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Expanding the clinical description of autosomal recessive spastic ataxia of Charlevoix-Saguenay

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ABSTRACT

Background and purpose: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) diagnosis is based on the presence of three main clinical features: 1) ataxia, 2) pyramidal involvement, and 3) axonal neuropathy. This study aimed to explore, among a cohort of adults with ARSACS, the prevalence of other signs and symptoms than those commonly describe in this disease and compare their prevalence between younger (< 40 years) and older (≥ 40 years) participants.

Methods: A clinical interview based on a standardized questionnaire was conducted. It included the following items: memory and concentration problems, hearing impairment, epilepsy, spasms, choreathetosis, neuropathic pain, cramps and fecal incontinence.

Results: A total of 43 participants were interviewed, with a mean age of 38.9 years and 51.2% were men. Spasms (55.8%), cramps (53.5%), and concentration problems (39.5%) were the most frequent manifestations. Except for choreathetosis, which was present in only one participant, all other signs and symptoms were present in 9.3% to 29.3% of participants.

Conclusions: People with ARSACS may experience many other clinical manifestations than the most commonly described. This study is a preliminary step toward the development of a comprehensive evidence-based clinical care guideline for this population.

1. Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) has been described in the French Canadian population for almost 40 years now [1]. It is an autosomal syndrome caused by mutations in the *SACS* gene, the first mutation having been identified in 2000. Since then, over 100 SACS mutations were uncovered in 14 countries [2–4]. Two mutations [c.8844delT (6594delT) and c.7504C > T (5254C > T)] accounted for 92.6 and 3.7% of carrier chromosomes in the Charlevoix-Saguenay area (Quebec, Canada), respectively [5].

ARSACS diagnosis is historically based on the presence of three main clinical features: 1) ataxia (appendicular and gait ataxia, saccadic alteration of smooth ocular pursuit and dysarthria) 2) pyramidal involvement (spasticity in the lower limbs and bilateral abnormal plantar responses), and 3) axonal neuropathy (pes cavus, intrinsic hand amyotrophy and absent Achilles reflex) [2]. However, the absence of one of the three clinical features has been recently reported in few cases [6,7]. In addition, over the years, several other signs and symptoms have been reported mainly from clinical case reports, including deafness and generalized seizure [2]. Information is needed about the frequency of these other signs and symptoms in ARSACS and their onset in the disease process. This would help to determine if they are part of the clinical spectrum and thus should be included in clinical follow-up, to better inform anticipatory guidance.

The objectives of the study were: 1) to explore the prevalence of

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other signs and symptoms in adults with ARSACS; and 2) to compare their prevalence between younger (< 40 years) and older (≥ 40 years) participants.

2. Methods

2.1. Subjects

Participants were recruited in 2015, as part of a larger study aiming to describe the ARSACS natural history, from the registry (n = 175) of the Neuromuscular Clinic of the *Centre Intégré Universitaire de Santé et de Services Sociaux* (CIUSSS) *du Saguenay–Lac-St-Jean* (Quebec, Canada) (see previously published papers on this cohort [8,9] for inclusion and exclusion criteria). The study was approved by the Ethics Review Board of the *CIUSSS Saguenay–Lac-St-Jean* and written informed consent was obtained from all participants.

