1. INTRODUCTION

Friedreich’s 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, pes cavus, positive Babinski sign and scoliosis. The mean life span of FA patients is ~35 years. Frequently reported causes of death are cardiomyopathy and diabetic complications (1). Friedreich’s ataxia is caused by mutations in frataxin gene (mapped on chromosome 9q13). The product of the gene, the other 2% are due to point mutations (1). The rest of the cases of FA are due to expansion of a GAA trinucleotide repeat (4). Longer expanded repeats cause more profound frataxin deficiency and are associated with earlier onset and severe for of FA (5, 6).

2. CASE REPORT

The proband was born after uneventful pregnancy and delivery to healthy young parents. Progressive signs of ataxia in this child were noted before the age of twelve. At the referral, this twelve years old child had hypoactive knee and ankle jerks, unstable gait with subtle incoordination of limb movements. In addition, impairment of position and vibratory senses, dysarthria, dysmetria, intentional tremor, pes cavus, Babinski sign and scoliosis were also discovered. All the signs progressed, and now at the age of 19 years she is bound to a wheelchair unable to walk. Her brother started to show ataxia at the age of 8 years and subsequent analysis also showed hypertrophic cardiomyopathy. His mutational analysis revealed the same frataxin abnormality with +300 GAA repeats. So far, no signs of diabetes occurred. The parental DNA was not available for analysis.

Key words: Friedreich’s ataxia, diabetes mellitus type 1, hypertrophic cardiomyopathy, siblings

3. 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). Hiroyama 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 diabe-
tes (14) and in those with cardiomyopat-
y (14, 15, and 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 mitochondrial dysfunction (18). In addition, studies on heathy 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 described two sisters with FA, insulin dependent diabetes mellitus and diabesity type T wave inversion (20). He speculated that the link between FA and IDDM is due to pleiotropic effects of an abnormal gene in homoygotes. A mounting body of evidence further confirmed the high frequency of diabetes among patients with FA (21, 22, 23, and 1). Indeed, FA is associated with a high incidence of diabetes mellitus (24, 1). 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 keto-acidosis, after FA and the hypertrophic cardiomyopathy were 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 Albo-
rías et al (31). All of them had ECG re-
orientation abnormalities. Gúnal et al. (32) also reported high per-centange (58%) of cardiomyopathy in children with FA. The proband and her brother with FA in our family had also been proven to have hypertrophic cardiomyopathy.

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 therapeu-
tics (18). Erythropoetin increased fra-
taxine levels in lymphocytes and reduced the oxidative stress markers but did not bring clinical improvement (33). Tri-
al with idebenone (a mitochondrially localized antioxidant) seemed to show amelioration of the cardiomyopathy in FRDA patients (34).

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