ARTICLE

Development and validation of a disease severity index for ataxia of Charlevoix-Saguenay

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Neurology® 2019;93:e1543-e1549. doi:10.1212/WNL.0000000000008313

Abstract

Objective

To develop a disease-specific severity index for adults with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) (DSI-ARSACS) that considers the 3 components (pyramidal, cerebellar, neuropathic) of the disease, and to document its content validity, internal consistency, and construct validity.

Methods

The Beta DSI-ARSACS (17 items) was developed based on literature review and expert inputs and then administered to 26 participants. Items reduction was based on Cronbach α and desirable criteria. Performance measures were administered to assess the construct validity of the final version of the DSI-ARSACS.

Results

The final DSI-ARSACS have 8 items that can be easily performed during usual medical follow-up. The mean score was 19.6 ± 8.1 (range 6.0–35.5) and the Cronbach α was 0.912. The DSI-ARSACS score increased with disease stage and age ($p \leq 0.001$) and was closely correlated with other measures assessing similar construct (9-Hole Peg Test, 10-Meter Walk Test, Scale for the Assessment and Rating of Ataxia, Berg Balance Scale, Barthel Index) ($r_s = 0.75–0.95$, $p < 0.01$). A moderate but not significant correlation was found with the 6-Minute Walk test ($r_s = -0.611$, $p = 0.108$).

Conclusions

The DSI-ARSACS is a valid measure of disease severity for the adult ARSACS population that is able to distinguish between patients with different clinical profiles. Further documentation of metrologic properties is necessary, but these first results are promising.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

6MWT = 6-Minute Walk Test; **9HPT** = 9-Hole Peg Test; **10MWT** = 10-Meter Walk Test; **ARSACS** = autosomal recessive spastic ataxia of Charlevoix-Saguenay; **BBS** = Berg Balance Scale; **CIUSSS-SLJS** = Centre Intégré Universitaire de Santé et de Services Sociaux du Saguenay Lac-St-Jean; **DSI-ARSACS** = disease-specific severity index for autosomal recessive spastic ataxia of Charlevoix-Saguenay; **SARA** = Scale for the Assessment and Rating of Ataxia; **SF-12** = 12-Item Short-Form Health Survey.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), first described in 1978,[1] is the most common inherited recessive ataxias in the province of Quebec (Canada)[2,3] and the most frequent recessive ataxia worldwide after Friedreich ataxia.[4,5] It is an early-onset ataxia characterized by symptoms from 3 components: pyramidal (e.g., spasticity), cerebellar (e.g., ataxia), and neuropathic (e.g., distal amyotrophy), each of them being expressed at different levels from one individual to another. Consequently, a high variability is shown among patients with ARSACS, regardless of their age.[6] Patients become regular wheelchair users around 40 year old (ranging from 17 to 58 years).[6,7] To date, no curative treatment is available for ARSACS. With the advancement of knowledge on molecular pathogenesis, therapeutic trials could be available soon. A validated neurologic assessment tool is necessary to assess ARSACS-specific symptoms and their severity. There are a number of generic ataxia rating scales, like the International Cooperative Ataxia Rating Scale[8] and the Scale for the Assessment and Rating of Ataxia (SARA),[9] but none includes the 3 components of ARSACS, and they are thus not completely suitable for this population. A disease-specific scale might better document the overall disease severity and the natural history of the disease and help patient recruitment based on level of impairment in each component.

The objectives of this study were to (1) develop a disease-specific severity index for ARSACS (DSI-ARSACS) and (2) document its internal consistency and construct validity among an adult population.

Methods

Participants

Participants were recruited in 2015 using a stratified random sampling strategy according to age (18–59 years) and sex among a subset of 175 people with ARSACS listed at the Neuromuscular Clinic of the Centre Intégré Universitaire de Santé et de Services Sociaux du Saguenay Lac-St-Jean (CIUSSS-SLJS) (Quebec, Canada). Inclusion criteria were (1) 18 years or older, (2) diagnosis of ARSACS confirmed by DNA analysis, and (3) able to provide informed consent. Patients with other diseases causing functional limitations, having a Baclofen intrathecal pump, or being pregnant were excluded.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Review Board of the CIUSS-SLSJ, and written informed consent was obtained from each participant.

Data collection and instruments

This study was part of a larger data collection where participants were seen over 3 half-day sessions, 2 weeks apart. Beta version of the DSI-ARSACS was administered at the second visit only. The preliminary version contains 17 items addressing the pyramidal, cerebellar, and neuropathic features of the disease and the total score ranges from 0 to 74, a higher score indicating a higher level of severity. A questionnaire was also completed by all participants to obtain data about their age, sex, mobility level, and walking aids. Data about disease duration were not collected since this approximately corresponds to age, the diagnosis usually being made at gait initiation in our cohort. To validate the final version of the DSI-ARSACS, several tests were performed during the 3 visits at the clinic.

