Frequency and phenotypic spectrum of spinocerebellar ataxia 27B and other genetic ataxias in a Spanish cohort of late-onset cerebellar ataxia.

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Abstract

Background

Dominantly inherited GAA repeat expansions in the fibroblast growth factor 14 (*FGF14*) gene have recently been shown to cause spinocerebellar ataxia 27B (SCA27B). We aimed to study the frequency and phenotype of SCA27B in a cohort of patients with unsolved late-onset cerebellar ataxia (LOCA). We also assessed the frequency of SCA27B relative to other genetically defined LOCAs.

Methods

We recruited a consecutive series of 107 patients with LOCA. 64 remained genetically undiagnosed. We screened these 64 patients for the *FGF14* GAA repeat expansion. We next analysed the frequency of SCA27B relative to other genetically-defined forms of LOCA in the cohort of 107 patients.

Results

Eighteen of 64 patients (28%) carried an *FGF14* $(GAA)_{\geq 250}$ expansion. The median age at onset was 62.5 years (range, 39-72). The most common clinical features included gait ataxia (100%) and mild cerebellar dysarthria (67%). In addition, episodic symptoms and downbeat nystagmus were present in 39% (7/18) and 37% (6/16) of patients, respectively. SCA27B was the most common cause of LOCA in our cohort (17%, 18/107). Among patients with genetically defined LOCA, SCA27B was the main cause of pure ataxia, *RFC1*-related disease of ataxia with neuropathy, and *SPG7* of ataxia with spasticity.

Conclusion

We showed that SCA27B is the most common cause of LOCA in our cohort. Our results support the use of *FGF14* GAA repeat expansion screening as a first-tier genetic test in patients with LOCA.

1. INTRODUCTION

Late-onset cerebellar ataxias (LOCAs) are a group of neurodegenerative disorders manifesting with a progressive cerebellar syndrome after the age of 30[1,2]. The underlying causes of LOCA have until recently remained largely unknown[3], as suggested by the results of a recent Spanish registry study, in which around 50% of patients with LOCA remained without genetic diagnosis[4].

Recently, dominantly inherited GAA repeat expansions in the first intron of the fibroblast growth factor 14 (*FGF14*) gene have been shown to cause spinocerebellar ataxia 27B (SCA27B; MIM 620174)[5,6], which appears to be one of the most common genetic causes of LOCA identified to date[5,6]. This finding is changing the diagnostic approach to LOCA by increasing the diagnostic yield of genetic testing in this group of disorders.

Here, we present the frequency and phenotypic profile of SCA27B in a single-centre cohort of patients with LOCA from Spain, and compare the frequency of SCA27B to other genetically defined LOCAs in this cohort.

2. MATERIAL AND METHODS

Patients were eligible for inclusion if developing progressive ataxia of known or unknown genetic cause after the age of 30 years, not having a diagnosis of probable multiple system atrophy cerebellar type defined by the 2008 criteria[7], and no acquired cause. We recruited 107 consecutive patients between September 2020 to December 2022 at the Donostia University Hospital. Clinical data were retrospectively collected from medical records using a standardized data collection sheet.

40% of patients had a previously known molecular diagnosis (43/107). The remaining 64 patients with genetically undefined LOCA were screened for *FGF14* GAA expansions, as previously described[8]. In patients without a molecular diagnosis, 83% (53/64) were screened for intronic *FXN* GAA repeat expansions, 92% (59/64) for SCA 1, 2, 3, 6, 7, 12, 17, and DRPLA, 100% (64/64) for *RFC1* expansions, and 61% (39/64) for *FMR1* premutation. Targeted next-generation sequencing gene panels were performed in 34% of these patients (22/64) and did not identify pathogenic variants.

Correlations between repeat size and age at onset or scale for the assessment and rating ataxia (SARA) score[9] were calculated using Pearson's correlation coefficient. We analysed the data in GraphPad Prism 6. P-values < 0.05 were considered significant. All analyses were two-tailed.

This study was approved by the ethics committee of the Donostia University Hospital (JRM-PD-2020-01) and written informed consent was obtained from all patients. The study conforms with the World Medical Association Declaration of Helsinki.

3. RESULTS

Clinical features of patients with SCA27B

The baseline characteristics of the 107 patients with LOCA included in this study are presented in Supp. Table 1. The genetic cause was known in 43 patients (40%) while 64 patients remained without a molecular diagnosis (60%).

Among the 64 patients with idiopathic LOCA, 18 (28%) carried a pathogenic *FGF14* $(GAA)_{\geq 250}$ expansion. The main clinical features of these patients are shown in Fig.1A and Suppl.Table 2. Allele size distribution in the screened patients is shown in Suppl.Fig.1A.

