SHORT REPORT

Clinical heterogeneity of recessive ataxia in the Mexican population

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Approximately 75% of Indo-European patients with recessive ataxia are homozygous for frataxin gene (*FXN*) mutations and have either typical or atypical Friedreich ataxia (FRDA). Our previous analysis of 134 Mexican Mestizo recessive ataxia patients showed that FRDA is relatively uncommon in the Mexican population (10.4%). This article reports the evaluation of the phenotypes of these patients. Over half of the patients with clinical diagnostic criteria for FRDA did not carry *FXN* mutations, constituting a "FRDA-like" phenotypic subgroup. Analysis of non-FRDA patients revealed a subgroup with early onset recessive cerebellar ataxia and cognitive deficit. These two phenotypic subgroups accounted for approximately 60% of all patients, indicating that the cause for recessive ataxia in the Mexican population is distinct from other populations and remains largely unknown.

The cerebellar ataxias are a heterogeneous group of neurodegenerative diseases which may be hereditary or acquired. Although family history often shows the inheritance pattern of the disease, apparently sporadic cases may also be due to mutations in any of the ataxia-causing genes.¹ The primary cause of early-onset ataxia in the Indo-European population is Friedreich ataxia (FRDA; MIM 229300), which accounts for about 75% of all patients with autosomal recessive and sporadic ataxia.^{2–3} Most patients with the homozygous frataxin gene (*FXN*) mutations fulfil the clinical diagnostic criteria for typical FRDA,^{2–4} and about 25% of patients have atypical FRDA, including late-onset FRDA (>25 years),⁵ FRDA with retained deep-tendon reflexes⁶ or unusually slow progression of disease.

The differential diagnosis of a patient with recessive ataxia of early onset includes FRDA, Charcot–Marie–Tooth disease type 1, ataxia with vitamin E deficiency, abetalipoproteinaemia, ataxia with oculomotor apraxia types 1 and 2 (AOA1 and AOA2) and autosomal recessive ataxia of Charlevoix–Saguenay. Other causes of early-onset recessive or sporadic ataxia may be easier to rule out on the basis of their particular clinical features, including ataxia–telangiectasia, ataxia of mitochondrial origin, infantile-onset spinocerebellar ataxia, Behr's syndrome, Refsum's disease and Marinesco–Sjögren syndrome.⁷ However, there is anecdotal evidence of patients with FRDA-like symptoms who do not have *FXN* mutations and who do not have any of the above-mentioned diseases, suggesting the existence of genetic heterogeneity.^{4–8–10}

On the other hand, for the aetiological diagnosis of sporadic ataxia, it is important to rule out acquired, non-genetic causes of ataxia, such as alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumours, or paraneoplastic diseases, as treatment may be available for some of them.¹ Among the apparently sporadic cases of ataxia, about 13–19% of patients with the

late-onset disease have mutations in genes causing dominant or recessive spinocerebellar ataxia.^{11–12} Finally, multiple-system atrophy (MSA), particularly the "C" (cerebellar) subtype, may be the cause of the ataxic syndrome. However, despite efforts to characterise the aetiology of their ataxia, many patients remain with the non-specific diagnosis of idiopathic late-onset cerebellar ataxia (ILOCA).^{11–13}

Little is known about the causes of recessive and sporadic ataxia in the Mexican population. We therefore analysed a cohort of 134 patients with recessive or sporadic progressive ataxia from the Mexican Mestizo (mixed) population for genetic and non-genetic causes of ataxia. Among those who tested negative for *FXN* gene mutations,¹⁴ we identified several patients who fulfilled the clinical criteria for FRDA. On analysing the clinical features of patients without the clinical or genotypic characteristics of FRDA, we identified a phenotypic subgroup of patients with early-onset recessive ataxia with frequent cognitive deficit. However, despite extensive investigations, most of our patients remained without an aetiological diagnosis.

PATIENTS AND METHODS

The 134 patients with ataxia were from the Mexican Mestizo population. The Mexican Mestizo designation was based on birth in Mexico of all patients, as well as both parents and at least three of four grandparents. Most patients originated from Mexico City and its vicinity, and the rest were mainly from the southern and central states of Mexico. None of the patients spoke any native Indian languages or were self-described as belonging to any of the Native Mexican ethnic (Indian) populations. In all, 54 patients were from 36 families with recessive ataxia and 80 had sporadic ataxia. Informed consent was obtained and genetic testing was carried out according to the guidelines of the institutional review boards at the Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez (Mexico City, Mexico) and University of Oklahoma Health Sciences Center (Oklahoma City, Oklahoma, USA).

