BRIEF REPORT

The Cerebellar Cognitive-Affective Syndrome Scale Reveals Consistent, Early, and Progressive Neuropsychological Deficits in Autosomal-Recessive Spastic Ataxia of Charlevoix-Saguenay: A Large International Cross-Sectional Study

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ABSTRACT: Background: Neuropsychological deficits have been observed in patients with cerebellar damage, but never thoroughly investigated in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS).

Objectives: The goal is the characterization of presence, severity, and profile of neuropsychological deficits in ARSACS using the cerebellar cognitive-affective syndrome (CCAS) scale.

Methods: Prospective study including a discovery cohort from Saguenay/Canada (n = 31, median [inter-quartile range] age: 57 [54–62] years), and a validation cohort from Tübingen, Germany (n = 17, 35 [21–43] years) with matched controls (n = 19).

Results: All ARSACS patients failed in multiple CCAS-related subtests and exceeded cutoffs for "definite CCAS." Even the younger validation cohort failed more subtests than controls (5 [3–7] vs. 1 [1–2], $P < 0.001$) and had lower CCAS total scores (81 [67–86] vs. 101 [91–106], $P < 0.001$). Total scores worsened in the older discovery cohort (40 [25–52], $P < 0.001$) and correlated with age/disease duration ($\rho = -0.575$, $P < 0.001$) and

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ataxia severity (Scale for the Assessment and Rating of Ataxia: $\rho = -0.527$, $P = 0.003$).
Conclusions: Neuropsychological deficits consistent with CCAS are consistent in ARSACS, present early, and progress in the disease course.

Key Words: cognition; cerebellar cognitive-affective syndrome; movement disorders; neuropsychology; spastic ataxia of Charlevoix-Saguenay

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a frequent recessive ataxia worldwide.[1,2] ARSACS involves progressive degeneration of the cerebellum, corticospinal tract and peripheral nerves, and leads to motor manifestations such as limb incoordination, dysarthria, and impaired mobility.[3,4] Recent studies also observed neuropsychological deficits in ARSACS (eg, reduced verbal learning, processing speed, visuospatial ability, and mental rigidity).[5-9] These deficits are possibly linked to the cerebellar cognitive-affective syndrome (CCAS), which is characterized by impaired executive functions, linguistic processing, visuospatial function, and affect regulation.[10-12] CCAS has been described after acquired cerebellar damage and in several genetic ataxias,[13-23] but not systematically in ARSACS. However, characteristics of neuropsychological deficits need to be better understood in ARSACS, as cognitive-affective rigidity and poor self-awareness are related to employment in ARSACS,[24] and because neuropsychological deficits likely affect the validity of patient-reported outcomes in upcoming treatment trials.

Therefore, this large prospective cross-sectional international bi-center study systematically explored the presence, severity, and profile of neuropsychological deficits in 48 ARSACS patients using the Cerebellar Cognitive-Affective Syndrome scale (CCAS scale)—a scale developed for a targeted screening for the syndrome in cerebellar disorders.[20] The study leverages an aged discovery cohort from Saguenay (Canada) and a younger independent validation cohort with a different geographic and heterogeneous genetic background. Onset, progression, and relation to motor impairment of neuropsychological deficits are characterized by comparison with matched controls and correlation with ataxia severity.

Patients and Methods

Forty-eight patients with genetically confirmed ARSACS and able to give free and informed consent were recruited at two centers: a "discovery cohort" (n = 31) at the Neuromuscular Clinic of the Centre Intégré Universitaire de Santé et de Services Sociaux du Saguenay–Lac-St-Jean (Quebec, Canada) in 2018 to 2019; and a "validation cohort" (n = 17) at the Ataxia Clinic of the University Hospital Tübingen (Germany) in 2020 to 2021 (see Supplement for recruitment and data collection). Patients in the discovery cohort were homozygous for the 8844delT mutation, except one compound heterozygous with a 7504C>T mutation, whereas the validation cohort covered a broad spectrum of mutations (Table S2). For the younger validation cohort, 19 healthy controls matched for sex, age, and education were selected from the larger German validation cohort of the CCAS scale.[25] Education was quantified by total years of schooling to ensure comparability across different education systems. Disease duration in the discovery cohort was approximated by age given the uniform onset with early motor developmental delay around age 1 year.

