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Diagnostic Delay and Clinical Features in Friedreich's Ataxia

Friedreich Ataksisinde Tanı Gecikmesi ve Klinik Özellikler

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Abstract

Objective: Friedreich ataxia (FRDA) is the most frequent hereditary ataxia characterized by progressive gait and limb ataxia, dysarthria, sensory loss, and muscular weakness. Due to insufficient awareness of patients and their relatives, poor knowledge of healthcare professionals, and difficulty in accessing diagnostic tests, delay in diagnosis is seen in many diseases, especially in rare diseases. In this study, the diagnostic delay, and clinical features of individuals with FRDA were investigated.

Materials and Methods: Individuals who fulfilled the criteria for Harding clinical diagnosis and who had increased GAA repetition in the genetic examination were included in the study. Demographic and clinical data of the patients such as initial symptoms, age at symptom onset, time from the onset of symptoms to the diagnosis, and comorbid conditions were recorded. In addition, detailed neurological examinations of the patients were made, and they were evaluated with the scale for the assessment and rating of ataxia (SARA).

Results: A total of 22 patients, 12 males, and 10 females, were included in the study. The mean age of the individuals was 30.4±6.3 (19-41). Age of symptom onset was 19±5.6 (9-32), age at diagnosis was 22.1±6.1 (13-33), and the time from onset of symptoms to diagnosis was 3.03±2.66 (0.2-9) years. While the first symptom of 19 patients (86.4%) was trunk ataxia, the first symptom of 3 patients (13.6%) was extremity ataxia. Eight (36.4%) patients were non-ambulatory and 14 (63.6%) were ambulatory. The mean total SARA score was 18.2±6.7 [median 19.5 (7-30)].

Conclusion: This study is the first study to evaluate the diagnosis delay in patients with FRDA in our country. Although FRDA was the most common hereditary ataxia, in our study, it was shown that there was a significant delay in diagnosis in patients with FRDA. There is a need for studies that will raise awareness of public and health professionals about FRDA.

Keywords: Friedreich's ataxia, diagnostic delay, hereditary ataxia

Öz

Amaç: Friedreich ataksisi (FRDA) progresif yürüyüş ve ekstremite ataksisi, dizartri, duyu kaybı ve kas güçsüzlüğü ile karakterize en sık kalıtsal ataksidir. Birçok hastalıkta, özellikle nadir hastalıklarda; hasta ve hasta yakınlarının yetersiz farkındalığı, sağlık uzmanlarının bilgi birikiminin yeterli olmaması ve tanı testlerine erişmekte güçlük nedeniyle tanı gecikmesi görülür. Bu çalışmada, FRDA'lı bireylerin tanı gecikmesi ve klinik özellikleri araştırılmıştır.

Gereç ve Yöntem: Harding klinik tanı kriterlerini karşılayan ve genetik incelemede artmış GAA trinükleotid tekrarı olan bireyler çalışmaya alınmıştır. Hastaların başlangıç semptomları, semptom başlangıç yaşı, semptom başlangıcından tanıya kadar geçen süre ve komorbid durumlar gibi demografik ve klinik verileri kaydedilmiştir. Ayrıca hastaların detaylı nörolojik muayeneleri yapılmış ve ataksi değerlendirme ve derecelendirme skalası (SARA) ile kaydedilmiştir.

Bulgular: Çalışmaya 12 erkek ve 10 kadın olmak üzere toplam 22 hasta dahil edildi. Bireylerin yaş ortalaması 30,4±6,3 (19-41) idi. Semptom başlangıç yaşı 19±5,6 (9-32), tanı yaşı 22,1±6,1 (13-33) ve semptomların başlamasından tanıya kadar geçen süre 3,03±2,66 (0,2-9) yıl idi. On dokuz olgunun ilk belirtisi (%86,4) gövde ataksisi iken, 3 olgunun (%13,6) ilk belirtisi ekstremite ataksisi idi. Sekiz (%36,4) olgu ambulatuvar iken 14 (%63,6) olgu non-ambulatuvar idi. Ortalama toplam SARA skoru 18,2±6,7 idi [medyan 19,5 (7-30)].

