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Involvement of the Superior Cerebellar Peduncles in GAA-*FGF14* Ataxia

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Abstract

Objectives

GAA-*FGF14* ataxia (SCA27B) is a recently reported late-onset ataxia caused by a GAA repeat expansion in intron 1 of the *FGF14* gene. After the clinical observation of superior cerebellar peduncle (SCP) involvement in some affected patients, we sought to verify the prevalence of this finding in our cohort and 4 additional independent cohorts of patients with SCA27B.

Methods

We performed a retrospective review of the brain MRI scans of a total of 87 patients (median age at MRI 69 years; range 28–88 years) from different independent cohorts to assess the presence of SCP involvement, defined as abnormally high T2 signal along the SCP tract.

Results

We observed SCP involvement in 52 patients (52/87; 59.8%) from all the cohorts combined. The finding was replicated at rates ranging from 50% to 62.8% in the cohorts taken separately.

Discussion

SCP involvement in SCA27B is frequent. Its detection may facilitate the diagnostic process of patients with SCA27B.

Introduction

GAA-*FGF14* ataxia (spinocerebellar ataxia SCA27B; OMIM 620174) is a late-onset cerebellar ataxia (LOCA) caused by dominantly inherited GAA-TCC repeat expansion in the first intron of *FGF14*, which encodes the fibroblast growth factor-14.[1,2] SCA27B is estimated to be one of the most common forms of late-onset and autosomal dominant ataxias, especially in the French Canadian and European population.[3] Initial review of brain MRI findings has revealed cerebellar atrophy in 74% of patients with SCA27B, with further data reporting vermian atrophy in over 90% of patients.[1,4] The presence of superior cerebellar peduncle (SCP) involvement has never been reported before in patients with SCA27B. After the clinical observation of bilateral SCP involvement in some patients with SCA27B, we aimed to assess the prevalence of signal

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abnormalities along this tract in our cohort of patients with SCA27B and in 4 independent cohorts.

Methods

We performed a retrospective analysis of the available MRI scans of the 39 patients with SCA27B included in the cohort referred to the Montreal group. Included MR images were acquired on either 1.5T (36 patients) or 3T (3 patients) MR machines. Patients were included if (1) their phenotype was clinically compatible with SCA27B, (2) the genetic testing performed according to a standardized protocol[5] documented a $(GAA)_{\geq 250}$ expansion in *FGF14*, and (3) available MRI scans comprised at least 3D FLAIR (fluid-attenuated inversion recovery) T2-weighted images and/or axial or coronal T2. Patients were excluded if they presented other CNS conditions or if the quality of the MR images was suboptimal.

For all included patients, we collected demographic and clinical data.

All images were reviewed collegially by the authors (S.C., R.S., C.A., and R.L.P.) blinded to disease severity and symptoms. Each MRI scan was evaluated twice, 3 months apart. Team disagreements were resolved by consensus.

We assessed the presence of SCP involvement defined as T2 hyperintense signal at any level of the SCP course, from the cerebellum to the midbrain. We also classified the SCP involvement as prominent or faint according to the signal intensity compared with the surrounding tissue (eFigure 1).

Because the Montreal cohort included mostly patients of French Canadian or French descent (87.2%) and because we wanted to verify whether the detection of SCP involvement was consistent across cohorts, raters, and scanning conditions, we asked neurologists and radiologists from 4 additional centers (M.S., B. Bender, E.I., S.M.B., P.I.A., A.L.M.A., J.I.C., E.M.L., R.S.B.) to review the brain MR images of their patients with SCA27B to assess the presence of SCP involvement comparing with provided reference images (eFigure 1). The Montreal group also independently reviewed the same MRI scans, blinded to the treating teams' conclusions. Inter-rater agreement was calculated using the Cohen K coefficient. Disagreement between the 2 ratings was then solved by collegially reviewing the images and reaching a consensus.

MR images were acquired on scanners with a field strength of either 1T (3 patients), 1.5T (44 patients), or 3T (11 patients). The protocols of the MRI scans were not standardized because they were requested for clinical indication across different hospitals, thus limiting the systematic analysis of MR data. Like for the Montreal cohort, we included patients with at least 3D FLAIR T2-weighted images and/or axial or coronal T2.

Clinical-Radiologic Correlations

We compared the prevalence of SCP involvement between patients symptomatic for ≤5 years and for >5 years at the time of initial MRI because most patients become permanently ataxic after an average of 5 years since disease onset; between patients aged 60 years or younger and those older than 60 years at the time of their initial MRI; and between patients with GAA expansion size ≤300 and those with size ≥300. We assessed differences between groups with the Fisher exact test.

