Original Article

Revisiting Friedreich's Ataxia: Phenotypic and Imaging Characteristics

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Abstract

Background and Aim: Friedreich's ataxia (FRDA) is a common cause of autosomal recessive cerebellar ataxia. The phenotype is dependent on the repeat size and duration of the disease. We aimed to study the clinical, electrophysiologic, and radiologic profiles in a large Indian cohort of genetically proven FRDA patients. **Subjects and Methods:** A retrospective cross-sectional, descriptive analysis of genetically proven FRDA patients was performed. A detailed review of all the hospital case records was done to analyze the clinical, radiologic, and electrophysiologic details. **Results:** A total of 100 FRDA patients were selected for the analysis. Eighty-six patients had an age at onset between 5 and 25 years. Eight patients (8%) were classified as late-onset FRDA and six patients (6%) as early-onset FRDA. The median age at presentation was 19 years. The median age at onset was 14 years, and the median duration of illness was 4 years. All patients had gait ataxia as the initial symptom. Gait ataxia, loss of proprioception, and areflexia were seen in all patients. Dysarthria, nystagmus, amyotrophy, spasticity, extensor plantars, pes cavus, and scoliosis occurred in one-third of patients. Cardiomyopathy (18%) and diabetes (5%) were less common. Sensory polyneuropathy (87.5%) was the most common nerve conduction abnormality. Cortical somatosensory evoked responses were absent in all 43 tested patients (100%). Brainstem auditory evoked response test was done in 24 patients and it showed absent reactions in six patients (25%). Visual evoked potential was tested in 24 patients and it showed absent P100 responses in five patients (21%). Cerebellar and cord atrophy was seen on magnetic resonance imaging in 50% of patients. **Conclusion:** Most FRDA patients (86%) had an age at onset of less than 25 years, with typical symptoms of gait ataxia, areflexia, and loss of proprioception found in all patients. Dysarthria, nystagmus, amyotrophy, spasticity, extensor plantars, pes cavus, scoliosis, cardiomyopathy, and diabetes were not seen in all patients. Cerebellar atrophy can occur in FRDA patients. Knowledge regarding the clinical, radiologic, and electrophysiologic profile of FRDA will aid in proper phenotypic characterization.

Keywords: Cerebellum, Friedreich's ataxia, triplet PCR

Introduction

Friedreich's ataxia (FRDA) is an autosomal recessive, multisystem degenerative disorder affecting the central and peripheral nervous systems, musculoskeletal system, myocardium, and endocrine pancreas.[1] The prevalence of FRDA in Caucasians is about 1/50,000, with a carrier frequency of about 1 in 90.[2] The original description of FRDA was given by Nicholaus Friedreich in 1863, wherein the patient presented with ataxia and dysarthria as the early findings, followed by sensory loss and muscle weakness. Scoliosis, foot deformity, and cardiomyopathy were the accompanying symptoms.[3] In 1882, the term Friedreich's ataxia was proposed by Brousse. In 1981, Harding[4] reported the first large series on FRDA, describing the clinical and genetic features of 115 FRDA patients. The causative mutation was discovered in 1996.[5] A homozygous GAA triplet expansion in the first intron of the frataxin gene (*FXN*) on both alleles was seen in 95% of cases. The remaining 5% of patients showed one GAA expansion in one allele and an intragenic inactivating *FXN* mutation (a point mutation or exon deletion outside the GAA repeat region) in the other allele, termed as compound heterozygotes.[6,7] The typical age of onset (AOO) is around 10 years, but early-onset FRDA (EOFA) as well as late- and very late-onset FRDA have been described. The phenotypic profile of large cohort of Indian patients with FRDA are few. Here, we aimed to study the clinical, electrophysiologic, and radiologic profiles in genetically proven FRDA patients.

