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Evaluation of the Cases with Friedreich Ataxia

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SUMMARY

Friedreich ataxia is an autosomal recessive neurodegenerative disease, which is the most common cause of inherited ataxias. About 95% of the patients demonstrate an expansion of a GAA trinucleotide repeat in intron 1 of the FRDA gene on chromosome 9q13. This leads to reduced levels of frataxin which has an important role in iron homeostasis. Friedreich ataxia is the result of accumulation of iron in mitochondria leading to excess production of free radicals, defects in specific mitochondrial enzymes, enhanced sensitivity to oxidative stress, and eventually free-radical mediated cell death. Currently there is no effective therapy for the disease, but antioxidant therapy has shown promise especially in cardiac involvement. Early identification of individuals with Friedreich ataxia and precise characterization of impairments and functional limitations gain importance as symptomatic treatment, rehabilitation and genetic counseling are considered. Here, we present the clinical findings of five cases with Friedreich ataxia who had homozygous GAA trinucleotide expansion and emphasize that Friedreich ataxia should be considered in the differential diagnosis of cases who present with progressive ataxia.

Key words: *Friedreich ataxia, child, progressive ataxia*

ÖZET

Friedreich Ataksili Olgularımızın Değerlendirilmesi

Friedreich ataksi otozomal resesif geçişli nörodejeneratif bir hastalık olup kalıtsal ataksilerin en sık nedenidir. Hastaların %95'inde kromozom 9q13 üzerinde bulunan FRDA geninin birinci intronunda GAA trinukleotid tekrar artışı mevcuttur. Bu durum demir homeostazında önemli bir role sahip olan frataksin proteininin düzeyinde azalışa yol açar. Friedreich ataksi hastalığının patogenezinden mitokondrilerde demir birikimi ve bunun neden olduğu spesifik mitokondriyal enzim eksiklikleri, oksidatif strese artmış duyarlılık ve serbest radikal aracılı hücre ölümü sorumludur. Günümüzde hastalığın etkin bir tedavisi yoktur, ancak antioksidan tedaviler özellikle kardiyak tutulumda umut vaat etmektedir. Friedreich ataksili olguların erken tanınması ve işlevsel kısıtlılıkların zamanında belirlenmesi rehabilitasyon, semptomatik tedavi ve genetik danışma açısından önemlidir. Bu yazıda homozigot GAA artışına sahip beş hastanın klinik özellikleri sunulmakta ve ilerleyici ataksi ile başvuran hastalarda ayırıcı tanıda Friedreich ataksinin düşünülmesinin gerekliliğini vurgulamaktır.

Anahtar kelimeler: *Friedreich ataksi, çocuk, ilerleyici ataksi*

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Introduction

Friedreich ataxia is a neurodegenerative disorder which is characterized with progressive ataxia. It is first described by Nikolaus Friedreich in 1863, and it is the most common cause of hereditary ataxia. The prevalence of the disease ranges between 1/30000 and 1/50000 (1). The prevalence in Turkey is unknown. It is an autosomal recessive disease and the related gene is FRDA which is located on chromosome 9q13 (2). Homozygous GAA expansion in the first intron of FRDA gene is found in approximately 95-98% of cases (3). Point mutations in the same region are reported in 2-5% of cases (4). Truncal ataxia, areflexia, loss of vibration sense, extensor plantar reflex, pes cavus, dysmetria, nystagmus, dysarthria, scoliosis and abnormal electrocardiography are the most common findings of the disease (5). There is not an effective treatment for the disease and physical rehabilitation, antispasticity drugs and correction of scoliosis and deformities are the mainstays of treatment.

Material and Methods

Five cases with Friedreich ataxia who had homozygous GAA trinucleotid expansion were included in the study. The cases are regularly followed in Dokuz Eylül University School of Medicine Division of Child Neurology. The clinic, radiologic and genetic features of the cases was evaluated. DNA isolation was performed using Miller's salting out procedure. First intron of the Frataxin Gene containing GAA trinucleotide repeat site was amplified using FAF (gggATTggTTgCCAgTgCTTAAAAgTTAg) and FA R (gATCTAAggACCATCATggCCACACTTgCC) primer pair. PCR was performed using TaKaRa LATaq™ Hot Start DNA polymerase (Takara Bio Inc. Japan) and the protocol supplied by manufacturer. Electrophoresis of the PCR products was carried out on 1% agarose gel during 1.5 h at 100 V. The gel was imaged and evaluated using *UVI*tech (UVItech Limited, England)

gel imaging and documentation system. Approximate GAA tri-nucleotide expansion was calculated by subtracting 475 (basic PCR product in bp) from the molecular weight of the amplicons and dividing by 3.