The CCAS scale was used to screen for neuropsychological deficits.[26] This scale comprises 10 subtests, each rated as "passed" or "failed" according to a cutoff score (see Supplement S3 for details of outcome measures). The sum of raw scores for each subtest yields a total score, with a score of ≥82 considered normal (maximum = 120).[9] The number of failed subtests determines the likelihood of CCAS: 1 = "possible CCAS"; 2 = "probable CCAS"; and 3 = "definite CCAS."[9] To account for false positives, the number of failed tests in the validation cohort was also compared against individual cutoffs adjusted for age, sex, and education, which have been modelled for German cohorts.[27] The Friedreich Ataxia Rating Scale (FARS) functional staging was used as global disease severity staging (0 = normal to 6 = wheelchair/total disability). The Scale for the Assessment and Rating of Ataxia (SARA) was used to assess the severity of the motor syndrome of ARSACS.[28] In the validation cohort, the Montreal Cognitive Assessment (MoCA) was applied as an independent, well-established, and more global neuropsychological screening tool 1 to 2 hours before the CCAS scale.

Descriptive results are presented as median (interquartile range), or frequency (percentage). Fisher's exact test and Mann–Whitney tests were used to compare categorical and continuous variables, respectively, and Spearman correlation to explore associations between scores and demographic/clinical variables, all with SPSS Version 30.0 (IBM; Armonk, NY).

Results

In the discovery cohort (age: 57 [54–62] years; education: 11 [9–12] years), the median CCAS total score

TABLE 1 Characteristics of participants

Characteristics	ARSACS cohort		Control cohort (n = 19)	Cohort comparisons (*P*-value)[a]	
	Discovery cohort (n = 31)	Validation cohort (n = 17)		Discovery vs. validation	Validation vs. control
Sex, n (%)					
Men	17 (54.8)	11 (64.7)	9 (47.4)	0.555	0.335
Women	14 (45.2)	6 (35.3)	10 (52.6)		
Age, yr; median (IQR) [range]	57 (54–62) [51–66]	35 (21–43) [14–58]	40 (25–48) [19–77]	<0.001	0.350
Education, yr; median (IQR) [range]	11 (9–12) [0–17]	10 (9–11) [7–14]	10 (10–10) [9–17]	0.285	0.456
Disease duration, yr; median (IQR) [range]	57 (54–62)[f] [51–66]	22 (15–30) [12–52]	Not applicable	–	–
Mobility level, n (%)					
No walking difficulty	0 (0)	0 (0)	Not available	<0.001	–
Walking difficulty, no walking aid	0 (0)	5 (29.4)			
Walk with aid and support	2 (6.5)	8 (47.1)			
Wheelchair user	29 (93.5)	4 (23.5)			
FARS stage; median (IQR) [range]	5 (5–6) [4–6]	4 (2–5) [1–5]	Not applicable	<0.001	–
SARA[b]; median (IQR) [range]	32 (27–35) [18–40]	16 (11–26) [3–33]	Not applicable	<0.001	–
MoCA[c]; median (IQR) [range]	Not available	22.4 (3.8) [12–26]	Not available	–	–
CCAS					
Total score[d]; median (IQR) [range]	40 (25–52) [10–64]	81 (67–86) [37–93]	101 (91–106) [91–112]	<0.001	<0.001
Failed test[e]; median (IQR) [range]	8 (8–10) [5–10]	5 (3–7) [3–10]	1 (1–2) [0–4]	<0.001	<0.001
Definite CCAS, n (%)	31 (100)	17 (100)	3 (16)	–	–
Probable CCAS, n (%)	0 (0)	0 (0)	5 (26)	–	–
Possible CCAS, n (%)	0 (0)	0 (0)	7 (37)	–	–
>1 failed test above cutoff adjusted for age, sex, and education	Not available	16 (94%)	3 (16%)	–	<0.001

[a]Comparisons of variables between cohorts were made using the Fisher's exact test for sex and mobility level proportions and Mann–Whitney test for age, education, SARA, FARS stage, and CCAS total score and failed tests.
[b]SARA maximum score is 40.
[c]MoCA maximum score is 30.
[d]CCAS total score is 120.
[e]CCAS total number of tests is 10.
[f]Represented by age, given development onset.
Abbreviations: ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; IQR, interquartile range; FARS, Friedreich Ataxia Rating Scale; SARA, Scale for the Assessment and Rating of Ataxia; MoCA, Montreal Cognitive Assessment.

was 40 [25–52], and all 31 participants failed ≥5/10 subtests, indicating "definite CCAS" for the entire cohort (Table 1). Eight participants (25%) failed all 10 subtests. Five subtests (semantic fluency, phonemic fluency, category switching, 3D draw/copy, and digit span forward) were failed by ≥90% of the discovery cohort (Table 2).