Subjects and Methods

Subject recruitment and clinical evaluation

This was a retrospective cross-sectional, descriptive analysis of patients with FRDA conducted at a quaternary care hospital

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in India. The inclusion criterion was genetic confirmation of FRDA. The exclusion criteria were ataxia of other genetic etiology, acquired causes of ataxia, and FRDA patients' case records with incomplete data. The sampling method was convenience sampling without predetermined sample size. Hospital records of patients diagnosed as FRDA between 2017 and 2022 were searched, and genetically confirmed FRDA patients were included. A detailed review of genetically proven FRDA patients' hospital case records was done. The baseline demographic and clinical details, which included age at presentation, age at onset, duration of illness, initial symptom, presence of consanguineous parentage, siblings/family members involved, duration from symptom onset to loss of ambulation, presence or absence of gait ataxia, limb ataxia, speech disturbance, dysphagia, vision and hearing disturbances, history of diabetes mellitus, cardiac disorder and its duration, clinical signs that included the presence of pes cavus, hammer toes, kyphoscoliosis, cardiac findings, visual acuity, fundus examination for optic atrophy, auditory tests, saccades, pursuits, nystagmus, square-wave jerks, dysarthria, titubation, amyotrophy, tone, deep tendon reflexes, muscle power, proprioception, pain and touch sensation, upper and lower limb incoordination, gait ataxia, and plantar responses, were recorded. Details such as ataxia rating scales scores and modified Rankin scale score, if available, and treatment details were recorded. Details about echocardiography, nerve conduction study, evoked potentials, and brain and spine magnetic resonance imaging (MRI) findings were recorded. Age at onset was defined as the age at which the patient or relatives noticed the first appearance of symptoms such as gait or limb ataxia. Late-onset FRDA (LOFA) was defined as age at onset ≥25 years, and EOFA was defined as age at onset ≤5 years.[8-10] The prognosis was assessed based on the time of attainment of disease from its onset to wheelchair dependency. Institute Ethics Committee approval was obtained for the retrospective analysis of the data. The study was conducted in accordance with the Declaration of Helsinki (1964).

Triplet polymerase chain reaction

The GAA repeats tract in the FRDA locus was analysed by triplet-primed polymerase chain reaction (TP-PCR) as described earlier.[11] Polymerase chain reaction (PCR) was conducted using the primer sequences P1 5′-GCTGGGATTACAGGCGCGCGA-3′, P3 5′-TACGCATCCCAGTTTGAGACG-3′, and P4 5′-6-FAM TACGCATC-CCAG TTTGAGACGGAAGAAGAAGAAGAAGAAGAA-3′. fluorescein amidite-labeled PCR products were evaluated on an automatic sequencer ABI3500XL to reveal characteristic expanded ladders with 3 bp periodicity.

Statistical analysis

The demographic, clinical, echocardiography, nerve conduction study, evoked potentials, and brain and spine MRI data were entered in the proforma. Data was expressed using descriptive statistics. Continuous variables were expressed as mean/median with standard deviation/interquartile range (IQR), respectively, whereas categorical variables were expressed as frequencies and percentages. Statistical analysis was performed using International Business Machine Statistical Package for the Social Sciences software version 22.

Results

The hospital records of 100 patients with FRDA were used for the retrospective analysis. There were 60 males and 40 females. The median age at presentation was 19 years (IQR 14–24 years). The median age at onset was 14 years (IQR 10–18 years). The median duration of illness was 4 years (IQR 3–8 years). Eight patients (8%) were classified as LOFA and six patients (6%) as EOFA. A history of consanguineous parentage was present in 37 patients (37%). Eleven patients (11%) had similar symptoms in their siblings.

Clinical data

Clinical characteristics (N = 100)

The clinical characteristics of the study participants are presented in Figure 1 and Supplementary Video 1.

The first symptom was gait ataxia in all patients, except one patient who had scoliosis as the first symptom. All patients had gait ataxia at the time of presentation (100%). Incoordination of limbs was seen in 66 patients (66%). Dysarthria in the form of ataxic dysarthria occurred in 37 patients (37%). Thirty-seven patients (37%) had gaze-evoked nystagmus. Only one patient had titubation. Three patients had square-wave jerks (3%). Impaired saccades were seen in 23 patients (23%). Optic atrophy was noted in five cases (5%), and sensorineural hearing loss (SNHL) was observed in six patients (6%). Forty patients (40%) had pes cavus and 33 patients (33%) had scoliosis. Peripheral nerve involvement was seen in all patients as loss of proprioception in the lower limbs and reduced to absent deep tendon reflexes. Twenty-seven patients had amyotrophy in the lower limbs (27%). Pyramidal involvement occurred in 20 patients in the form of spasticity in the lower limbs (20%). Extensor plantar response was seen in 30 patients (30%). Five patients had diabetes mellitus (5%). Echocardiography showing hypertrophic obstructive cardiomyopathy was noted in 18 patients (18%). The median

