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Phenotypic and Genotypic Analysis of Hereditary Ataxia Patients in Sakarya City, Turkey

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ABSTRACT

Introduction: Hereditary ataxias are a group of heterogeneous diseases in regard to their clinical and genetic characteristics. Ataxia that progresses slowly may be accompanied by pyramidal and extrapyramidal findings, articulation disorders, ophthalmic movement disorders, neuropathic complaints, cognitive and behavioral abnormalities, and epilepsy. Definitive diagnosis in hereditary ataxias is based on molecular assays. History, clinical examination, laboratory and neuroimaging assist diagnosis. In our study, thirty-seven patients of suspected hereditary ataxia were examined with their clinical and genetic aspects, and the results compared with literature.

Method: Our study included 37 patients in 22 families who presented to our center between 2010–2016, and whose familial history and phenotypic features indicated hereditary ataxia. The patients were studied for clinical findings, family tree, neuroimaging, and laboratory findings. Advanced genetic investigations were performed on peripheral venous blood samples for hereditary ataxia.

Results: Of the 37 patients included in our study, 21 were females and 16 were males. Genetic analyses resulted in spinocerebellar ataxia (SCA) in four families (10 patients), Friedrich ataxia (FA) in three families (eight patients), and recessive ataxia due to point mutation in one family (two patients). SCA subtyping revealed SCA 1, 2, 6 and 8 in our patients. The remaining 16 patients included in our study could not be solved so far and are under investigation.

Conclusion: Hereditary ataxias are rare neurodegenerative disorders. Large genetic pool, ethnic and local differences complicate diagnosing even further. Our study contributes to the literature by reflecting phenotypic and genotypic characteristics of hereditary SCA patients in our region and reporting rare hereditary ataxia genotypes.

Keywords: Hereditary ataxia, genotype, phenotype, spinocerebellar ataxia, Friedrich's ataxia MRE-11 gene

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INTRODUCTION

Hereditary ataxias are a group of neurodegenerative disorders, dominated by clinically progressive ataxia, with heterogeneous clinical, radiological and genetic transmission properties (1). Inheritance may be of different forms including autosomal dominant (AD), autosomal recessive (AR), X-linked or mitochondrial (2).

Global epidemiological prevalence of hereditary spinocerebellar ataxia (HSCA) involve 0.0–5.6/10^5 for the AD form compared to 0.0–7.2/10^5 for the AR form (3). The most prevalent form is dominant spinocerebellar ataxia type 3 (SCA-3), followed by spinocerebellar ataxias type 2 (SCA-2) and type 6 (SCA-6) (1–3). The most common AR-HSCA is Friedreich's ataxia (FA), followed by oculomotor apraxia and ataxia telangiectasia (3, 4).

With many genetic subtypes, hereditary ataxia varies with region and ethnicity (4–6), which makes it difficult to determine the exact prevalence of the disease. The purpose of the present study is to investigate phenotypic and genotypic features of patients with hereditary ataxia in Sakarya City, to determine the particularity of the mutations and clinical findings observed in these patients, and to compare the results with the data from Turkey and international literature.

METHOD

Our study included 37 patients who were under follow-up for ataxia by our center and whose definitive diagnosis could not be established and who had clinically and radiologically suspected HSCA. We research