Upper extremity functions

Fine dexterity was assessed with the 9-Hole Peg Test (9HPT),[10] which presents excellent intrarater and interrater reliability.[11]

Mobility

Balance was assessed with the Berg Balance Scale (BBS)[12] (validated in ARSACS[13]); walking speed was assessed with the 10-Meter Walk Test (10MWT)[14] at comfortable speed and maximum speed; walking endurance was assessed using the 6-Minute Walk Test (6MWT).[15,16] The 10MWT and 6MWT both have excellent interrater reliability in ARSACS.[13]

Disease severity scale

The SARA was used.[9] Even if 2 items of the final disease-specific severity index are similar to those of the SARA, it was decided to administer the SARA as it is a recognized scale to assess severity of cerebellar ataxia in other ataxias. In addition, the 2 items are not assessed and scored in the same way.

Participation was assessed using the Barthel Index[17] and quality of life using the 12-Item Short-Form Health Survey (SF-12), v2.[18]

Development of the scale

The Beta DSI-ARSACS was developed according to the method proposed by Streiner and Norman.[19] The planning phase includes defining the population, instrument objectives, and desirable criteria, as well as a literature review of the concept under study. The development team included 5 ARSACS experts: 2 neurologists, an occupational therapist, and 2 physical therapists. The construction phase includes the selection of the sources of items and their selection. The

sources of items were based on items present in available scales based on a systematic review of the literature with the following key words: (rating scale) combined with (ataxia or spastic* or pyramidal or neuropathic) (not pharmacologic treatment), using language (English, French), species (human research), and date restrictions (until April 2012). The following databases were consulted: PUBMED, CINAHL, AMED, ACCESS MEDICINE, SCOPUS, and ACADEMIC SEARCH COMPLETE. An extraction table was constructed including each component (e.g., ataxia) and potential items from existing scales (e.g., finger-to-nose test from the SARA). The selection of items for the Beta version was based on a consultation of experts using the Delphi method (2 rounds) and pretest among 60 patients during their medical follow-up. During the process, the following desirable criteria oriented the development of the scale: (1) it should rate motor functional impairments and their progression, and should therefore not include neurologic signs without functional implications; (2) it should focus on the main ARSACS signs; less common features should be recorded in an inventory of signs and symptoms; (3) no technical equipment should be necessary to administer the scale, and items should be based on standard neurologic examination and allow the standardization of testing and rating procedures; and (4) the administration time should be short enough to be done during clinical follow-up. Impairments that are stable (e.g., nystagmus) were not retained in the Beta version of the disease-specific severity index since they would not be able to capture the progression of disease severity over time.

Validation

The construct validity of the final DSI-ARSACS was assessed using hypothesis testing according to COSMIN methodology,[20] and hypotheses were formulated a priori by the research team.

Convergent validity

The total score of the DSI-ARSACS should be higher when age and the SARA and 9HPT total score increase. The DSI-ARSACS score should be lower when the BBS, Barthel Index, 10MWT, 6MWT, and the physical component of the SF-12 scores increase.

Discriminant validity (known-group validity)

(1) The DSI-ARSACS score will be different between participants in each age group (≤29; 30–39; ≥40 years); the score should be higher among older participants. (2) The DSI-ARSACS score will be different between participants at a different mobility disease stage (first walking difficulty, use of a walking aid, wheelchair); the score should be higher among participants with more severe stage of the disease. (3) The DSI-ARSACS should not be able to distinguish between men and women. In addition, floor and ceiling effects were documented. The proportion of participants getting the maximum (ceiling effect) and the minimum (floor effect) possible scores must be less than 15%[21] and skewness statistics should range from −1 to +1.[22]