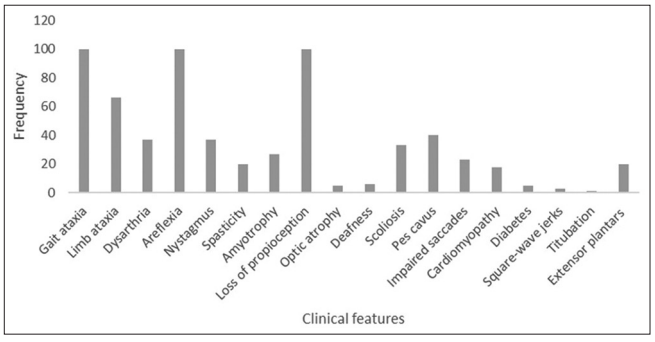

Figure 1: Frequency of clinical features of Friedreich's ataxia

duration from the onset of symptoms to loss of independent ambulation was 5 years (IQR 4–7 years; range: 3–12 years). There was no difference in the frequency of clinical features between genders.

Early-onset Friedreich's ataxia (n = 6) and late-onset Friedreich's ataxia (n = 8)

Table 1 shows a comparison of the clinical characteristics between EOFA and LOFA patients.

The median AOO in EOFA patients was 5 years, and the median age at presentation was 14 years (range: 10–18 years). Two EOFA patients were born of consanguineous parentage. The age of wheelchair dependency ranged from 3 to 6 years of the onset of symptoms. The median AOO in LOFA patients was 28 years, and the median age at presentation was 29 years (range: 26–35 years). The median duration of illness was 4 years. All patients had electrophysiologic evidence of sensory neuropathy. Due to the small sample size, comparison among patients with early, late, and typical onset of symptoms for statistical significance was not carried out.

Imaging findings

Supplementary Figure 1 shows the imaging findings.

MRI brain and spine (n = 85)

Findings of brain and spine MRI were available in 85 patients. Brain and spine MRI was normal in 16 patients (19%). Cerebellar atrophy was seen in 35 patients (41%). Cord atrophy was seen in 36 patients (42%), with atrophy of the cervical cord in 18 patients (50%).

Electrophysiologic tests

A nerve conduction study was done in 80 patients. Abnormality was noted in all patients in the form of sensory polyneuropathy in 70 patients (87.5%) and sensorimotor axonal polyneuropathy (12.5%) in 10 patients. Somatosensory evoked potential (SSEP) test was done in 43 patients, and abnormalities were noted in all 43 patients in the form of absent cortical somatosensory evoked responses. Brainstem auditory evoked response (BAER) test results were available in 24 patients and were abnormal in the form of absent responses in six patients (25%). Visual evoked potentials (VEPs) were tested in 24 patients and were found to be abnormal in the form of absent P100 responses in five patients (21%).

Table 1: Comparison of clinical characteristics between EOFA and LOFA patients

EOFA (*n*=6)	LOFA (*n*=8)
Short stature (*n*=2; 33.3%)	Gait and limb ataxia (*n*=8; 100%)
Pes cavus (*n*=6; 100%)	Dysarthria (*n*=8; 100%)
Scoliosis (*n*=6; 100%)	Impaired proprioception (*n*=8; 100%)
Gait and limb ataxia (*n*=6; 100%)	Absent reflexes (*n*=8; 100%)
Ataxic dysarthria (*n*=4; 66.7%)	Spasticity (*n*=4; 50%)
Spasticity (*n*=1; 16.7%)	Scoliosis (*n*=0)
Myoclonus (*n*=1; 16.7%)	Pes cavus (*n*=0)
Cardiomyopathy (*n*=4; 66.7%)	Cardiomyopathy (*n*=0)

EOFA=early-onset Friedreich's ataxia, LOFA=late-onset Friedreich's ataxia

Treatment profile

Most of the patients received symptomatic treatment for ataxia in the form of amantadine (100–200 mg/day) in 40 patients and idebenone (45 mg thrice a day) in 30 patients.

