Clinical Features and Molecular Genetics of Autosomal Recessive Ataxia in the Turkish Population

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Background: Autosomal recessive cerebellar ataxias (ARCAs) are a heterogeneous group of inherited neurodegenerative disorders. The aim of this study was to present the clinical and genetic features of patients with ataxia complaints and those genetically diagnosed with ARCAs. Materials and Methods: Thirty-one children with ARCA were retrospectively analyzed. Results: Fourteen (45.2%) were boys and 17 (54.8%) were girls with the mean age at onset of symptoms of 46.13 ± 26.30 months (12–120 months). Of the 31 patients, 21 (67.7%) were from consanguineous marriages. Eight patients had Friedreich's ataxia, five had ataxia telangiectasia, three had l-2-hydroxyglutaric aciduria, three had Joubert syndrome, three had neuronal ceroid lipofuscinosis, two had megalencephalic leukoencephalopathy with subcortical cysts, two had ataxia with ocular motor apraxia type 1, one had cytochrome c oxidase deficiency, one had autosomal recessive spastic ataxia of Charlevoix-Saguenay, one had Niemann-Pick type C, one had congenital disorders of glycosylation, one had adrenoleukodystrophy, and one had cobalamin transport disorder. Conclusion: The prevalence of hereditary ataxia can vary among countries. The consanguineous marriage is an important finding in these diseases. These genetic tests will increase the number of ARCA patients diagnosed.

Keywords: Clinical findings, genetic study, hereditary ataxia

INTRODUCTION

The hereditary ataxias are a clinically and genetically heterogeneous group of disorders characterized by slowly progressive incoordination of gait and are often associated with poor coordination of hands, speech, and eye movements. Frequently, atrophy of the cerebellum occurs.[1]

The hereditary ataxias are categorized by mode of inheritance and gene in which causative mutations occur, or chromosomal locus. The hereditary ataxias can be inherited in an autosomal dominant, autosomal recessive, X-linked manner, or through maternal inheritance if part of a mitochondrial genetic syndrome.[2] The genetic forms of ataxia are diagnosed by family history, physical examination, neuroimaging, and molecular genetic testing.

Autosomal recessive cerebellar ataxias (ARCAs) are a heterogeneous group of inherited neurodegenerative disorders that affect the cerebellum, the spinocerebellar tract, and/or the sensory tracts of the spinal cord. They are characterized by prominent progressive cerebellar ataxia in association with other neurological or extra-neurological signs.[1,3,4] Friedreich's ataxia (FTRA) and ataxia telangiectasia (AT) are known to be the two most frequent forms of ARCAs.[3,5]

To the best of our knowledge, very few studies related to ARCAs in childhood have been conducted. We presented the characteristics of the patients who came with ataxia complaints and detected ARCA.
Materials and Methods

Patients with ataxia complaints and genetic diagnosis were included in the study. This was a retrospective study of 31 children diagnosed with ARCAs, which was conducted at Cukurova University Hospital, Adana, Turkey, between 2012 and 2018. We reviewed clinical examination and laboratory, imaging, electrophysiological, and molecular investigations.

The data were retrospectively collected from the clinic files and included sex, age, age at onset of symptoms; stage of mental and motor development before the onset of symptoms; family history; consanguinity; presence of microcephaly or macrocephaly; mental retardation; deep tendon reflexes; seizures; polyneuropathy; cerebral magnetic resonance imaging (MRI) findings; levels of serum α-fetoprotein, vitamin E, vitamin B₁₂, lipids; the results of metabolic tests, and enzymes for lysosomal and peroxisomal disorders; and genetic analysis. Acquired and autosomal dominant ataxias were excluded.

On the basis of MRI findings, patients were grouped into three categories: those with normal or nonspecific findings, those with cerebellar atrophy only, and those with cerebellar atrophy combined with other changes.

Results

Twenty-nine children, mean age 105.32 ± 33.70 months (19–180 months), were included in this study. Among the 31 patients, 14 (45.2%) were boys and 17 (54.8%) were girls, and the mean age at onset of symptoms was 46.13 ± 26.30 months (12–120 months).

Eight patients had Friedreich’s ataxia (FRDA), five had AT, three had l-2-hydroxyglutaric aciduria, three had Joubert syndrome (JS), two had neuronal ceroid lipofuscinosis (NCL), two had megalencephalic leukoencephalopathy with subcortical cysts (MCL), two had ataxia with ocular motor apraxia type 1 (AOA1), one had cytochrome c oxidase deficiency, one had autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), one had Niemann-Pick type C (NPC), one had congenital disorders of glycosylation (CDG), one had adrenoleukodystrophy (ALD), and one had cobalamin transport disorder.

The diagnosis of FRDA, AT, NCL, NPC, ARSACS, MLC, ALD, AOA1, JA, l-2-hydroxyglutaric aciduria, and cobalamin transport defect was confirmed genetically. l-2-hydroxyglutaric aciduria was diagnosed based on urine organic acid analyses, cobalamin transport defect using a biochemical test for transcobalamin levels, and CDG by transferrin isoelectric focusing.