We had previously analysed these patients for GAA repeat expansions and point mutations in the *FXN* gene, according to standard protocols.¹⁴ All mutation-free patients were evaluated for other known causes of ataxia (described in Results). Clinical evaluation and review of charts were carried out by AR.

RESULTS

We have previously reported that screening of all patients for GAA repeat expansions in the *FXN* gene resulted in the identification of 14 (10.4%) homozygotes for the mutation out of 134 patients.¹⁴ The 120 patients without *FXN* mutations were further screened and found not to have mutations in

Abbreviations: AOA, ataxia with oculomotor apraxia; FRDA, Friedreich ataxia; *FXN*, frataxin gene; ILOCA, idiopathic late-onset cerebellar ataxia; MSA, multiple-system atrophy

the aprataxin gene (by single-strand conformational polymorphism screening), or expansions in the genes responsible for spinocerebellar ataxias (SCA1, SCA2, SCA3/MJD, SCA6, SCA7, SCA8, SCA10, SCA12 or SCA17). α -Tocopherol and γ -tocopherol levels ruled out vitamin E deficiency, and normal lipid profiles and ophthalmological examination excluded the possibility of abetalipoproteinemia. All patients had previously undergone screening for non-genetic causes of ataxia, which were also ruled out, and patients remained without a confirmed aetiological diagnosis.

Patients were classified as having the FRDA phenotype ($n = 30$) if they had the clinical criteria proposed by Harding,¹⁵ or clinical features consistent with late-onset FRDA or FRDA with retained deep-tendon reflexes. All others were classified as having a non-FRDA phenotype ($n = 104$).

Most patients had the non-FRDA phenotype and formed a heterogeneous group. Of these 104 patients, 32 showed clear evidence of autosomal recessive inheritance. We analysed their clinical features in an attempt to identify specific subgroups. On the basis of their age at disease onset, patients were divided into early-onset (≤ 25 years) and late-onset (> 25 years) groups (table 1). Patients with early onset had a longer duration of disease (mean (standard deviation (SD)) = 13.5 (8.7) v 9.4 (6.6) years; $p < 0.01$) and a higher frequency of cognitive deficit (56.6% v 23% in the late-onset group; $p < 0.01$). Review of the available magnetic resonance images or computed tomography scans did not suggest Joubert's syndrome, a known cause of early-onset ataxia and mental retardation. Most patients with non-FRDA with recessive inheritance belonged to the early-onset group (27 v 5 in the late-onset group; $p < 0.01$), indicating the possibility of a defined aetiology in this subgroup.

The patients with late-onset ataxia did not have any distinguishing features and the cause of their ataxia remains to be determined, with the possible exception of six patients who had findings compatible with those seen in probable multiple system atrophy type C.¹³

Of the 30 patients with the FRDA phenotype, 14 were homozygotic for *FXN* mutations. More importantly, the remaining 16 (53.3%) patients with the FRDA phenotype had both GAA-repeat alleles within the normal range and had no other *FXN* mutations. Ten showed autosomal recessive inheritance and the remaining six had sporadic ataxia. This is unlike in previous European studies where almost all patients who met Harding's diagnostic criteria for FRDA were subsequently found to have *FXN* gene mutations.^{2-5 16 17} We designated this group "FRDA-like" phenotype because despite the absence of *FXN* gene mutations, the age at onset, disease duration and clinical features were similar to those of the patients who were homozygotic for

expanded GAA-repeat alleles, findings that are suggestive of non-allelic genetic heterogeneity of recessive ataxia in this population. However, we noticed a tendency among this group of patients to display more severe ataxia and cerebellar atrophy ($p = 0.02$).