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review boards of each participating institution approved the use of clinical data for the retrospective study.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

We reviewed MR images from a total of 87 patients with SCA27B. MR images were acquired on a 1T (3 patients), 1.5T (77 patients), or 3T (7 patients) scanner. 3D FLAIR T2-weighted images were available for 20 patients (20/87; 23%). Longitudinal studies were available for 23 patients (23/87; 26.4). The follow-up MR studies were acquired on a 1.5 (17) or 3T (6) scanner.

Specifically, from the 39 patients of the Montreal cohort, we included 35 individuals (Quebec = 27; Nancy = 3; Perth = 3; Bengaluru = 2). From the 58 patients with SCA27B of the 4 independent cohorts, we reviewed images of 52 patients (eTable 1).

Ten patients were excluded for suboptimal image quality.

Demographic and clinical features of all cohorts are summarized in Table 1.

SCP Involvement

We observed SCP involvement in a total of 52 patients (52/87; 59.8%) from all cohorts combined. For the Montreal cohort, the SCP involvement was documented in 22 patients (22/35, 62.8%): prominent in 16 (16/22, 72.7%) (Figure 1, A–D, I–L) and faint in 6 (6/22, 27.2%) (Figure 1, E–H). For the validation cohorts, the SCP involvement was detected in 30 patients (30/52, 57.7%): prominent in 15 (15/30; 50%) and faint in 15 (15/30; 50%). SCP T2 hypersignal was best captured by 3D FLAIR T2 images (Figure 1, A–C). eTable 1 provides the results for each independent cohort.

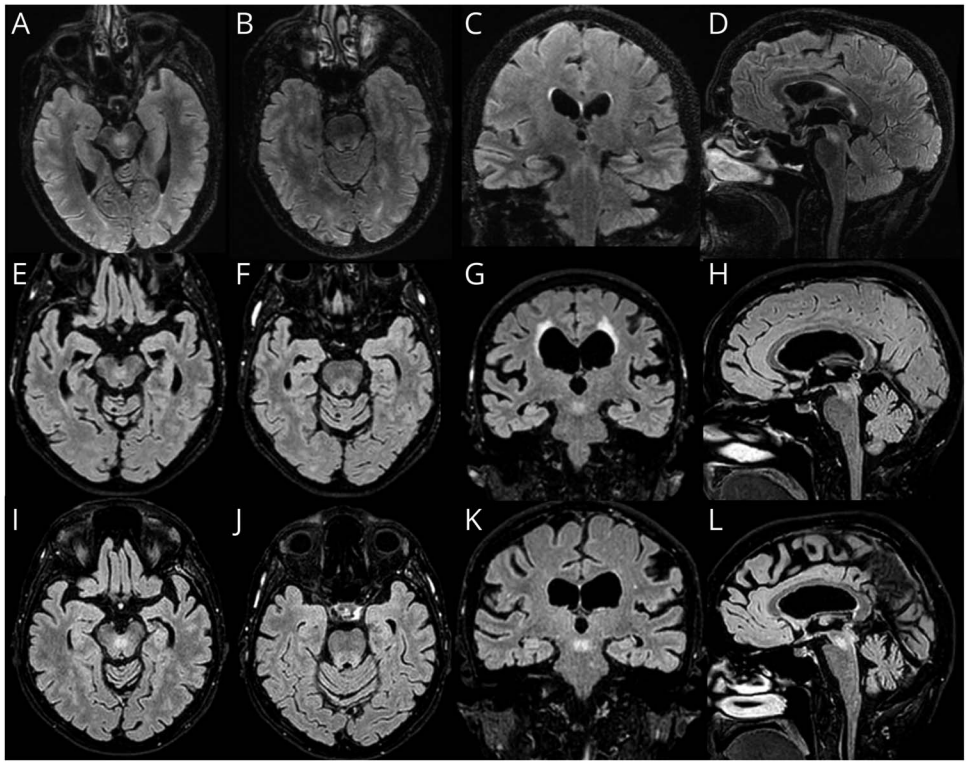
In the assessment of the validation cohorts, the inter-rater agreement between the local raters and the Montreal group

Table 1 Demographic, Clinical, and Radiologic Findings of 87 Patients With GAA-*FGF14* Ataxia