Results

Demographic, genetic, laboratory and clinical features of five cases with Friedreich ataxia who had homozygous trinucleotide expansion are presented in (Table I and II).

There were three girls and two boys, and the age of patients ranged between 10 and15 years. The parents of two cases (case 2 and 5) were consanguineous.

The first symptom in all cases was ataxia. Case 5 also had dysarthria as a presenting symptom. Physical examination of the cases revealed ataxia, dysfunction in cerebellar tests, areflexia, weakness and loss of vibration sense. All of the cases also had pes cavus. None of the cases had nystagmus and one case (case 5) had dysarthria.

All of the cases had hypertrophic cardiomyopathy of variable severity at presentation. Three cases had kyphoscoliosis and all of these cases were girls (case 2, 3 and 4). The kyphoscoliosis of the cases was mild and was controlled with corset and physical rehabilitation. None of the cases had diabetes mellitus.

Neurophysiological evolutions including nerve conduction velocity and somatosensorial evoked potentials showed varying degrees of abnormalities like polyneuropathy. Craniospinal magnetic resonance imaging of one case (case 2) revealed cerebellar and cervicothoracal atrophy (Figure 2 A,B)

The patients are still followed in our department regularly and continue physical rehabilitation.

Discussion

Friedreich ataxia is a neurodegenerative disorder which is characterized with progressive ataxia. The disease primarily affects medulla spinalis, brainstem and cerebellum. First of all, sensory neurons in the

Table I. Demographic and genetic features of cases

Number of the case	The number of GAA trinucleotid expansion	Sex	Age	Consanguinity	The age of onset of symptoms	Age of diagnosis
1	Cannot be calculated due to large expansion	Boy	15	-	7	14
2	~ 750/750	Girl	10	+	3	7
3	~ 500/675	Girl	13	-	7	10
4	~ 675 /925	Girl	12	-	10	12
5	~ 850/1000	Boy	13	+	5	13

Table II. Clinical and laboratory features of cases

Number of the case	First sign of disease	Neurologic examination findings	Neurophysiologic evaluations	Neuroradiologic evaluations	Cardiac involvement
1	Gait imbalance	Ataxia Loss of reflexes Pes cavus	Sensorimotor polyneuropathy	Normal	Hypertrophic cardiomyopathy
2	Gait imbalance	Ataxia Loss of reflexes Scoliosis Pes cavus	Abnormal somatosensorial evoked potentials	Cerebellar and cervicothoracal atrophy	Hypertrophic cardiomyopathy
3	Gait imbalance	Ataxia Loss of reflexes Scoliosis Pes cavus	Abnormal somatosensorial evoked potentials	Normal	Hypertrophic cardiomyopathy
4	Gait imbalance	Ataxia Loss of reflexes Scoliosis Pes cavus	Sensorimotor polyneuropathy	Normal	Hypertrophic cardiomyopathy
5	Gait imbalance and dysarthria	Ataxia Loss of reflexes Pes cavus	Sensorimotor polyneuropathy	Cervical hydromyelia	Hypertrophic cardiomyopathy

dorsal root of medulla spinalis are affected and as the disease progresses, neurons of the dorsal column, spinocerebellar and corticospinal tracts undergo neurodegeneration. Afferent visual pathways may also be affected. Besides nervous system, degeneration of cardiomyocytes and β cells of pancreas are also reported (6,7). Although symptoms of the disease start between the ages of 5-15, there may be early and late onset cases (5). First symptoms of the disease are ataxia, gait imbalance and weakness. Impairment in language and fine motor skills may occasionally be the first findings of disease. Ataxia is slowly progressive and mainly affects upper extremities and truncus. Truncal ataxia, areflexia, loss of vibration sense, extensor plantar reflex, pes cavus, dysmetria, nystagmus, dysarthria, scoliosis and abnormal electrocardiography are the most common findings in advanced cases. Approximately 10-15% of cases develop diabetes mellitus due to the destruction of β cells in pancreas. The patients generally become bedridden in 15-20 years of age. Echocardiographic

