -10 GAA (490 bp). **Course**: All the signs progressed, and now at the age of 19 years the girl is bound to a wheel chair unable to walk without help. The brother is ataxic and still able to function on his own.

Discussion

The prevalence of FA has been estimated at 1/50.000 in Caucasians; it is rare among sub-Saharan Africans and was not reported in the Far East (7). Hirayama et al., (8) estimated prevalence of FA in 2, 4% of all Japanese patients with spino-cerebellar degeneration (4,53 per 100,000 for all forms). High frequency of FA in Cyprus was reported in Cyprus and Quebec (9, 10). The incidence of FA estimated from the frequency of parental consanguinity in Italy was between 1 in 22.000 and 1 in 25.000 (11). In the general population of Finland, the carrier frequency was only 1 in 500, corresponding to a birth incidence of 1 in a million (12). Most of the cases of FA (97-98%) are due to expansion of a GAA trinucleotide repeat in intron 1 of the FXN gene (3, 13). The rest of the cases of FA are due to point mutations in the FXN gene. The mean allele length was significantly higher in FA patients with diabetes (14) and in those with cardiomyopathy (15,16). In addition, larger GAA expansions correlated with earlier age at onset and shorter times to loss of ambulation (17). FA does not show typical features observed in other dynamic mutation disorders, such as anticipation (16). Frataxin insufficiency leads to mitochrondrial dysfunction (18). In addition, studies on hearth biopsies and fibroblast

cultures showed that the iron-induced oxygen radicals affect the oxidative phosphorylation in FA. A direct frataxin action on mitochondrial energy activation and oxidative phosphorylation was also demonstrated (19). In his 1970 report Podolsky and Sheremata described two sisters with FA, insulin dependent diabetes mellitus and diffuses precordial T wave inversion (20). He speculated that the link between FA and IDDM is due to pleitropic effects of an abnormal gene in homozygotes. A mounting body of evidence further confirmed the high frequency of diabetes among patients with FA (1, 21, 22, 23). Indeed, FA is associated with a high incidence of diabetes mellitus (1, 24). Twenty-three percent of FA patients were found to have diabetes and 4 developed diabetic ketosis terminally (25). Clinically apparent diabetes is seen in approximately 18% of the affected individuals, while impaired glucose tolerance is present in up to 39% of FA patients (26). It was speculated that a heterozygous expansion of the X25/frataxin GAA repeat in healthy individuals is also associated with insulin resistance and could be a genetic co-factor in the pathogenesis of mitochondrial types of diabetes (26). These findings support the concept that a membrane abnormality that alters the binding function of the insulin receptor is present in FA (27). Rapid progression from chemical to clinical diabetes suggests that patients with FA and mild abnormalities of glucose tolerance should be regularly reassessed for insulin-dependent DM (28, 29). The proband we described manifested the diabetes as ketoacidosis, after FA and the hypertrophic cardiomyopathy was diagnosed. Bertoni et al., (30) showed high percentage (45%) of cardiac involvement in FA patients presented as left ventricular hypertrophy. Hypertrophy was of concentric type in 27% and in 18% of cases was of asymmetric type. Concentric left ventricle thickening, the most common echocardiographic finding, was detected in 68% of children with FA by Alborias et al. (31). All of them had ECG depolarization abnormalities. Günal et al., (32) also reported high percentage (58%) of cardiomyopathy in children with FA. The proband and her brother with FA in our family had also been proven to have hypertrophic cardiomiopathy. No effective treatment for FA is available so far. Gene therapy and protein replacement strategies for FA are promising approaches for the future. In addition, a number reports have focused on small molecule activators of FXN gene expression as potential therapeutics (18). Erythropoietin increased frataxine levels in lymphocytes and reduced the oxidative stress markers but did not bring clinical improvement (33). Trials with idebenone (a mitochondrially localized antioxidant) seemed to show amelioration of the cardiomyopathy in FRDA patients (34). Coenzyme Q and vitamine E have been also tried without convincing effects (35).

Conclusion

This is a report of family with FA. The 14 years old girl with had progression of signs of ataxia and complete manifestations of FA. In addition, she patient developed type 1 diabetes mellitus and, consequtively signs of hyperthrophic cardiomyopathy. Moreover, her brother was shown to have FA and hypertrophic cardiomyopathy. The frataxin gene analysis showed GAA trinucleotide repeat expansion in intron 1 with + 300 GAA repeats (1490bp) (normal: 5 to 30 GAA repeat expansions) in both probands. Heterozygocity was proven in the parents. Although relatively frequent accompanying conditions in FA, diabetes mellitus type 1 and hypertrophic cardiomyopathy are infrequently present in one patient.

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