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22 family which of them had family history or not, but their disease duration were long and clinically suspected herediter ataxia so all of them accepted to the study. All patients underwent cerebral and spinal MRI scan. Using neuroimaging methods, etiologic factors that should be considered in differential diagnosis were ruled out, and possible comorbidities including particularly cerebellar, brainstem, cerebral and spinal cord atrophy were also investigated. Vascular, demyelinating, infectious, congenital factors and other factors such as space-occupying lesions that could cause ataxia in the patients included in the study were excluded. Physical examination findings including detailed neurological examination, presence of dysmorphic features, consanguineous marriage, and familial history of a similar condition were recorded for all patients, and they were categorized by phenotypic features. Families' potential genetic transmission characteristics were determined using the pedigree analysis. In addition, whole blood count, biochemistry panel (glucose, renal-liver function tests, electrolytes, lipid profile, creatine kinase (CK), hemoglobin A1 c, vitamin B12, vitamin E levels) and hormone profiles (thyroid function tests) were studied, patients assessed for celiac disease, and oral glucose tolerance test was performed for patients with suspected FA. Definitive diagnoses were made with advanced genetic analysis. Peripheral venous blood samples collected (in EDTA-containing tubes) from the patients were analyzed at the research laboratory of the molecular biology and genetics department of Boğaziçi University using the polymerase chain reaction (PCR) analytic method for cytosine-adenine-guanine (CAG) expansion in spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, 17, cytosine-thymine-guanine (CTG) expansion in SCA type 8, and for guanine-adenine-adenine (GAA) expansion for FA, and full exome sequencing analysis was performed in relevant patients. Patients who had no family history, firstly underwent to GAA expansion analyzes, but patients that had AD transmission and/or FA negative result, underwent to CAG and CTG expansion analyses.

This retrospective study was approved by Sakarya University Faculty of Medicine Ethic Committee (01.06.2016 - 103).

RESULTS

The patients (n=37) had an age range of 19–56 and an overall mean age of 28.2±6.1; 31.0±8.7 years in males and 26.3±5.8 years in females. Eight index patients were diagnosed genetically with HSCA; six of these were females and two were males. After HSCA subtyping, four patients were found to have SCA, three had FA, and one autosomal recessive ataxia due to an MRE-11 mutation.

Among the four SCA families, one had SCA-1, another family had SCA-2, a third family had SCA-6 in two individuals and yet another family had SCA-8 in five individuals.

Family history of patients who were genetically diagnosed with MRE-11 and FRDA had AR transmission, all SCAs had AD transmission with the exception of the SCA 1 patient who was a sporadic case.

Clinical feature of index cases were for SCA-1, dysartria, ataxic gate, tremor, for SCA-2, oculomotor complaints (restriction of upper gaze), dysarthria, ataxic gate, areflexia, age of onset was 20, for SCA-6, dysarthria, ataxic gate, saccadic nystagmus, age of onset was 35, for SCA-8, horizontal nystagmus, dysarthria, dysmetria, ataxic gate, areflexia, and age of onset was 25 (Table 1).

Three of the index patients with recessively inherited ataxias were diagnosed with FA with increased GAA trinucleotide in the frataxin gene. Clinical features of index case in the family with four affected individuals, were wheelchair dependence, dysmetria, areflexia, thenar, hypothenar and interosseous muscles atrophy, deformities (contractures, scoliosis, pes cavus) and bilateral extensor plantar responses (Table 1). Clinical features of the other index case with FA, included horizontal nystagmus, severe dysarthria, dysmetria, ataxic gate, deformities (scoliosis, cope palate), bilateral extensor plantar responses and an age of onset 15 (Table 1). Clinical feature of index case in the family with two FA individuals included, dysarthria, pes planus, severe ataxic gate, at an age of onset 14 (Table 1).

In the other family with an autosomal recessive inheritance, a homozygous G464C mutation was observed at exon 6 of the MRE-11 gene in two siblings. Clinical features of index case were severe dysarthria, ataxic gate, at an age of onset 2. Table 1 compiles the demographic, clinical, and genotypic features of all index patients along with their affected family members. In the remaining patients so far unsolved, the molecular analysis is ongoing.