Sonuç: Bu çalışma ülkemizde FRDA hastalarında tanı gecikmesini değerlendiren ilk çalışmadır. Her ne kadar FRDA en sık kalıtsal ataksi olsa da, çalışmamızda FRDA'lı hastalarda tanıda önemli bir gecikme olduğu gösterilmiştir. Toplumun ve sağlık profesyonellerinin FRDA konusunda farkındalıklarını artıracak çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Friedreich ataksisi, tanısal gecikme, kalıtsal ataksi

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Introduction

Hereditary ataxias are genetic diseases that progress with symptoms such as slow walking, gait ataxia, impaired coordination and speech disturbance. Friedreich's ataxia (FRDA) is the most common hereditary ataxia that occurs as a result of an increase in the number of GAA triplet repeats in the frataxin gene (*FXN*) (1). Homozygous GAA trinucleotide repeat expansions in the first intron of FXN occur in 96% of affected individuals and reduce frataxin expression. The remaining individuals are compound heterozygous for a GAA expansion (2). Its estimated prevalence is reported to be 3-4 per 100,000 (3). Lack of frataxin protein leads to decreased mitochondrial ATP production, increased mitochondrial iron and oxidative stress (4). Progressive gait and limb ataxia, decreased vibration sensation, and reflex loss in the lower extremities form the basis of the comprehensive clinical phenotype. However, cardiomyopathy, scoliosis, and diabetes mellitus often accompany the disease. The initial neurological symptoms of FRDA most often occur during puberty, but there are also early-onset and late-onset variants. However, in many patients, diagnosis can only be made years after initial symptoms appear (3). Non-neurological symptoms, especially scoliosis and pes cavus, may appear a few years before neurological symptoms. Ataxia occurs as a result of peripheral sensory neuropathy and degeneration of the spinocerebellar tract and deep cerebellar nuclei (5). Life expectancy is on average 40 to 50 years; however, patients sometimes survive well in the sixth, seventh, or even eighth decade (3). The most common cause of death in FRDA is cardiac dysfunction, i.e. congestive heart failure or arrhythmia. A study evaluating 61 individuals with FRDA retrospectively reported an average age of mortality of 36.5 years (6). Other causes of death include stroke, ischemic heart disease and pneumonia.

No treatment has yet been approved for FRDA. The proposed treatment options include protein and gene replacement therapies, antioxidants, iron chelators, inflammation modulators and medications that increase frataxin levels (1,7). Also, interferon-gamma (IFN-γ) has been shown to induce frataxin production in many cell types and its benefits have been shown in clinical studies (8,9).

Delayed diagnosis is a common problem, especially in rare diseases. Although the definition of the rare or orphan disease varies, diseases seen less than 1/2,000 in Europe and less than 1/200,000 in the United States are defined as rare diseases (10). In many studies, the time until the diagnosis of various diseases has been investigated and it has been shown that there may be a delay in diagnosis in many rare or common diseases (11,12,13). Early diagnosis is important to ensure that affected individuals receive appropriate support, multidisciplinary management as well as genetic counseling, if they wish to. On the contrary, delayed diagnosis causes problems such as uncertainty about the future, lack of information, and difficulty in having access to appropriate health services.

Despite demographic data and clinical features that have been described well in studies on FRDA, data on delayed diagnosis are limited. In this study, the demographic and clinical characteristics of individuals with FRDA who were genetically diagnosed in a university hospital were described, and the time from the onset of the first symptom to the diagnosis was investigated.

Materials and Methods

The Ethics Committee approval was obtained from the Faculty of Medicine of Erciyes University (decision no: 220/271, date: 10.06.2020). Subjects who fulfilled the Harding clinical diagnostic criteria (14) and who were definitely diagnosed with increased GAA repeats based on a genetic study between 01.01.2015 and 30.12.2019 at the Neurology Clinic of Erciyes University were included in the study. Informed consent was obtained from all participants included in the study. The demographic data, initial symptoms, age at the time of onset of initial symptoms, the time from onset of symptoms until the diagnosis, and additional diseases of the patients were recorded. In addition, detailed neurological examinations of the patients were performed, and findings were recorded using the scale for the assessment and rating of ataxia (SARA).

The SARA is a semi-quantitative scale scored from 0 (no ataxia) to 40 (most severe ataxia). It consists of 8 items: (1) Gait (score, 0-8); (2) stance (score, 0-6); (3) sitting (score, 0-4); (4) speech disturbance (score, 0-6); (5) dysmetria in finger chase (score, 0-4); (6) tremor in the nose-finger test (score, 0-4); (7) fast alternating hand movements (score, 0-4); and (8) heel-shin slide (score, 0-4). Limb kinetic functions in items 5, 6, 7, and 8 are independently graded for both sides and the arithmetic mean of both sides is included in the SARA total score (15). At least 2 points of increase in the SARA score between before and after treatment during the follow-up period was defined as a clinical benefit for idebenone and IFN-γ.

Endocrinological and cardiological evaluations were performed in all patients. Also, motor and sensory nerve conduction studies were performed using Medelec Synergy (Oxford Instruments Medical, Surrey, the UK) device for the presence of neuropathy.

Statistical Analysis

The data were analyzed using IBM SPSS V23. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether data were distributed normally. Mann-Whitney U test was used for comparison of non-normal distribution data and analysis results were presented as median (minimum-maximum). Independent samples t-test was used to compare data that were normally distributed, and the results of the analysis were presented as mean ± standard deviation. Categorical data were examined by using chi-square test and the results were presented as frequency (%). The level of significance was taken as $p<0.05$.