2.2. Procedure

Since the main objective of the larger study was focused toward describing motor impairments and included a large number of clinical assessments, it was decided at the beginning of the project to only include a small questionnaire to explore the prevalence of other signs and symptoms. A specific clinical inventory was thus developed by the research team based on a literature review. This inventory was reviewed and validated by three ARSACS expert neurologists. Data were collected by a trained examiner. Signs and symptoms were defined and assessed as followed: 1) Hearing impairment: partial or complete deafness; 2) Epilepsy: diagnosis/medication; 3) Memory impairment: difficulty to remember names, objects or appointment; 4) Concentration problems: trouble to stay focus during work or any cognitive task; 5) Neuropathic pain in lower limbs: pain needing treatment; 6) Paroxysmal choreathetosis: attacks of involuntary movements triggered by sudden voluntary movements; 7) Cramp: sudden, involuntary, localized and painful muscular contractions needed massaging or stretching to improve; 8) Spasm: sudden involuntary contraction of a muscle or a group of muscles; 9) Fecal incontinence: item taken from the Barthel Index [10], occasional incontinence means once a week. A demographic questionnaire was also completed by all participants to collect information about age, sex and walking aid. Disease stage was determined based on participant's mobility and the use of walking aid (according to stages defined in the SARA development study [11]): Stage 1) No walking difficulty without any walking aid; Stage 2) First walking difficulty, no walking aid; Stage 3) Walk with aid or support; and Stage 4) Wheelchair user.

2.3. Statistical analysis

Data are expressed as mean ± standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. Prevalence of signs and symptoms are reported as number and percentage of participants presenting the symptoms. The total number of signs and symptoms present for each participant was also reported. For the second objective, participants were categorized into younger than 40 years old and 40 years old or older, taking into account that ARSACS patients become constant wheelchair users around this age [12,13]. Comparisons between the two groups were performed using a chi-square test for independence. Data were analysed using IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp).

3. Results

Participants' characteristics are presented in Table 1. From the 175 individuals followed at the Neuromuscular Clinic, 46 were recruited as part of the larger research project, of which 43 participants had complete data about other signs and symptoms and were thus included in this study. A total of 38 participants are homozygous for the c.8844delT (6594delT) mutation in *SACS* gene. The five other participants are heterozygous, i.e. they have the c.8844delT mutation on one allele and the 4744G > A mutation (2 participants), 7504C > T mutation (2 participants), and 814C > T mutation (1 participant) on the other allele. Participants had a mean age of 38.9 years and 51.2% were men. A total of 19 participants (44.2%) were constant wheelchair users.

Table 1
Characteristics of the study population (n = 43).

Characteristic	Total group	< 40 years	≥ 40 years
		n = 26	n = 17
Age, (y)			
Mean (SD)	38.9 (10.9)	31.4 (5.7)	50.4 (5.6)
Range	16–61	16–39	41–61
Gender, n (%)			
Men	22 (51.2)	12 (46.2)	10 (58.8)
Women	21 (48.8)	14 (53.8)	7 (41.2)
Disease stage, *n (%)*			
No walking difficulty	0 (0.0)	–	–
First walking difficulties	10 (23.3)	10 (38.5)	0 (0.0)
Walk with aid or support	14 (32.6)	10 (38.5)	4 (23.5)
Wheelchair user	19 (44.2)	6 (23.1)	13 (76.5)

Signs and symptoms are presented in Table 2. Most frequent are spasms (55.8%), cramps (53.5%), concentration problems (39.5%) and fecal incontinence (29.3%). Most participants (81.4%) reported one to four (out of nine) signs and symptoms, four participants reported between five to seven, and four participants did not report any sign or symptom. The proportion of participants presenting spasms and fecal incontinence is different between younger and older, meaning that older ARSACS patients present proportionally more frequently these two symptoms than younger ones.

Table 2
Prevalence of other signs and symptoms in ARSACS.