	Total cohort	Montreal cohort	Validation cohorts
Demographics and clinical information	**n (%) - total 87**	**n (%) - total 35**	**n (%) - total 52**
Sex F; M	36; 51 (41.4; 58.6)	15; 20 (42.8; 57.2)	21; 31 (40.4; 59.6)
Geographic origin and ancestry	Canadian, FC: 27 (31) German, Eur D: 27 (31) Spanish, Eur D: 18 (20.7) Austrian, Eur D: 7 (8.1) French, Eur D: 3 (3.4) Australian, Eur D: 3 (3.4) Indian: 2 (2.3)	Canadian, FC: 27 (77.1) French, Eur D: 3 (8.6) Australian, Eur D: 3 (8.6) Indian: 2 (5.7)	German, Eur D: 27 (51.9) Spanish, Eur D: 18 (34.6) Austrian, Eur D: 7 (13.5)
Median age at onset, y (range)	59 (22–81)	52 (25–75)	61 (22–81)
Median age at MRI, y (range)	69 (28–88)	63 (28–88)	71 (29–88)
Median disease duration, y (range)	5 (1–34)	9 (1–34)	5 (1–28)
Median GAA-TCC repeat expansion (range)	358 (252–578)	378 (265–508)	354 (252–578)
Permanent ataxia at time of MRI[a]	83 (95.4)	29 (93.5)	50 (96.2)
Episodic ataxia at time of MRI[a]	4 (4.6)	2 (6.5)	2 (3.8)
Median follow-up duration[b] **(range)**	5 (1–16)	3.5 (1–16)	5 (1–14)

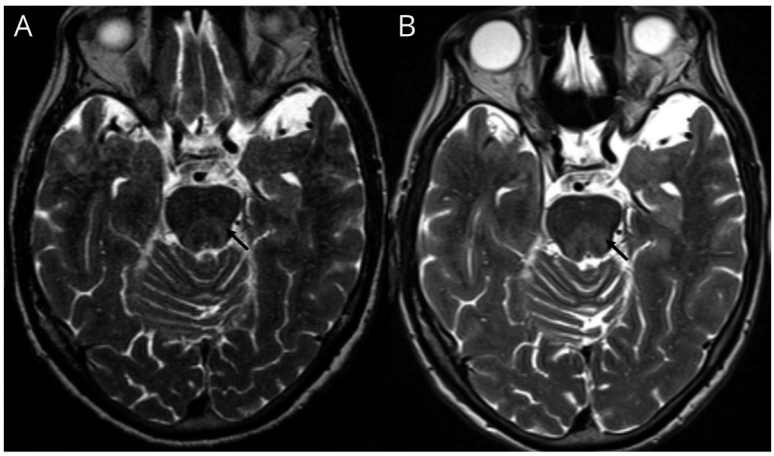
Abbreviations: Eur D = European descent; FC = French Canadian.
[a] Data missing for 4 patients.
[b] Data available for 23 patients.

Figure 1 Involvement of the Superior Cerebellar Peduncles (SCPs)



Multiplanar FLAIR T2-weighted images of 3 patients showing bilateral and symmetric involvement of the SCP and its decussation within the midbrain. T2 hyperintense signal is visible in the central region of the midbrain in both the axial (A, E, I) and sagittal views (D, H, L), as well as in the coronal plane (C, G, K). The SCPs are involved for their entire length, as shown in the axial views (B, F, J) and in the coronal image (C). The images are from a patient in their 70s with 5 years of disease duration (GAA-TCC expansion size >300) acquired on a 3T MR scanner (A–D), a patient in their 80s with 10 years of disease duration (GAA-TCC expansion size <300) acquired on a 1.5T MR scanner, and a patient in their 70s with 21 years of disease duration (GAA-TCC expansion size >300) acquired on a 1.5T MR scanner (I–L).

Figure 2 SCP Involvement, Longitudinal Study



Axial T2-weighted images in a patient in their 70s with 2 (A) and 4 (B) years of disease duration (GAA-TCC expansion size >300), acquired on a 1.5 (A) and 3T (B) scanner. The SCP involvement is stable over time and can be seen at both a lower and higher magnetic field strength (black arrow).

was substantial, with a Cohen K value of 0.76 (SE of kappa = 0.090; 96% CI = from 0.584 to 0.935).

Longitudinal Studies

Among the 23 patients with longitudinal MRI studies, SCP involvement was observed on the initial scan in 11 (11/23, 47.8%) and remained stable over time (Figure 2). In 3 cases, follow-up MRI was performed at a higher magnetic field strength than the initial MRI; the SCP involvement was already detectable at lower field (Figure 2). One case showed new-onset SCP involvement 4 years after the initial MRI study.