The median age at onset was 63 years (range, 39-72). The median age and disease duration at last examination were 76 years (range, 62-87) and 14 years (range, 4-33), respectively. Seven patients (39%) reported episodic symptoms at disease onset, two of whom initially developed acute episodes of diplopia and downbeat nystagmus that were first thought to be caused by brainstem stroke. Family history was positive in seven patients (41%). Walking aids were used by nine patients after a median disease duration of 12 years (range, 4-26) (Suppl.Table 2).

Gait ataxia was found in all patients (18/18, 100%) while appendicular ataxia on finger-nose test (8/18, 44%) and heel-shin test (10/18, 54%) was less frequent. Downbeat nystagmus was observed in 37% (6/16) and mild cerebellar dysarthria in 67% (12/18) of patients. Mild distal reduced vibration sense was documented in 50% of patients (9/18). Two of six patients with hypoacusis or tinnitus (6/18, 33%) first developed symptoms at ages 30 and 45 years, respectively.

Cross-sectional SARA score was available for 14 patients, with a median of 11.25 points (range, 1-20). Analysis of the sub-items of the SARA revealed that gait (41%), stance impairment (19%), and lower limb ataxia on heel-shin test (12%) contributed the most to ataxia severity (Fig.1B). The repeat count of the expansion was not significantly associated with age of onset (Pearson's r=-0.160, p=0.526) (Suppl. Fig. 1B), ataxia severity measured by the SARA (Pearson's r=0.217, p=0.456) (Suppl. Fig. 1C) and annualized SARA score (ratio of SARA score divided by disease duration) (Pearson's r=-0.226, p=0.437) (Fig.Suppl.1D).

Brain MRI was available for 15 patients (Suppl.Fig.2) and showed isolated vermis atrophy in 13% (2/15) and diffuse cerebellar atrophy in 47% (7/15) of patients. Nerve conduction studies were performed in eight patients and showed mild axonal sensorimotor polyneuropathy in one patient. This patient also had a history of alcohol abuse which might have contributed to the development of polyneuropathy.

Five patients received treatment with 4-aminopyridine at a dose of 10mg twice a day. Two of them stopped the treatment during the first few weeks because of side effects (dizziness and worsened unsteadiness). Another patient had initial benefit although he stopped treatment after 3 months due to worsening dizziness. The two remaining patients showed objective gait improvement as measured by the 25-feet walk test (Fig. 1D). Of note, drug withdrawal led to acute gait deterioration in one of these patients, which improved after reintroduction of the drug.

Late-onset ataxia cohort features (Fig.2)

Following *FGF14* GAA repeat expansion screening, the underlying genetic cause was identified in 61 of the 107 cases (57%) from the whole LOCA series (Suppl.Fig.3, Suppl.Table 3). The most common causes of LOCA were repeat expansion disorders (42/61, 69%) (Suppl.Fig.3B) while non-repeat expansion disorders accounted for 31% (19/61) of cases (Suppl.Fig.3B).

We next assessed the frequency of the different genetic causes in subgroups of patients with pure cerebellar ataxia, ataxia with neuropathy, and spastic ataxia (Fig.2). Eight patients showed ataxia, neuropathy and spasticity and were included in both the ataxia plus neuropathy and ataxia plus spasticity groups.

Pure ataxia (43/107, 40%). This phenotypic subgroup had the highest number of patients without a causative gene identified (25/43; 58%). SCA27B was the most common cause in this sub-group (12/43, 28%), followed by *CACNA1A1*-related disease, including SCA6 (3/43, 7%) and episodic ataxia type 2 (1/43, 2%).

Ataxia and neuropathy (47/107, 44%). Polyneuropathy was diagnosed on nerve conduction studies or defined clinically by the presence of neuropathic symptoms, decreased distal sensation, and decreased ankle reflexes[10]. This group had the highest proportion of patients with a genetic diagnosis (34/47; 72%). The most frequent genetic cause was *RFC1*-related ataxia (15/47; 32%). Polyneuropathy was diagnosed on nerve conduction studies in 1 patient and clinically in 4 patients with SCA27B (5/47; 11%). Other genetic causes were less common in this phenotypic subgroup (Fig. 2).

Ataxia and spasticity (25/107, 23%). Twelve patients from this subgroup remained without a genetic diagnosis (48%). Among patients with a genetic diagnosis, variants in *SPG7* were the most common etiology (8/25; 32%). SCA27B was present in only one patient (4%).

4. DISCUSSION

Here, we studied the frequency of SCA27B in a cohort of patients with LOCA and showed that it represents the most frequent genetic cause of LOCA in our single-centre Spanish cohort. Specifically, we showed that SCA27B was particularly frequent in patients with pure cerebella ataxia.