Discussion

This study aimed at describing the clinical, electrophysiologic, and radiologic profiles of a cohort of genetically proven FRDA patients from a tertiary care center in South India. The initial clinical criteria proposed for the diagnosis of FRDA were Quebec Cooperative Study criteria, which are progressive gait ataxia without remission, dysarthria, loss of joint position and vibration sense in the lower limbs, muscle weakness, deep tendon areflexia in the lower limbs, and onset before the age of 20 years.[12] These criteria were later modified by Harding as autosomal recessive inheritance, onset before the age of 25 years, absence of lower limb reflexes, and presence of pyramidal signs.[4] Since the discovery of the FRDA gene, the phenotypic spectrum has widened, and about 25% of patients do not fulfill the above criteria.

FRDA is an autosomal recessive ataxic syndrome with variable phenotype based on the length of the expanded repeats. Normal alleles contain 5–33 repeats.[13] However, in FRDA, the repeats range varies from 66 to 1700. The most common GAA repeat length observed is between ~ 600 and 1200.[14] LOFA phenotypes commonly have between 100 and 500 repeats. The length of the expanded repeats, particularly the shorter one (GAA1), inversely correlates with age at disease onset, disease severity, and rate of progression.[15] The gold standard molecular diagnostic test for the diagnosis of FRDA is Southern blotting, which is also helpful in determining the size of the repeats for FRDA. However, it is a very cumbersome and expensive method for routine diagnostic purposes.[11] TP-PCR has been used to screen expanded alleles in the FRDA gene, wherein a characteristic peak pattern confirms the existence of expanded triplet repeats in the gene.[16] TP-PCR is a rapid test, which is not labor-intensive and is appropriate for routine laboratory practice.[17] In our cohort, the confirmation of FRDA diagnosis was done by TP-PCR. We have not determined the repeat size due to the nonavailability of Southern blotting.

We reviewed a large cohort of patients with FRDA reported so far and compared it with our cohort in relation to the clinical, radiologic, and electrophysiologic features. Harding[4] reported a large cohort of 115 cases of FRDA with a mean age at onset of 10 years ranging from 1.5 to 27 years and mean duration of illness of 22 years. Gait and limb ataxia, dysarthria, pyramidal signs, scoliosis, pes cavus, impaired proprioception, and areflexia were the most common clinical features in their cohort. Nystagmus, deafness, and optic atrophy were less common. Head titubation was rare. The mean age of becoming chairbound was 25 years (range: 11–58 years), and the mean interval of being wheelchair bound from the age