Clinical-Radiologic Correlations

We did not document any statistically significant differences in the SCP involvement between patients with ≤5 years and those with >5 years of disease duration in the total cohort of 87 patients, nor between patients with GAA size ≤300 and those with >300, although for the latter comparison, group sizes were considerably unequal, thus affecting statistical testing. The involvement of the SCP was more prevalent in younger patients (60 years or younger at MRI) in the total cohort and the Montreal cohort ($p < 0.001$), but not in the validation cohorts. All p values are reported in eTable 2.

Discussion

We documented that the involvement of the SCPs is frequent in patients with SCA27B. We validated the finding in different cohorts of various geographic origins—although mostly of European ancestry—at very similar rates ranging from 50% to more than 60% and on images acquired with different parameters and field strengths.

Abnormal T2 hypersignal along the SCP tract like the one we observed has been previously seen only in some patients with POLR3-related disorder.[6,7] Conversely, microstructural changes and reduced volume along the SCP, without visible signal abnormality, have been observed in SCA2, SCA6, and Friedreich ataxia.[8-13]

The retrospective nature of our study limited the availability of ideal sequences, and it is thus reasonable to suspect that SCP involvement may be even more prevalent than what we observed.[1,4] SCP changes were best captured by 3D T2 FLAIR images; hence, we recommend including 3D FLAIR T2-weighted MR sequences when assessing patients with SCA27B.

SCP involvement was more represented in patients younger than 60, although not in all cohorts. The fact that we documented it in longitudinal examinations argues against its transitory nature; in addition, reviewed MRI scans were acquired over a 20-year span of time and the SCP region may not have been well visualized in outdated MRI protocols.

Although statistical analysis was limited by unequal sample sizes between groups, we observed SCP involvement in patients with (GAA) repeat expansion size less than and more than 300. Therefore, SCP involvement may be a useful imaging feature, particularly in patients with an incompletely penetrant $(GAA)_{250\text{-}299}$ repeat expansion, in earlier stages of disease, and as a marker distinguishing this disorder from other LOCAs.[14,15]

Prospective studies using standardized imaging protocols will elucidate the diagnostic value of the SCP involvement, its association with age or clinical features, and its role in the disease pathophysiology.

In conclusion, we described a novel MRI finding of SCP involvement in patients with SCA27B whose detection can orient and accelerate the diagnosis.

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Author Contributions

S. Chen: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. C. Ashton: major role in the acquisition of data; analysis or interpretation of data. R. Sakalla: analysis or interpretation of data. G. Clement: major role in the acquisition of data. S. Planel: major role in the acquisition of data; analysis or interpretation of data. C. Bonnet: major role in the acquisition of data; analysis or interpretation of data. P.J. Lamont: major role in the acquisition of data. K. Kulanthaivelu: major role in the acquisition of data. A. Nalini: major role in the acquisition of data. H. Houlden: major role in the acquisition of data. A. Duquette: major role in the acquisition of data. M.-J. Dicaire: major role in the acquisition of data; analysis or interpretation of data. P. Iruzubieta Agudo: major role in the acquisition of data; analysis or interpretation of data. J. Ruiz-Martinez: major role in the acquisition of data; analysis or interpretation of data. E. Marco De Lucas: major role in the acquisition of data; analysis or interpretation of data. R. Sutil Berjon: major role in the acquisition of data; analysis or interpretation of data. J. Infante Ceberio: major role in the acquisition of data; analysis or interpretation of data. E. Indelicato: major role in the acquisition of data; analysis or interpretation of data. S.M. Boesch: major role in the acquisition of data. M. Synofzik: major role in the acquisition of data; analysis or interpretation of data. B. Bender: major role in the acquisition of data; analysis or interpretation of data. M.C. Danzi: major role in the acquisition of data. S. Zuchner: major role in the acquisition of data. D. Pellerin: major role in the acquisition of data; analysis or interpretation of data. B. Brais: major role in the acquisition of data; analysis or interpretation of data. M. Renaud: major role in the acquisition of data. R. La Piana: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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Disclosure

A. Duquette has received consultancy honoraria from AavantiBio, Novartis, Pfizer Canada, PTC Therapeutics, and Reata Pharmaceuticals, all unrelated to the present manuscript. M. Synofzik has received consultancy honoraria from Ionis, UCB, Prevail, Orphazyme, Servier, Reata, GenOrph, AviadoBio, Biohaven, Zevra, Lilly, and Solaxa, all unrelated to the present manuscript. B. Bender is the cofounder, shareholder and CTO of AIRAmed GmbH. R. La Piana has received speaking honoraria from Novartis unrelated to the present manuscript. Go to Neurology.org/NG for full disclosures.

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