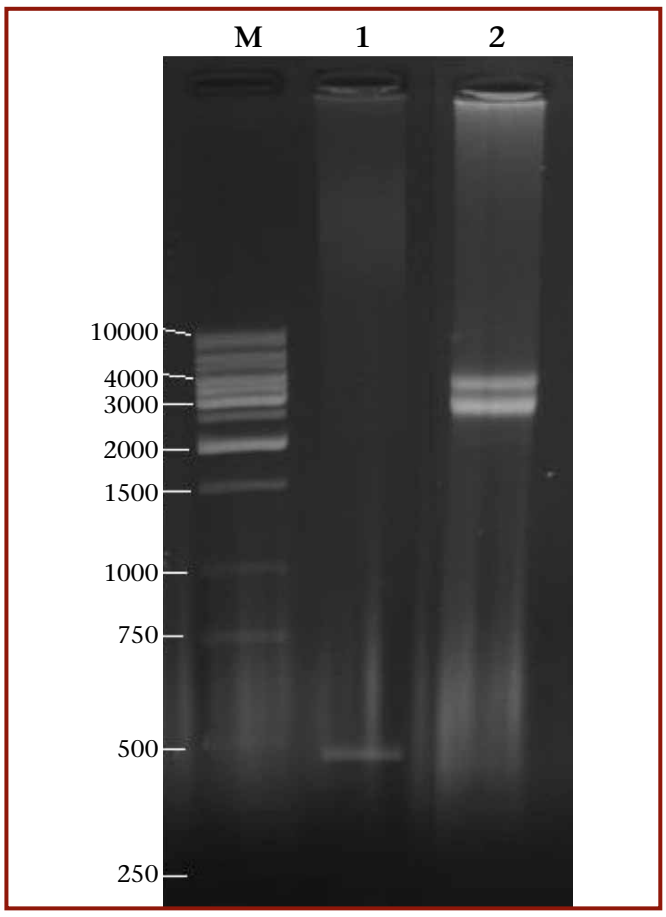

Figure 1. PCR products of specimens on 1% agarose gel (Marker; 1Kb Gene Ruler, Fermentas), **1:** Control (approximately 4-37 trinucleotid expansion), **2:** Patient (approximately 850/1000) trinucleotid expansion).

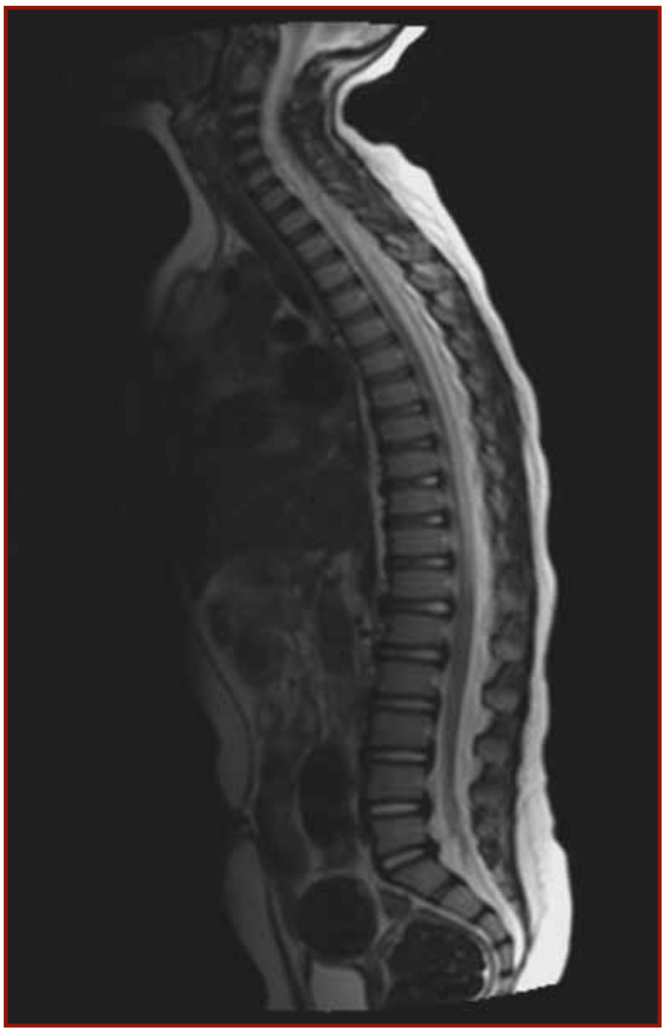

Figure 2A. spinal magnetic resonance imaging demonstrating cervicothoracal atrophy.

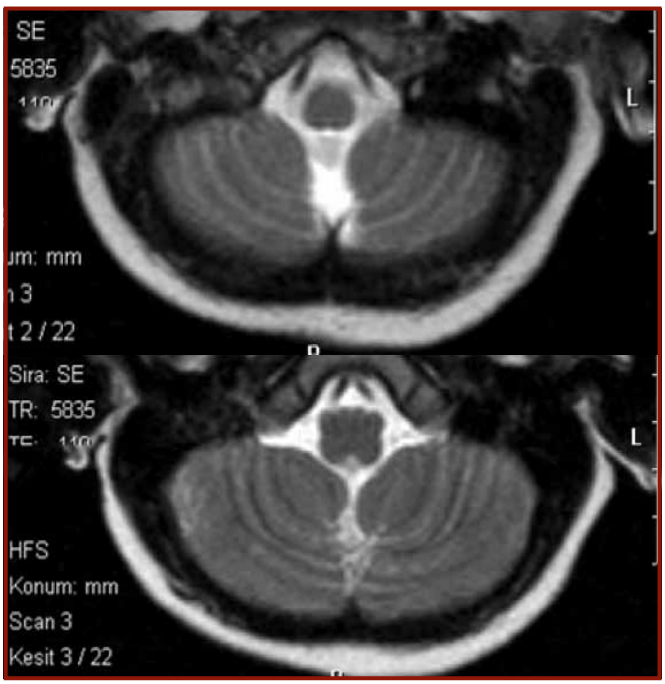

Figure 2A. Brain magnetic resonance imaging demostrating cerebellar atrophy.