The 17 participants in the validation cohort were younger and presented at an earlier ataxia stage than the discovery cohort (age: 35 [21–43] years; SARA: 16 [11–26], both $P < 0.001$), but also showed reduced CCAS total scores of 81 [67–86] (Table 1)—although this reduction was less pronounced than in the older, later-stage discovery cohort ($P < 0.001$). All

TABLE 2 Performances in each CCAS scale component for all participants

CCAS components	Total score median (IQR)			Cohort comparisons (*P*-value)[a]		No. of participants who failed n (%)			Cohort comparisons (*P*-value)[b]	
	Discovery cohort (n = 31)	Validation cohort (n = 17)	Control cohort (n = 19)	Discovery vs. validation	Validation vs. control	Discovery cohort (n = 31)	Validation cohort (n = 17)	Control cohort (n = 19)	Discovery vs. validation	Validation vs. control
Semantic fluency (/26)	5 (3–7)	16 (12.5–19)	24 (20–26)	0.015	<0.001	31 (100)	7 (41)	0 (0)	<0.001	0.005
Phonemic fluency (/19)	3 (1–5)	7 (5–8.5)	12 (9–14)	0.002	<0.001	30 (96.8)	14 (82)	4 (21)	0.191	0.004
Category switching (/15)	1 (0–2)	10 (7.5–12)	12 (9–15)	0.011	0.052	31 (100)	8 (47)	5 (26)	<0.001	0.374
Digit span forward (/8)	4 (3–4)	4 (4–5.5)	7 (6–7)	0.047	<0.001	28 (90.3)	13 (77)	4 (21)	0.251	0.005
Digit span backward (/6)	3 (2–3)	3 (2.5–4.5)	4 (3–5)	0.015	0.431	26 (83.9)	9 (53)	7 (37)	0.079	0.503
3D draw/copy (/15)	6 (3–9)	13 (10–15)	15 (12–15)	<0.001	0.118	29 (93.5)	7 (41)	1 (5)	<0.001	0.026
Verbal delayed recall (/15)	7 (4–10)	14 (10.5–15)	14 (13–14)	<0.001	0.811	21 (67.7)	4 (24)	1 (5)	0.015	0.234
Similarities (/8)	2 (2–6)	6 (5–7)	8 (8–8)	0.001	<0.001	27 (87.1)	11 (65)	0 (0)	0.191	<0.001
Go/no-go (/2)	1 (0–2)	2 (0–2)	1 (1–2)	0.543	0.931	16 (51.6)	6 (35)	4 (21)	0.368	0.503
Affect (/6)	4 (3–5)	5 (2.5–5.5)	6 (6–6)	0.574	<0.001	21 (67.7)	8 (47)	0 (0)	0.251	0.004

[a]Comparison between cohorts using Mann–Whitney test, with Benjamini-Hochberg correction for multiple comparisons.
[b]Comparison between cohorts using Fisher's exact test, with Benjamini-Hochberg correction for multiple comparisons.
Abbreviations: CCAS, cerebellar cognitive-affective syndrome; IQR, interquartile range.

participants failed ≥3 of 10 subtests, indicating "definite CCAS" for the entire validation cohort, as for the discovery cohort. Although failure rates across subtests were generally lower than in the discovery cohort, phonemic fluency and digit span forward were still failed by at least 75% of the validation cohort (Table 2).

CCAS total scores in the validation cohort were also lower (81 [67–86] vs. 101 [91–106], $P < 0.001$), and the number of failed subtests was higher than in matched controls (5 [3–7] vs. 1 [1–2]; $P < 0.001$) (Table 1). In a control analysis, 16 of 17 ARSACS participants (94%) also exceeded their individual CCAS cutoffs adjusted for age, sex, and education—as compared to 3 of 19 controls.

CCAS total scores were correlated to disease duration as well as FARS stage and SARA scores as measures of ataxia severity—both in the discovery cohort ($\rho = -0.58$, $\rho = -0.37$, and $\rho = -0.53$; $P < 0.041$) and validation cohort ($\rho = -0.53$, $\rho = -0.62$, and $\rho = -0.51$; $P < 0.037$). Education was correlated with CCAS total scores in the older discovery cohort (Table S4).

Both CCAS total scores and the number of failed subtests were highly correlated with the MoCA score ($\rho = 0.88$ and $\rho = -0.79$; $P < 0.001$). The MoCA indicated severe cognitive impairment in 1 of 15 participants (12 points), mild cognitive impairment in 10 of 15 (19–25 points), and cognitive levels in the low-normal range (26 points) in the remaining participants. Correlations of the MoCA score with disease duration or ataxia severity were not significant (Table S4).

The most frequent neuropsychiatric feature in the CCAS subtest "affect" was difficulty with focusing attention or mental flexibility, both in the discovery cohort (87%) and the validation cohort (59%). Emotional lability and irritability/aggressiveness were also highly prevalent neuropsychiatric features (~40%), followed by lack of empathy, apathy, or blunted affect (25–30%) (Supplement S5, including also discussion of interview results).