	Total (n = 43)	< 40 years (n = 26)	≥ 40 years (n = 17)	Chi^2 (p-value)
Memory impairment				
Present	11 (25.6)[a]	5 (19.2)	6 (35.3)	0.238
Absent	32 (74.4)	21 (80.8)	11 (64.7)	
Concentration problems				
Present	17 (39.5)	9 (34.6)	8 (47.1)	0.415
Absent	26 (60.5)	17 (65.4)	9 (52.9)	
Hearing impairment				
Present	6 (14.0)	4 (15.4)	2 (11.8)	0.738
Absent	37 (86.0)	22 (84.6)	15 (88.2)	
Epilepsy				
Present	4 (9.3)	3 (11.5)	1 (5.9)	0.532
Absent	39 (90.7)	23 (88.5)	16 (94.1)	
Spasms				
Present	24 (55.8)	10 (38.5)	14 (82.4)	*0.005*
Absent	19 (44.2)	16 (61.5)	3 (17.6)	
Paroxysmal choreathetosis				
Present	1 (2.3)	0	1 (5.9)	0.211
Absent	42 (97.7)	26 (100.0)	16 (94.1)	
Lower limb neuropathic pain				
Present	10 (23.3)	6 (23.1)	4 (23.5)	0.973
Absent	33 (76.7)	20 (76.9)	13 (76.5)	
Cramps				
Present	23 (53.5)	16 (61.5)	7 (41.2)	0.191
Absent	20 (46.5)	10 (38.5)	10 (58.5)	
Fecal incontinence[b]				
Present[c]	12 (29.3)	4 (16.7)	8 (47.1)	*0.035*
Absent	29 (70.7)	20 (83.3)	9 (52.9)	

[a] Results are presented as n (%).
[b] There were two missing data.
[c] Meaning that fecal incontinence occurs about once a week.

4. Discussion

The most frequent signs and symptoms found in this study outside the classic triad description were spasms, cramps, concentration problems, and fecal incontinence. The high frequency of self-reported memory and/or concentration problems even before 40 years old will need to be investigated further but should already been considered during clinical follow-up. Previous studies showed a decrease in non-verbal mental abilities (object assembly and digit symbol) in adult [1], school problems in the paediatric population [14], and cognitive impairments (information analyse speed, speech functions, visual logical reasoning and sustained attention) [15]. However, the issue of cognitive impairment in ARSACS is poorly documented and should be further studied using standardized quantitative assessments. In addition, personality traits and neuropsychiatric disorders should also be further investigated based on recent case reports [16,17].

Cramps and spams have been previously described in ARSACS [18,19], and were reported by a high proportion of participants in this study (53.5% and 55.8% of participants, respectively). Since they can be associated with pain, health care professionals should be better informed about the presence of these symptoms to propose potential treatments.

Lower limb neuropathic pain is relatively frequent in this study (23.3%), higher than in the general Canadian population (between 7.7 and 11.5% (irrespective of the site of pain) [20]). Prevalence of epilepsy reported in this ARSACS cohort (9.3%) is also much higher than in the Canadian population (0.6%) [21]. It is slightly lower to the one found by Duquette (15.5%) [14] among paediatric patients, but could be potentially explain by the clinical observation that epilepsy tend to resolve with age in this population. It was somewhat higher than Bouchard (7.2%) [12] in its original description of the disease from an adult population. It has also been reported among family with other mutations [6].

One of the limits of the study is the relative genetic homogeneity of this population; although more than a hundred mutations are described in ARSACS, 88% of the participants in our study are homozygous for the c.8844delT mutation in *SACS* gene thus limiting the phenotype spectrum possibly associated with other mutations. Otherwise, the representativeness of the sample is somewhat limited by the exclusion of paediatric and older patients. Consequently, it could have excluded paediatric and aging-related presenting signs and symptoms. This could explain why paroxysmal choreathetosis was only documented in one participant (2.3%) since it is a symptom more prevalent in younger ARSACS patients and less frequent when weakness becomes more important. In addition, some systems were not formally assessed as no signs or symptoms were reported in the literature including cardiac (valvulopathy) and pulmonary systems (apnea, weak cough effectiveness). Associations between these and ARSACS population should be explore in a future research.

In conclusion, this study is providing stronger empirical evidences for the presence of manifestations previously described in different ARSACS cohorts. It is a preliminary step toward developing a comprehensive evidence-based clinical care guideline for this population. Future research with validated outcome measures will be required to document multi-systemic manifestations more precisely in term of frequency and severity.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Declarations of interest

None.

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