When our patients with hereditary ataxia were examined according to their phenotypic features; their presenting complaints were gait disturbance, imbalance in 32 patients, and speech disturbance in 5. When their most recent examinations were reviewed, speech was severely dysarthric in 6 patients, mildly dysarthric in 3 patients, and in the form of explosive speech in 5 cases. Gait was ataxic in 32 patients and 4 patients were wheelchair-bound. The onset of complaints was chronic in 5 patients and sub-acute in 31 patients. With physical examination, 5

Table 1. Patients' demographic, clinical and genotypic feature along with family history

Patients	Index 1	Index 2	Index 3	Index 4	Index 5	Index 6	Index 7	Index 8
Age	50	35	43	59	31	26	19	30
Age of onset	30	20	35	25	20	14	15	2
Clinical findings	dysartria ataxic gate, tremor	oculomotor complaints (restriction of upper gaze), dysarthria, ataxic gate, areflexia	dysarthria, ataxic gate, saccadic nystagmus	horizontal nystagmus, dysarthria, dysmetria, ataxic gate, areflexia	depended on wheelchair, dysmetria, areflexia, thenar, hypothenar, interosseous muscles atrophy, deformities (contractures scoliosis, pes cavus), bilateral extensor plantar responses	horizontal nystagmus, severe dysarthria, dysmetria, ataxic gate, deformities (scoliosis, cope palate), bilateral extensor plantar responses	dysarthria pes planus, severe ataxic gate	severe dysarthriaataxic gate
Additional affected individuals	0	1	2 (an individual was ex)	4	3	1	1	1
Consanguinity in parents	no	no	no	no	no	no	no	yes (3. degree)
Follow up period	4 years	4 years	3 years	4 years	3 years	2 years	2 years	2 years
Genetic results	SCA-1	SCA-2	SCA-6	SCA-8	FA	FA	FA	MRE-11

patients had nystagmus, 1 patient had restriction of upper gaze, 8 patients had dysmetria, 3 patients had tremor, 2 patients had kyphoscoliosis, 3 patients had mild atrophy in the arms and 1 patient had pes cavus, 1 patient had pes planus. None had claw hand, drop foot, contracture or pseudohypertrophy. Six patients had consanguineous parents (second degree: 3, third degree: 2, fourth degree: 1).

DISCUSSION

Hereditary ataxias are rare conditions, the diagnoses of which are difficult to establish. Thanks to recent rapidly-developing molecular genetic methods, significant advances have been made in understanding the molecular origin of hereditary ataxias, and in establishing firm molecular diagnosis. The number and type of mutations in HSCA patients differ among populations (1–4). To the best of our knowledge, this is the first study in the Sakarya region of Turkey.

Genetic transition in HSCAs may be of different patterns including autosomal dominant, autosomal recessive, X-dependent or mitochondrial (2, 4). AR-inherited FA constitutes 50% of the HSCAs. In accordance with the literature, although small in size, in our series, half of the patients had FA.

Typical clinical findings such as ataxic gait, presence of dysarthria and nystagmus which may accompany decreased finger and hand coordination, and hereditary features should be well documented in HSCA diagnosis (4, 6, 7). In addition, alcoholism, vitamin deficiencies, toxic materials, demyelinating disease, infections diseases, primary or metastatic tumors, paraneoplastic syndromes, drug-related conditions, and other differential diagnoses should also be borne in mind (6–8). Only individuals who have similar cases in their family and herediter ataxia was the cause of their complaints, were included in our study, and secondary causes were ruled out.

AD HSCAs are frequently referred as SCA (7). The number of genetic loci described for SCAs reached 40 as a result of recent genetic advances (6, 8, 9). SCAs are divided into four main groups based on their underlying mechanism, as CAG repeats, intronic disorders, conventional mutations, widespread duplications and deletions (9, 10). In our study, genetic analyses of exonic CAG mutations in SCA and intronic GAA repeats in FA patients reveal that three patients had the disease due to expended CAG repeats in ATXN 1, 2 and 8, a patient had expended CAG repeats in CACNA1A gene, while four patients had pathologic GAA repeats in the FXN gene.