Of the 31 patients, 21 (67.7%) were from consanguineous marriages. Twenty-one patients (72.4%) had mental retardation, 8 (25.8%) had seizures, 4 (13.8%) had macrocephaly, and 3 (10.3%) had microcephaly. Electromyelography was performed in 12 of the 31 cases. Polyneuropathy was detected in seven (22.6%) patients. Two patients (6.5%) had normal or nonspecific findings on MRI, 22 (71%) had cerebellar atrophy only, and 7 (22.5%) had cerebellar atrophy combined with other changes. The characteristics of the patients are shown in Table 1.

Discussion

In ARCAs, progressive cerebellar ataxia is usually, yet not invariably, the salient feature. However, often other neurological or non-neurological symptoms coexist. The overall estimated prevalence rate is approximately 2.2–7 per 100,000, but varies per population. In the past few years, several novel forms of ARCA have been recognized, based on identified novel loci and genes.

FRDA and AT were reported to be the two most frequent forms of ARCA (3,5). Other forms of ARCA are much less common. The primary cause of early-onset ataxia in the Indo-European population is FRDA, which accounts for about 75% of all patients with autosomal recessive and sporadic ataxia. Most patients with the homozygotic frataxin gene (FXN) mutations fulfill the clinical diagnostic criteria for typical FRDA, and about 25% of patients have atypical FRDA, including late-onset FRDA (>25 years). FRDA with retained deep tendon reflexes, or unusually slow progression of disease. Anheim et al. studied 102 suspected ARCA cases from Eastern France. Fifty-seven patients were diagnosed by molecular analysis. Of the 57 patients, 36 were diagnosed with FRDA and 4 with AT. In another study, Rasmussen et al. analyzed 134 patients with recessive or sporadic progressive ataxia from the Mexican Mestizo (mixed) population. Of the 134 patients, 14 (10.4%) were diagnosed with FRDA. To the best of our knowledge, only one study has been reported among children with a broad spectrum of ARCAs in Turkey. Arslan et al. reported FRDA in five (12.8%) patients and AT in three (7.6%) in their study. We found FRDA in eight (25.8%) patients and AT in five (16.1%) patients. Similarly, FRDA and AT were the common etiologies in our study.

A number of leukodystrophies can present with ataxia. Macrocephaly is the most important finding of leukodystrophies. Leukodystrophy should be considered in the presence of ataxia, macrocephaly, and neuroimaging findings, and genetic analysis should be performed accordingly.
leukodystrophies in 10.2% of the 39 patients with ARCA, including l-2-hydroxyglutaric aciduria in 5.1% and MLC in 5.1%. We detected three (9.7%) patients with l-2-hydroxyglutaric aciduria and two (6.5%) with MLC. Macrocephaly was found to be present in four of five patients with leukodystrophy.

JS is characterized by cerebellar ataxia, hypotonia, AOA1, intellectual disability, and specific mid-hindbrain malformation (“molar tooth sign,” MTS). JS is associated with MTS, a radiologic finding that includes cerebellar vermis hypoplasia or dysplasia, thick and horizontally oriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa.\[15\] We diagnosed JS in three patients with ataxia. Our patients had a clinical and radiological pattern of JS, and we confirmed genetic analysis. Arslan et al.\[13\] reported no JS in their study, but they reported two patients with pontocerebellar hypoplasia type 2.

ARSACS is caused by mutations of the SACS gene, characterized by late-infantile-onset spastic ataxia and other neurological features. ARSACS has a high prevalence in northeastern Quebec, Canada.\[16\] Recently, several ARSACS cases have been reported from outside Canada.\[17\] We reported typical clinical and neuroimaging features in a child that confirmed genetic diagnosis of ARSACS.

In patients with ataxia, neuroimaging plays an important role in diagnosis. The most common neuroimaging finding is cerebellar atrophy. On performing MRI of the brain of the patients in their study, Arslan et al.\[13\] reported normal or nonspecific findings in 12 (30.8%), cerebellar atrophy only in 10 (25.6%), and cerebellar atrophy with other changes in 8 (20.5%). We performed MRI of the brain in all of our patients. The most common abnormality was vermian atrophy and/or cerebellar atrophy according to cranial MRI findings for 31 patients. In our study, 2 (6.5%) patients had normal or nonspecific findings, 22 (71%) had cerebellar atrophy only, and 7 (22.5%) had cerebellar atrophy combined with other changes.

The prevalence of hereditary ataxia can vary among countries.\[18\] The consanguineous marriage is an important finding in these diseases.\[7\] Consanguineous marriage is common in our country. In a study conducted in Turkey, Arslan et al.\[13\] reported a rate of consanguineous marriage as 82.1%. We found 67.7% to be the rate of consanguineous marriages.

The genetic studies have increased in recent years. These genetic tests will increase the number of ARCA patients diagnosed. It will be even more important, especially where relatives are married.

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Conflicts of interest
There are no conflicts of interest.

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