at onset was 15 years. Dysarthria and pyramidal weakness were seen in patients within 5 years of onset of disease. Durr *et al.*[18] (1996) studied 187 patients with FRDA; of them, 140 patients had homozygous, nine had heterozygous, and the remaining 38 patients had no GAA repeat expansion. The mean age at onset of the disease was 15.5 years, ranging from 2 to 51 years. Typical FRDA phenotype was seen in 106 patients with homozygous GAA expansion. Gait ataxia was the initial symptom in all patients, except seven patients who had scoliosis as the first symptom. Gait and limb ataxia, dysarthria, impaired proprioception, areflexia, and extensor plantar reflex were seen in majority of patients. Scoliosis and pes cavus were seen in half of the patients. Axonal neuropathy was seen in almost all tested patients. Cardiomyopathy on echocardiography was noted in two-thirds of the tested patients, and diabetes occurred in 30% of their cohort patients. Around 34 patients with homozygous GAA expansion had atypical FRDA phenotype in the form of retained reflexes, age at onset ≥25 years, and brisk reflexes. The size of the smaller GAA expansion had an inverse relation with both age at onset and time until confinement to a wheelchair. The frequencies of areflexia, extensor plantar, pes cavus, scoliosis, amyotrophy, and cardiomyopathy increased with repeat size. Dysarthria, impaired vibration, decreased visual acuity, hearing loss, and swallowing difficulties were related to the duration of the disease.[18] Schöls *et al.*[19] reported 36 patients with FRDA, and 34 patients had age at onset before 25 years and two patients had late onset. Gait and limb ataxia, dysarthria, lower limb areflexia, decreased vibration, extensor plantar responses, and axonal sensory neuropathy occurred in all patients. Scoliosis, foot deformity, square-wave jerks, foot weakness, amyotrophy, and dysphagia were seen in most of the patients. Cardiomyopathy was reported in majority of patients, but none of the patients had diabetes. Cervical cord atrophy was seen in all patients and cerebellar atrophy in 50% of patients. A recent study published in 2015 from China about the frequency of FRDA in Chinese Han population showed that the GAA copy number of the subjects was between 5 and 16, unlike that of European population where the normal size range of GAA repeat is from 6 to 34 repeat copies; this suggests different genetic backgrounds and the ethnic differences between European and Chinese Han populations.[20] A study from Brazil reported lower frequency of expanded GAA alleles in Brazilian FRDA patients compared to that of Caucasian patients, reflecting a lower prevalence of FRDA in Brazil.[21] Rummey *et al.*[22] studied the correlation of GAA repeats and AOO and found that the number of GAA1 repeats predicts AOO (onset was 2.73 years earlier for every 100 repeats) and that the disease progression was faster with earlier AOO.

In our cohort, the median age at the onset of symptoms was 14 years, ranging from as early as 4 years to delayed onset at 35 years, similar to the above cohort. Gait ataxia was the initial symptom in all patients, except one who had thoracic scoliosis. All patients had gait ataxia and impaired proprioception, whereas limb ataxia occurred in 66% of patients, similar to the findings of other studies. The frequencies of pes cavus and scoliosis in our cohort were similar to those of the cohort in the study of Durr *et al*.[18] Dysarthria, nystagmus, saccadic dysfunction, and pyramidal tract involvement, including extensor plantar response and amyotrophy, were less common with a frequency of 20%–33% compared to other cohorts. Similarly, diabetes mellitus and cardiomyopathy on echocardiography were less frequent in our cohort. The frequencies of clinical features in different studies are summarized in Table 2.

We found a similar frequency of cord and cerebellar atrophy (41%) on MRI. Cortical evoked somatosensory responses were absent in all tested patients, whereas VEP and BAER were abnormal in 21%–25% of patients. SSEP abnormalities noted in FRDA suggest posterior column involvement. SNHL was seen in six patients, and BAER was absent in these six patients, suggesting possible degeneration of the spiral ganglion. Vanasse *et al*.[23] reported absent SSEP in eight out of 15 FRDA patients (53%) and absent BAER in six out of 13 tested patients (46%).

Bhidayasiri *et al.*[24] reported 13 patients of LOFA, wherein the mean age at onset was 29 years, ranging from 25 to 48 years. The frequencies of gait and limb ataxias, dysarthria, loss of vibration sense, and pes cavus were similar to those of typical FRDA patients, but spasticity and retained reflexes were more frequent in LOFA cases. Cardiomyopathy was not seen in LOFA patients. Cerebellar atrophy was seen in LOFA patients. We had eight patients with LOFA with a mean age at onset of 27 years, and one patient had an age at onset of 35 years. None of our LOFA patients had spasticity, retained reflexes, scoliosis,

Table 2: Comparison of frequencies of clinical and imaging features among the Friedreich's ataxia cohorts

	Harding *et al*. (*n*=115)	Durr *et al*. (*n*=180)	Schols *et al*. (*n*=36)	Present study (*n*=100)
Gait ataxia[a]	NA	100	100	100
Limb ataxia[a]	99	99	100	66
Dysarthria[a]	97	91	100	37
Areflexia[a]	99	87	100	100
Nystagmus[a]	20	40	37	37
Spasticity[a]	NA	NA	NA	20
Amyotrophy[a]	88	39	62	27
Loss of proprioception[a]	73	78	92	100
Optic atrophy[a]	18	13	0	5
Deafness[a]	8	13	47	6
Scoliosis[a]	79	60	96	33
Pes cavus[a]	55	55	86	40
Impaired saccades[a]	12	30	NA	23
Cardiomyopathy[a]		63	79	18
Diabetes[a]	10	32	0	5
Square-wave jerks[a]	NA	NA	81	3
Titubation[a]	NA	NA	NA	1
Extensor plantar[a]	89	79	100	20
Cord atrophy[a]	NA	NA	100	42
Cerebellar atrophy[a]	NA	NA	50	41