Results

A total of 22 patients, 12 males and 10 females, were included in the study. There were 18 index patients, and 4 patients were their relatives. The mean age was 30.4±6.3 years (19-41). Age at symptom onset was 19±5.6 years (9-32), age at diagnosis was 22.1±6.1 years (13-33), and the time from onset of symptoms to diagnosis was 3.03±2.66 years (0.2-9). Eleven patients (50%) were university graduates, 3 (13.6%) were high school and 8 (36.4%) were secondary school graduates. While the initial symptom of 19 patients (86.4%) was truncal ataxia, the initial symptom of 3 patients (13.6%) was extremity ataxia. The average total SARA score was 18.2±6.7 [median 19.5 (7-30)]. Eight (36.4%) patients were non-ambulatory and 14 (63.6%) were ambulatory. Cardiomyopathy, scoliosis, and neuropathy were present in 2

(22.7%), 16 (72.7%), and 5 (22.7%) patients, respectively. Demographic and clinical data of the patients are given in Tables 1 and 2. Also, the treatments received by the participants are listed in Table 3.

When the correlation between delayed diagnosis and other variables was evaluated, there was no significant correlation between educational status and delayed diagnosis ($p>0.05$), whereas time to diagnosis was statistically significantly shorter for patients who were relatives of the index patients, compared to index patients ($p<0.001$). Also, there was no correlation between diagnostic delay and GAA repeat number ($p>0.05$) and initial symptom ($p>0.05$).

Table 1. Demographic data

Demographic data	n	%	Mean ± SD	Median	Minimum	Maximum
Age			30.4±6.3	31	19	41
Sex						
Male	12	54.5	-	-	-	-
Female	10	45.5	-	-	-	-
Educational status						
Primary school	0	0	-	-	-	-
Secondary school	8	36.4	-	-	-	-
High school	3	13.6	-	-	-	-
University	11	50	-	-	-	-
Index-kinship						
Index	18	81.8	-	-	-	-
Relative	4	18.2	-	-	-	-
Age at symptom onset	-	-	19±5.6	19.5	9	32
Age at diagnosis	-	-	22.1±6.1	21	13	33
Diagnostic delay (year)	-	-	3.03±2.66	3	0.2	9

SD: Standard deviation

Table 2. Clinical data

Clinical data	n	%	Mean ± SD	Median	Minimum	Maximum
First symptom						
Trunk ataxia	19	86.4	-	-	-	-
Extremity ataxia	3	13.6	-	-	-	-
SARA						
Total	-	-	18.2±6.7	19.5	7	30
Gait	-	-	5.3±2.1	5.5	2	8
Stance	-	-	3.7±1.9	4	1	6
Sitting	-	-	1±1	1	0	3
Speaking	-	-	1.4±1.2	1	0	4
Finger chase	-	-	1.2±0.4	1	1	2
Nose-finger test	-	-	1.2±0.6	1	0	2
Fast alternating hand movements	-	-	1.8±0.7	2	1	3
Knee heel test	-	-	2.6±1.1	3	0	4
Cardiomyopathy	2	9.1	-	-	-	-
Scoliosis	16	72.7	-	-	-	-
Neuropathy	5	22.7	-	-	-	-

SD: Standard deviation, SARA: Scale for the assessment and rating of ataxia

Table 3. The treatments received by the participants

Treatment	n	%	Duration (month) (mean ± SD)	Clinical benefit* (n, %)	Change in SARA score (median, min-max)
Idebenone	20	90.9	17.9±9.4	2, 9.1	0, 0-2
Interferon-γ	18	81.8	9.27±4.7	11, 52.4	2, 0-4
Coenzyme Q10	11	50.0	59.4±15.4	NA	NA
Physiotherapy	5	22.7	50.7±17.1	NA	NA

*Percentage of patients with at least 2 points increase in the SARA score between before and after treatment. min: Minimum, max: Maximum, NA: Not applicable, SD: Standard deviation, SARA: Scale for the assessment and rating of ataxia

Discussion

This study is the first study to evaluate delayed diagnosis in patients with FRDA in Turkey. Although FRDA is the most common hereditary ataxia, our study demonstrated that there is a significant diagnostic delay in patients with FRDA.