Discussion

This study assessed neuropsychological deficits in ARSACS by applying the CCAS scale to geographically, genetically, and clinically distinct cohorts in a bi-center discovery plus validation cohort design. As major finding, we showed that all examined patients failed in multiple subtests of the CCAS scale, therefore, indicating "definite CCAS" as consistent neuropsychological deficit in ARSACS—at least in our cohorts. Given also the increased number of failed subtests and lower CCAS total scores in comparison to matched controls, and robust findings after adjustment for age, education, and sex, the detected neuropsychological deficits in ARSACS were not false positives (eg, because of higher age or lower education). Rather, they likely presented a genuine and—given the younger age of the validation cohort—relatively early feature of ARSACS.

Our results also suggest that CCAS-related neuropsychological deficits are progressive in ARSACS, as the number of failed subtests was higher, and the total score lower in the (older/later-stage) discovery cohort than in the (younger/earlier-stage) validation cohort. This difference in severity was likely driven by more advanced neurodegeneration, as it was paralleled by differences in ataxia severity (FARS stage, SARA), which was correlated with the CCAS total score.

Qualitatively, five subtests were failed by ≥90% of the discovery cohort: semantic fluency, phonemic fluency, category switching, 3D draw/copy, and digit span forward. These deficits relate to language, executive functions, visuospatial abilities, working memory, and attention, and are consistent with cognitive deficits suggestive of CCAS reported for heterogeneous cerebellar patients,[10,12] as well as in small case studies of ARSACS.[5,7,29] Quantitatively, however, CCAS total scores in our ARSACS cohorts were lower, and therefore, neuropsychological deficits more severe than in other cerebellar ataxias.[10,30] Notably, deficits were comparable to spinocerebellar ataxia type 2 and RFC1-disease with milder ataxia severity, but substantial extra-cerebellar involvement.[17,31-33] Furthermore, 68% of patients in the discovery cohort had impaired verbal recall, which presents a non-cerebellar cognitive domain. Together, this suggests that the severe neuropsychological deficits in ARSACS are probably not caused by cerebellar dysfunction only, but rather reflect additional extra-cerebellar involvement. Besides parietal atrophy on structural magnetic resonance imaging (MRI),[2,34] widespread reduction of supratentorial white matter volume and microstructural integrity of large associative fiber bundles (including the corpus callosum) have recently been shown in ARSACS by diffusion MRI.[35] Borderline correlations of the corresponding diffusion metrics with the MoCA further indicate that extra-cerebellar involvement contributes to the neuropsychological deficits in ARSACS[35]—in particular, because the MoCA putatively lacks sensitivity for CCAS caused by relatively "pure" cerebellar damage.[10]

Although our validation cohort covered the genetic diversity of ARSACS worldwide,[2] and therefore, enhanced generalizability, we cannot exclude that neuropsychological differences between cohorts may be partly attributable to different genotypes rather than disease progression alone. Furthermore, we did not explore whether application of the CCAS scale was affected by prior MoCA assessment or by motor impairment (eg, assessment of fluency by dysarthria[36] or drawing by incoordination and/or weakness).

Finally, non-inclusion of pediatric patients and patients with intellectual disability or severe cognitive impairment (lack of informed consent) may have limited insights across the full age spectrum, including the onset of neuropsychological deficits. In pediatric ARSACS, viewed as combined neurodevelopmental and neurodegenerative disorder, intellectual disability may represent one end of a spectrum of developmental cognitive and affective dysfunctions, detectable in approximately 50% of patients.[37] In older ARSACS patients, it remains to be demonstrated to what extent age (or co-pathology) exacerbates cognitive impairment, independent of ARSACS pathology.

In conclusion, our study highlights that neuropsychological deficits consistent with CCAS are a consistent, early, and progressive feature of ARSACS. Future studies combining in-depth neuropsychological assessments with neuroimaging studies are warranted to chart the evolution across the full age spectrum and to relate neuropsychological deficits to cerebellar versus extracerebellar involvement in ARSACS.[35]

Author Roles: Research Project: (1) A. Conception and Design, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.
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A.T.:2C, 3B.
D.T.: 2C, 3B.
R.L.P.: 1C.
B.B.: 1A, 3B.
J.D.: 1A.
I.C.: 2A, 2B, 2C, 3A, 3B.
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A.T.: 1A, 1B,1C, 2A, 2B, 2C, 3A, 3B.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request following the proper evaluation of the research protocol by the ethics review boards of the Centre Intégré Universitaire de Santé et de Services Sociaux du Saguenay-Lac-St-Jean (Saguenay, Québec, Canada) and University of Tübingen (Germany). The data are not publicly available because of privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.