






# BRAIN COMMUNICATIONS

## LETTER TO THE EDITOR

### Spinocerebellar ataxia 27B: episodic symptoms and acetazolamide response in 34 patients

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## Introduction

We recently reported the phenotypic profile and natural history progression of 50 German patients<sup>1</sup> with spinocerebellar ataxia 27B (SCA27B; MIM 620174), secondary to GAA repeat expansions in intron 1 of the fibroblast growth factor (*FGF14*) gene, confirming and extending previous reports showing that SCA27B is a late-onset, slowly progressive cerebellar syndrome.<sup>2,3</sup> In addition, we detailed the treatment response to 4-aminopyridine (4-AP) in seven patients, including three prospective n-of-1 treatment

experiences, suggesting symptomatic benefit of 4-AP in SCA27B.<sup>1</sup> Both 4-AP and acetazolamide have been used therapeutically in episodic ataxia and shown to have a largely similar efficacy.<sup>4–6</sup> Whether acetazolamide is also beneficial in SCA27B remains to be established. Here, we describe the real-world response to acetazolamide in cohorts of patients with SCA27B from Montreal (Canada), Innsbruck (Austria), Perth (Australia) and Nancy (France). We found acetazolamide to be only mildly beneficial in a minority of SCA27B patients and even precipitated episodic symptoms in one case. This observation of limited acetazolamide

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response may help inform management of patients with SCA27B.

## Materials and methods

A total of 107 patients with a pathogenic (GAA)<sub>≥250</sub> repeat expansion in the first intron of *FGF14* were identified across four sites, and the proportion of patients with recurrent episodic symptoms was recorded. The majority of the Montreal cohort (73/82), as well as the Perth and Nancy cohorts, have been previously reported. Phenotyping and treatment response were completed retrospectively from clinical records and, when possible, patient re-evaluation using a standardized data sheet.

Episodic symptoms were defined as the presence of a recognizable constellation of recurrent symptoms, which are intermittent, with clear onset and offset from the patient's established baseline and can appear unprovoked or be induced, for example, by exercise or small amounts of alcohol. Patients must have episodic cerebellar symptoms (gait ataxia, dysarthria, diplopia, oscillopsia or appendicular ataxia) but could also have other episodic symptoms.

Treatment response was recorded in a non-controlled manner, defined as a subjective reduction in frequency or severity of symptoms, as judged by the non-blinded patient. The response was sustained when present on serial clinical reviews or non-sustained if there was waning of initial benefit on subsequent reviews.

The institutional review boards of the Montreal Neurological Hospital (MPE-CUSM-15-915), the Centre Hospitalier de l'Université de Montréal (ND02.045), the Medical University of Innsbruck (1022/2020), the University of Western Australia (RA/4/20/1008) and the Centre Hospitalier Régional Universitaire de Nancy (2020PI220) approved this study, and all patients provided written informed consent. The study complies with the Declaration of Helsinki.

The *FGF14* repeat locus was genotyped as described previously.<sup>2,7</sup> Repeat sizes were measured by capillary electrophoresis of fluorescent long-range PCR amplification products. The motif of the repeat expansion was analysed by targeted long-read nanopore sequencing in 59 cases (56 French–Canadian patients and 3 Australian patients), as described previously.<sup>2</sup> Bidirectional repeat-primed PCRs targeting the 5'-end and the 3'-end of the locus were used to ascertain the presence of a GAA repeat expansion in the remaining cases. Expansions of at least 250 GAA repeat units were considered pathogenic.<sup>2,3</sup> We identified one case in the Austrian cohort who was homozygous for (GAA)<sub>264</sub> expansions. To exclude allele drop-out due to polymorphism at one of the primer-binding sites, we confirmed these initial findings using an alternate set of non-overlapping primers (forward: 5'-CCAGAGAGCAAATGACAGCA-3'; reverse: 5'-AGGCGCACTATATTGGGAAC-3').

## Results

Episodic features were present in 86 of 107 (80%) patients across the four cohorts: Montreal 67/82 (84%), Innsbruck

9/10 (90%), Perth 2/3 (67%) and Nancy 8/12 (67%). Of these, 34 received acetazolamide in the clinical setting for treatment of episodic ataxia (Montreal *n* = 23, Innsbruck *n* = 7, Perth *n* = 1 and Nancy *n* = 3), with total daily doses ranging from 250 to 1250 mg. Clinical features of these 34 patients are shown in Table 1. At baseline, patients reported variable duration of episodes, from minutes to hours, with a frequency, when documented, of approximately daily (*n* = 9), weekly (*n* = 8) or quarterly (*n* = 2). Episodic symptoms included diplopia (23/34; 68%), vertigo (15/34; 44%), gait ataxia (26/34; 76%) and dysarthria (20/34; 59%). One patient experienced sudden falls or 'drop attacks', as well as episodic dysarthria. Chronic non-episodic cerebellar features included gait ataxia (33/34; 97%), appendicular ataxia (31/34; 91%), dysarthria (25/34; 74%), gaze-evoked nystagmus (20/34; 59%) and downbeat nystagmus (20/34; 59%).

## Treatment response to acetazolamide

A subjective improvement to acetazolamide was reported in 15 of 34 patients (44%), with 13 patients describing a sustained benefit (Fig. 1). No patients had complete cessation of episodic symptoms. Of the patients with sustained response, this was documented to be only a mild or partial improvement in six. Side effects were reported by five patients and, when specifically documented, included cognitive slowing (*n* = 1), subjective worsening of baseline ataxia (*n* = 1), dysgeusia (*n* = 1) and acral and/or peri-oral paraesthesia (*n* = 1), as well as one patient who had precipitation of severe episodes of ataxia. No serious adverse effects, including renal calculi, were reported.

Three patients (one French-Canadian and two Austrian) received 4-AP treatment, with two patients describing a subjective benefit, one of whom had a complete cessation of severe ataxic episodes.

One male French–Canadian patient had a trial of acetazolamide in the clinic. Prior to taking 250 mg acetazolamide orally, he walked 15 m in a time of 16.52 s. He then walked the same distance in 15.17 s, 45 min after taking acetazolamide, with self-reported improvement and clinician observed improvement in the appearance of his gait with fewer difficulties in turning. At the time of the in-clinic trial, he complained of mild peri-oral paraesthesia. The patient later experienced a severe episode of ataxia and dysarthria 2 h after taking acetazolamide. Severe attacks of ataxia were precipitated on three additional separate ingestions of the medication. Despite this, the patient elected to continue the medication on an as-needed basis and found that on days with subjectively worse ataxia, daily doses up to 1250 mg resulted in mild to moderate improvement of his symptoms without precipitation of severe episodes. However, the patient discontinued acetazolamide after 3 months due to intolerable acral paraesthesia.

## Innsbruck cohort

Of the total previously unreported 10 patients with SCA27B from Innsbruck, 7 (70%) were male and 5 (50%) had no





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