Reetz et al.'s (16) comprehensive European FRDA consortium study conducted on 592 patients with FRDA reported gait ataxia as the most common initial symptom, as in the case of our study, and mean age at symptom onset as 15.7±10.4 years. Also, the initial symptom was gait ataxia in all individuals with FRDA in our previous study (8). Stephenson et al. (17) reported a mean age at symptom onset of 19.5±8.1 years and mean age at diagnosis of 22.1±8.1. In the study of "The European Friedreich's Ataxia Consortium for Translational Studies (EFACTS)", which investigated the natural course of individuals with FRDA, patients were evaluated at diagnosis and in the first and second years, and their SARA scores were recorded. The reported mean total SARA score at the time of diagnosis was 21.9±9.6. In our study, the mean total SARA score was 18.2±6.7. This difference can be ascribed to the lower average age of our cohort compared to that of the EFACTS study (30.4±6.3 years vs. 37.9±13.9 years). It is noteworthy that the clinical characteristics of patients with FRDA included in our study are consistent with those reported in larger patient series in the literature.

In our study, the median diagnostic delay, the median time from symptom onset to genetic diagnosis, was 3 years. The difference in diagnostic delay in various diseases can be explained in several ways. First, the prevalence of diseases in society affects the awareness of health professionals about the diseases, resulting in a later diagnosis of rare diseases (18). In addition, diseases such as amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy, which affect patients' daily activities more and disrupt psychomotor functions, are diagnosed in a shorter time (11,13). A diagnostic delay of 1 year was reported in patients with ataxia telangiectasia (19) and a diagnostic delay of 1.2 years was reported in individuals with ALS (20). However, longer diagnostic delays have been reported in the literature. Mean diagnostic delays reported in the literature were 25.3 years for Parkin-related Parkinson's disease (21), 13.5 years for dopa-responsive dystonia (22), and 9.9 years for X-linked adrenoleukodystrophy (23). Pierucci et al. (13) reported that index patients, first patients diagnosed as having definitive hereditary hemorrhagic telangiectasia in a particular family, were demonstrated to be diagnosed in a significantly longer amount of time than relatives of index patients who were defined as non-index patients. Also, a negative correlation was established between educational status and diagnostic delay (13). Similarly, in our study, index patients were shown to be diagnosed in a longer time, and no correlation was found between educational status and diagnostic delay. As expected, awareness of FRDA in healthcare professionals and the family has increased for non-index individuals. This awareness causes an individual to consult health professionals in a shorter time and enables health professionals to make a genetic diagnosis upon faster clinical suspicion. In our study, no relationship was found between the initial symptom type and the delay in diagnosis. Truncal ataxia was found to be the initial symptom in most individuals with FRDA and extremity ataxia in the remainder in this study. The fact that both initial symptoms seriously affect the daily life of individuals with FRDA may have caused the lack of significant difference in diagnosis delay time between the two groups. Although the genetic diagnosis of FRDA, the most common hereditary ataxia, is relatively easy, individuals with FRDA are often diagnosed late despite disrupting psychomotor functions affecting individuals' daily life seriously.

Study Limitations

The limitations of this study are as follows: The study is of a retrospective design, which might lead to a shorter or longer evaluation of the diagnostic delay than it is. In addition, the limited number of patients in the study resulting from the prevalence of FRDA is among the limitations. However, the diagnostic delay determined in our study arises from fundamental reasons, including the awareness about the disease symptoms of patients and their relatives, difficulty in accessing healthcare institutions, awareness about FRDA of healthcare professionals, and difficulty in accessing diagnostic facilities. Individual assessment of these factors will be useful for a better understanding of the underlying causes of diagnostic delay. The strengths of our study are the number of patients diagnosed using a genetic method, who were included in a study for a disease with low prevalence. In addition, the neurological examinations of these individuals were recorded using SARA, a valid and reliable scale for FRDA.

Conclusion

In conclusion, our study assessed the diagnostic delay in FRDA which is the most common autosomal recessive ataxia, and demonstrated that there was a serious diagnostic delay. Further studies are needed to increase awareness about FRDA of healthcare professionals as well as society. The general population should be educated about the symptoms and signs of the disease to detect ataxias in the early stages. Medical training programs on the signs and symptoms of hereditary ataxias for healthcare providers at all levels may shorten the time to diagnosis.

Ethics

Ethics Committee Approval: The Ethics Committee approval was obtained from the Faculty of Medicine of Erciyes University (decision no: 220/271, date: 10.06.2020).

Informed Consent: Informed consent was obtained from all participants included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.F.Y., M.G., M.A., A.Ç.S., R.B., M.C., H.P., Design: M.F.Y., M.G., M.A., A.Ç.S., R.B., M.C., H.P., Data Collection or Processing: M.F.Y., M.G., M.A., A.Ç.S., R.B., M.C., H.P., Analysis or Interpretation: M.F.Y., M.G., M.A., A.Ç.S., R.B., M.C., H.P., Literature Search: M.F.Y., M.G., M.A., A.Ç.S., R.B., M.C., H.P., Writing: M.F.Y., M.G., M.A., A.Ç.S., R.B., M.C., H.P.

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