SCA27B accounted for 28% of cases in our cohort of patients with unsolved LOCA, a frequency similar to that reported in other European series[5,6,8,11,12]. Patients with SCA27B consistently presented with a slowly progressive pan-cerebellar syndrome predominantly affecting the gait, with frequent downbeat nystagmus and episodic symptoms at disease onset. Thus, the phenotype of our patients did not differ from previous descriptions[5,6,11–14]. Although neuropathy does not appear to be a core feature of SCA27B[5,6,8], an observation further supported by our study, hypopallaesthesia (without corresponding abnormalities on nerve conduction studies) was present in 50% of our patients. Similar findings were recently identified in a German cohort, suggesting impairment of the afferent sensory tracts[13]. We also observed that 33% of patients from our series displayed dysautonomia, mainly manifesting as orthostatic hypotension Hypoacusis or tinnitus were present in a third of cases , including two cases in whom it began before 50 years of age. Two of our patients with SCA27B experienced acute episodes of diplopia and downbeat nystagmus at disease onset, suggesting that *FGF14* expansions should be screened in patients with subacute cerebellar syndrome in whom acquired causes have been excluded. In both patients, these episodes were self-limited and progressive ataxia started approximately two years later.

Furthermore, we presented longitudinal follow-up data on 2 patients treated with 4-aminopyridine, which showed some improvement of walking speed over up to 4 years of follow-

up. These findings are in agreement with other studies that have shown a benefit of 4-aminopyridine in some patients with SCA27B[5,13,15].

The main limitations of this study include its single-centre design, relatively small sample size, including only patients of European ancestry, absence of whole-exome sequencing in some patients with unsolved LOCA, and lack of longitudinal data in patients with SCA27B patients for the SARA score or other measures of non-ataxia burden (i.e. INAS).

In conclusion, we showed that SCA27B was the most common cause of LOCA in our series, thus supporting recent reports suggesting that screening for *FGF14* GAA repeat expansions should be a first-tier genetic testing in patients LOCA.

Conflict of interest

Stephan Zuchner has received consultancy honoraria from Neurogene, Aeglea BioTherapeutics, Applied Therapeutics, and is an unpaid officer of the TGP foundation, all unrelated to the present manuscript. The other authors declare no conflict of interest.

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Author contribution:

Conceptualization: PI, DP, AB, HH, ALM, JRM; Formal Analysis: PI, DP, AB, IA, EM, AV, JRM; Funding Acquisition: CC, AP, BB, HH, ALM; Investigation: PI, DP, AB, IA, EM, AV, RFT, FM, JE, DCC, JJP, MR, SF, MJD, MD, SZ, IC, MR, AS, CC, AP, BB, HH, ALM, JRM; Methodology: PI, DP, MJD, MD, SZ, IC, MR, AS, CC, AP, BB; Resources: CC, AP, BB, HH, ALM, JRM; Supervision: AB, SZ, MD, MJD, BB, HH, ALM, JRM; Visualization: PI, DP, AB, IA, HH, ALM, JRM; Writing – Original Draft Preparation; PI, DP; Writing – Review & Editing: all authors

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Captions

Figure 1. Main clinical features of patients with SCA27B. A) Frequency of symptoms, signs, and ancillary tests findings in our series of patients with SCA27B (n=18). Numerator and denominator in brackets indicate the number of affected patients and the number of patients assessed for this feature, respectively. bHIT= bedside Head Impulse Test. B) Contribution of different SARA items to the overall SARA score. Gait was the most severely affected system,

followed by stance and lower limb ataxia. C) Longitudinal follow-up of two patients with SCA27B treated with 4-aminopyridine. Functional response to treatment was measured by the timed 25-feet walking test. Sustained walking speed improvement was observed in both patients with a maximum speed improvement of 17% in patient 8 and 20% in patient 15.

Figure 2. Main genetic causes of LOCA by phenotypic subgroups. The genetic causes were assessed in subgroups with pure ataxia, ataxia plus neuropathy, and ataxia plus spasticity. In those without neuropathy or spasticity, ie pure ataxia (43/107, 40%), 58% remained without diagnosis (25/43) and SCA27B was the most frequent cause (12/43, 28%). In the subgroup with ataxia plus neuropathy (47/107, 44%), 28% patients remained without a genetic diagnosis (13/47) and, in patient with a diagnosis, *RFC1*-related disease was the most frequent cause (15/47, 32%). In the subgroup with ataxia plus spasticity, 48% remained without a diagnosis (12/25) and, in patients with a diagnosis, *SPG7* was the most common known cause (8/25, 32%). Eight patients with ataxia, neuropathy and spasticity were included in both the ataxia plus neuropathy and ataxia plus spasticity groups.