DISCUSSION

The main cause of early-onset ataxia among patients with recessive or sporadic ataxia in two comparable European studies is FRDA, with a relative frequency of about 75%.^{2 3} In Latin America, a study analysing Brazilian patients found that 64% of families with recessive ataxia had *FXN* mutations.¹⁸ Furthermore, almost all (96–100%) of the European patients who fulfil Harding's clinical diagnostic criteria for FRDA have mutations in the *FXN* gene.^{2-5 16 17} There is some evidence of non-allelic genetic heterogeneity underlying the FRDA phenotype, but this is rare.¹⁰

By contrast, we have shown that only about 10% of Mexican Mestizo patients with recessive or sporadic ataxia have FRDA and that $> 50\%$ of those who fulfil the clinical diagnostic criteria have no *FXN* gene mutation. This also contrasts with another Brazilian study in which 17 of 19 patients with typical FRDA were homozygotic for GAA expansions.¹⁹ In our cohort, Harding's diagnostic criteria for FRDA showed poor sensitivity (0.714 (95% confidence interval (CI) 0.454 to 0.883)) and positive predictive value (0.385 (95% CI 0.224 to 0.575)), but good specificity (0.867 (95% CI 0.794 to 0.916)) and negative predictive value (0.963 (95% CI 0.909 to 0.986)). This indicates that the use of clinical diagnostic criteria in Mexican Mestizo patients is useful for ruling out FRDA rather than for detecting true cases.

Most of our patients were classified as not having the FRDA phenotype. Contrary to reports in other populations that identified the cause of idiopathic ataxia in as many as 40% of their patients,¹¹ we were unable to identify the aetiology of the disease in 81 (75%) of our patients despite extensive investigation. The single common identifiable cause of ataxia in this group was probable MSA type C¹³ present in 6 of 104 (5.7%) patients. This is less than that reported by other groups, who found a prevalence ranging from 14% to 19% of their patients with ILOCA.^{10 11 20}

Further analysis of the patients with non-FRDA suggested that there are two different subgroups based on age at onset of disease. Most patients with autosomal recessive inheritance have an early age at onset (≤ 25 years) and a higher frequency of non-cerebellar manifestations compared with the late-onset group. These patients had a significantly higher prevalence of cognitive deficit (mental retardation or cognitive decline) than the late-onset group ($p < 0.01$) and longer duration of disease ($p < 0.01$). None of our patients with mutation-positive FRDA showed any cognitive decline.

To determine the aetiology of ataxia in the patients with FRDA-like disease, we ruled out most known causes for phenotypic overlap. Although we did not formally test our patients for AOA2 or autosomal recessive ataxia of Charlevoix-Saguenay, other potential causes of recessive ataxia, the absence of choreic or dystonic movements,^{21 22} and hypermyelinated fibres in their optic fundi make these diagnoses unlikely.

One possible source of bias in our study is that patients were recruited in an adult neurology facility, and despite our recruitment efforts to ascertain patients of all age groups with ataxia, we suspect that patients with very early onset are likely to be under-represented. Another important issue stems from the rather high prevalence of alcohol dependence in the Mexican adult population,²³ a potentially important cause of ILOCA²⁴; however, despite the likely under-reporting

Table 1 Non-Friedreich ataxia phenotype divided by age at onset of disease

	Early onset (≤ 25 years)	Late onset (> 25 years)	p Value
n	64	40	
Recessive:sporadic	27:37	5:35	0.01
Age at onset (years)*	14.22 (6.4)	42.1 (10.9)	
Duration of disease (years)*	13.5 (8.7)	9.45 (6.6)	0.01
Cerebellar atrophy (MRI; %)	40/54 (74.1)	29/36 (80.1)	NS
Seizures (%)	6/64 (9.4)	1/39 (2.6)	NS
Cognitive deficit (%)	17/30 (56.7)	6/26 (23.1)	0.02
Abnormal NCV (%)	25/37 (67.6)	10/21 (47.6)	NS

MRI, magnetic resonance imaging; NCV, nerve conduction velocity; NS, not significant.

*Values are mean (SD).

of this in our cohort, it is unlikely to affect the conclusions drawn from patients with early-onset ataxia.

Our data suggest that the aetiology of recessive ataxia in Mexico is different from the reported patterns in other populations. In the present series, the FRDA-like phenotype and early-onset recessive ataxia with cognitive deficit accounted for about 60% of all the recessive or sporadic cases. However, the underlying cause of their disease remains largely unknown. Identification of other genes that cause recessive ataxia in the Mexican population, via positional cloning or a candidate gene strategy, will provide important clues towards understanding the pathogenesis of spinocerebellar degeneration.

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