NA=not available, [a]Expressed as percentage

pes cavus, or cardiomyopathy. EOFA occurs due to the larger size of GAA1 repeats as well as due to the exonic deletion in the compound heterozygous state. Patients with exonic deletion have younger age at onset with rapid progression to wheelchair-bound status.[25,26] Anheim *et al*.[27] reported three cases of EOFA due to exonic deletion, wherein patients had cerebellar ataxia, extensor plantar response, dysarthria, areflexia, pes cavus, scoliosis, and cardiomyopathy. The time to wheelchair-bound status was 3–6 years. We had six patients with EOFA and all had ataxia, dysarthria, pes cavus, scoliosis, and cardiomyopathy. However, one patient had spasticity, one had myoclonus, and two patients had a short stature. The time to wheelchair dependency was 3–6 years.

Recent developments in the treatment of FRDA include omaveloxolone, which increases the levels of nuclear factor erythroid 2-related factor 2 by preventing its degradation. NRF2 binds to antioxidant response elements in DNA to activate genes protecting cells from oxidative damage. Omaveloxolone, at the optimal dose level of 160 mg/day, has been shown to improve neurologic function.[28] Other treatment options include increasing frataxin expression at the gene level by genome editing, oligonucleotide-based approaches, and synthetic transcription factor, frataxin replacement by gene therapy using synthetic lipid nanoparticles, antioxidants like acetyl-l-carnitine, and using deuterated polyunsaturated fatty acids to counteract the downstream effects of oxidative stress.[29]

The strength of this study was the descriptive analysis of genetically proven FRDA patients, including EOFA and LOFA patients. Its limitations were the retrospective analysis of patient data, convenience sampling, selection bias (as it was a hospital-based study), lack of phenotype–genotype correlation due to the nonavailability of GAA repeat data, and lack of long-term follow-up data of the patients to understand the natural history of the disease and its prognosis.

Conclusion

Majority of the FRDA patients (86%) had an age at onset of less than 25 years with common symptoms of gait and limb ataxia, areflexia, loss of proprioception in the lower limbs, and reduced to absent deep tendon reflexes. Dysarthria, nystagmus, amyotrophy, spasticity, pes cavus, and scoliosis occurred in one-third of patients. Cardiomyopathy (18%) and diabetes (5%) were less common in our cohort. Cerebellar atrophy and cord atrophy were seen in 50% of patients. Sensory neuropathy was the most common electrophysiologic abnormality. EOFA and LOFA patients had similar clinical features to those of typical FRDA patients. This study describes the frequencies of clinical, electrophysiologic, and radiological features in FRDA patients, which will aid in proper phenotypic characterization. Long-term prognosis of these patients needs to be studied in future.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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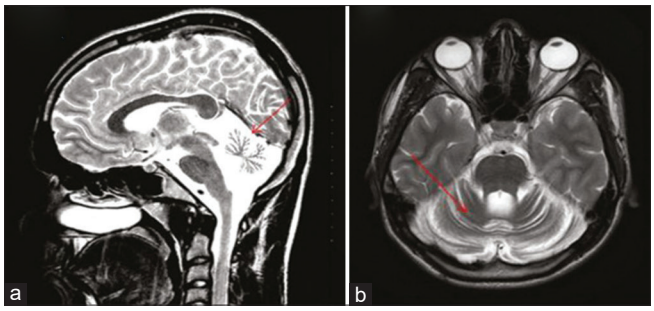

Supplementary Figure 1: Brain MRI sagittal view (a) and axial view (b) showing cerebellar atrophy (red arrow). MRI = magnetic resonance imaging