Worldwide the most common dominant ataxia was SCA-3, followed by SCA-2 and SCA-6 (2). SCA-2, representing 13–15% of all SCAs, is the most common SCA in Korea, while SCA-8 constituting 3% of all SCAs, is frequent in Finnish families although it has been reported also in Indian, Mexican and Japanese populations (6, 11, 12). SCA-1 is the most frequent SCA in Poland, SCA-6 is common in the eastern Asian countries like Japan, Korea and Thailand (13, 14). Patients with HSCA are only represented as case reports in literature.

And there is no wide resource in Turkey according to the literature. In Turkey, in line with other Mediterranean countries, the most common dominant ataxia is SCA-2. Four SCA patients in our study were diagnosed with SCA-1, SCA-2, SCA-6, and SCA-8 following genetic investigations.

FA is the most common AR-HSCA, followed by ataxias with oculomotor apraxia and ataxia telangiectasia (AT) (2, 3). Genetic examination of FA involves increased GAA trinucleotides in the gene encoding the frataxin protein (3, 15). Eight out of the 37 patients included in our study were found to carry an expanded FXN gene giving rise to FA. Interestingly, one of our AR ataxia cases has a rare disease, described as ataxia-like disorders (A-TLD) characterized by cerebellar degeneration, and a slight predisposition to cancer in certain families due to a mutation (p.G464C) in the gene encoding MRE-11 (16, 17). MRE-11 is a member of the MRN protein complex responsible of the activation of DNA repair proteins (Mre11/Rad50/NBS11) (17). This rare mutation was identified in two young siblings in our cohort.

Sixteen out of 37 patients included in this report could not be solved during the course of this study, but the analyses are ongoing. Recently a study showed an MME mutation for SCA-43 in a Belgian family (18). This study implies that rapidly-developing molecular genetic methods could be helpful in future in understanding the molecular origin of hereditary ataxia.

The disease severity, disability status and life expectancy in HSCA patients can drastically vary based on the disease subtype, thus the molecular investigation is crucial. Since there is no specific treatment for hereditary ataxias, other than vitamin E deficiency-related ataxia, medical treatment was not offered, but patients were instructed to receive physical therapy (1, 3, 6). Advanced genetic investigations in hereditary ataxia will make it possible to confirm the diagnosis, determine disease prognosis and foresee possible metabolic, neurologic, systemic and psychiatric comorbidities. On the other hand, narrowing the genotypic range by the use of phenotypic characteristics of HSCAs, which has quite a wide range, will be very useful in reducing both time loss and costs in molecular analysis. In addition, regional and ethnic studies will reveal data on the distribution of the subtypes of HSCA, making it possible to narrow down the potential range.

CONCLUSION

Our study reveals phenotypic and genotypic characteristics of hereditary ataxia in our city. There were five members of the same family with SCA-8 mutation. SCA-8 is a rare subtype among SCAs in the Turkish population. Our findings in FA patients (age of onset is last teens, initial symptoms are unsteadiness in standing and walking, with a slow progression) are consistent with the literature. Two siblings with MRE-11 mutation-related disease, as defined by exome sequencing in our study, underlines the importance of utilizing new-generation technologies in unsolved cases.

One of the most problematic issues is the low awareness and suboptimal body of knowledge in hereditary ataxias, resulting in a consequent inability to diagnose the disease at an early phase. Thus, the diagnostic odyssey is long and tiring. The option of these patients to reach treatment opportunities is based on molecular research, which in the era of genomic will hopefully soon gain the long-awaiting momentum.

Ethics Committee Approval: This retrospective study was approved by Sakarya University faculty of medicine etic committee with 01/06/16 date and 103 number decision.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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Author Contributions: Concept – DK; Design – SS, DK; Supervision- DK,NB; Resources – SS, DK; Materials – DK; Data Collection and/or Processing – DK, AGE, IŞ, CK; Analysis and/or Interpretation – AGE, IŞ, CK, NB; Literature Search – SS, DK; Writing Manuscript – SS, DK; Critical Review – SS, DK, AGE, IŞ, CK, NB.

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