and electrocardiographic abnormalities are reported in 79-90 of cases (5,8). The avarage age of death is 36 years and the most common cause of death is congestive heart failure (5). Regarding our cases, the mean age of onset of symptoms was 6.5 years and all of the cases were symptomatic at the age of 10 years. Although the number of our cases was scarce, the mean age of onset in our cases was earlier than the cases reported in classical literature. The presenting symptom in our cases was ataxia and all of the cases also had areflexia, loss of vibration sense, weakness and pes cavus. The clinical findings of the cases were in accordance with literature findings (5,9). Irrespective of disease duration and age onset of symptoms, all cases had varying severity of hypertrophic cardiomyopathy. Although the number of cases was scarce, hypertrophic cardiomyopathy was a striking finding. None of our cases had diabetes or impaired glucose metabolism. The epidemiologic data of Turkish cases are limited in the literature. We believe that the data of Turkish cases regarding genotype-phenotype correlations will increase in the near future because the number of laboratories working on genetic diagnosis of disease is increasing.

One of the most striking finding in our study was the fact that it took approximately five years in order to reach the exact diagnosis. The reasons for the delay in diagnosis may be socioeconomical conditions of the family, slow progression of disease and many unnecessary evaluations like detailed metabolic tests. Since Friedreich ataxia is the most common cause of hereditary ataxias, it should be considered as the first disease in the differential diagnosis of childhood cases who present with progressive ataxia. Although there is not an effective treatment for the disease, early diagnosis is very important for both genetic consultation and to prevent unnecessary evaluations. On the other hand, early diagnosis prevents many of the physical deformities and cardiac functions are more closely monitored.

The radiological abnormalities detected in craniospinal magnetic resonance imaging are mainly cerebellar and spinal atrophy (8). At present, only one of our cases has cerebellar and spinal atrophy, but as the disease progresses, the number of cases with abnormal radiologic findings may increase. Nerve conduction velocity and somatosensorial evoked potential of the cases showed varying degrees of abnormalities.

The gene responsible for Friedreich ataxia is FRDA which is located on chromosome 9q13 (2). It encodes frataxin protein which is composed of 210 aminoacids. Frataxin is located in the inner membrane of mitochondria and it plays important roles in iron metabolism. Expression of frataxin is markedly decreased in Friedreich ataxia. Mitochondrial functions are impaired and complex I, II and III of the respiratory chain complex become deficient in Friedreich ataxia. It is considered that iron accumulation and increase in the amount of free radicals cause mitochondrial dysfunction (10,11). It is demonstrated that frataxin plays a critical role in the synthesis of iron-sulphur proteins that are involved in electron transport and energy production (12). On the other hand, it acts as an iron chaperon in the regeneration of aconitase enzyme that takes place in citric acid cycle (13). Homozygous GAA expansion in the first intron of FRDA gene is found in approximately 95-98% of cases (9). Point mutations in the same region are reported in 2-5% of cases (10). A normal individual has 6 to 30 copies of this trinucleotide. In patients with Friedreich ataxia, the number of expansion ranges between 120 and 1700, and most of the cases have a trinucleotide expansion between 800 and 1000. The mechanism how GAA trinucleotid expansion causes decreased expression of frataxin is not completely understood. According to the "histon code theory", trinucleotid expansion impairs the structure of DNA and histon acytlase enzymes are activated. Activation of these enzymes breaks down the acetyl groups of histon proteins and as result of this, the gene becomes silent (14). The mean age of onset and the severity of symptoms are closely associated with the number of trinucleotid expansion (15). All of our cases had increased trinucleotid expansion. Two of our cases (case 2 and 5) whose trinucleotid expansions were more than other cases showed more severe symptoms like positive magnetic resonance imaging findings, severe ataxia and rapidly progressive disease compared with the others. The mean age of onset of these cases were also earlier than the others.

In conclusion, the clinical and laboratory features of our cases with homozygous GAA expansion are presented with their functional ambulatory findings. In the differential diagnosis of childhood cases who present with slowly progressive ataxia, Friedrich ataxia as the most common cause of hereditary ataxia

should be the first disease that should be considered in differential diagnosis.

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