Statistical analysis

Participants' characteristics are presented as the mean and SD for continuous variables and frequency and percentage for categorical variables. The normality of the distribution was determined using the Kolmogorov-Smirnov statistic (a non-significant result [$p > 0.05$] indicates a normal distribution). The skewness and kurtosis values were determined to obtain information concerning the scores' distribution. The skewness value provides information about the symmetry of the distribution; a value close to 0 indicates normal distribution, a positive value suggests that more individuals obtained low score (clustered to the left of the graph), conversely for a negative value.[23] Kurtosis value indicates how much the distribution is "peaked"; a negative value indicates that the distribution is relatively flat (many individuals in the extremes) while a positive value suggests that the distribution is peaked (clustered in the center).[23] The internal consistency was also determined using the Cronbach α coefficient, which determines if items of a scale measure the same construct of if they are redundant. An α coefficient around 0.90 indicates that the scale is reliable.[24] To assess the construct validity (convergent and discriminant), the DSI-ARSACS total score was correlated with disease duration and the scores of the 9HPT, grip and pinch strength, BBS, 10MWT, 6MWT, SARA, and Barthel Index using the Spearman ρ coefficient. The known-group validity was assessed using the Mann-Whitney *U* Test for sex, age, and disease stage groups. For disease stages and age groups, post hoc analyses were made to find out which groups were statistically different from one another by doing repeated Mann-Whitney *U* tests. To control for type 1 error, Bonferroni adjustment was applied to the α value; significance was determined with a revised α level of 0.017. Nonparametric analyses were conducted due to the sample size (lower than 30). Data were analyzed using IBM SPSS Statistics for Windows, version 24.0 (IBM, Armonk, NY).

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

A total of 26 participants completed the DSI-ARSACS and the other outcome measures and were thus included in this study. Characteristics of the participants are presented in table 1. The mean age was 40 years and 53.8% were men. Ten participants were able to perform the 10MWT and 8 were able to perform the 6MWT. Twenty-four participants (92.3%) are homozygous for the 8844delT mutation, and 2 are compound heterozygotes for the 7504C>T or the 814C>T and the common 8844 delT mutations.

Disease-specific severity index reduction

The Beta version of the disease-specific severity index included 17 items for a maximum score of 74 (indicating maximal severity). Cronbach α was initially 0.933. By

Table 1 Characteristics of the sample (n = 26)

Characteristic	Total group
Disease duration based on age, y	
Mean (SD)	40.0 (10.8)
Minimum–maximum	16–61
Sex, n (%)	
Men	14 (53.8)
Women	12 (46.2)
Disease stage, n (%)	
No walking difficulty	0 (0.0)
First walking difficulty	7 (26.9)
Walk with aid or support	5 (19.2)
Wheelchair	14 (53.8)
Age at disease stage, y, mean (SD) (min–max)	
First walking difficulty	28.1 (6.1) (16–35)
Walk with aid or support	42.4 (7.9) (34–52)
Wheelchair	45.1 (9.0) (34–61)
Age at confinement to wheelchair, y (n = 10)	
Mean (SD)	32.5 (8.5)
Minimum–maximum	19–48

Table 2 Final item selection[a]

Section	Item	Main component
Upper limb	Speech during normal conversation	Cerebellar
	Archimedes spiral	Cerebellar and neuropathic
	Standardized finger-to-nose test	Cerebellar
Lower limb	Circle with foot	Cerebellar and pyramidal
	Muscle tone: hip adductors	Pyramidal
	Bladder function	Pyramidal
	Lateral malleolus vibration	Neuropathic
Mobility	Mobility level	Cerebellar and pyramidal and neuropathic

[a] The complete scale with the user guide including complete administration instructions for all items has been deposited in the SAVOIRS UdeS repository (savoirs.usherbrooke.ca/handle/11143/15277). Permission is required to use the disease-specific severity index.

removing 4 items (foot deformities, tear a sheet, Achilles tendon retraction, and knee flexors muscle tone), Cronbach α reached 0.945. Five other items have been removed: fast alternating hand movements, standing position, sitting balance eyes open and closed, and LEMOCOT (lower limb coordination). Reasons to remove these items were high correlation with other items, poor reliability, material needed to perform the test, and lack of clinical relevance. The final Cronbach α of the 8-item DSI-ARSACS is 0.912 (table 2).

Validity of the DSI-ARSACS

The final DSI-ARSACS total score can range from 0 to 38. None of the 26 patients obtained the minimum or the maximum score, and the mean score is 19.6 ± 8.1 (ranging from 6.0 to 35.5). Scores were normally distributed (Kolmogorov-Smirnov p = 0.200), the skewness statistic is −0.219, and kurtosis is −0.755 (figure 1).

Construct validity

As expected, the total score increases with age and disease stages ($p \leq 0.001$). Post hoc analysis demonstrated a difference between the <29 years and >40 years groups ($p = 0.001$), and between the 30–39 years and the >40 years groups ($p = 0.002$), but no difference was seen between the 2 younger groups (figure 2). For disease stages (figure 2), there is a difference between the less severe disease stage (first walking difficulty) and the 2 others ($p < 0.003$).

The construct validity was also determined by correlating the DSI-ARSACS total score with 7 other outcome measures (table 3). Results showed that all a priori hypotheses are confirmed, except for the 6MWT. The correlation of −0.611 found between the 6MWT and the DSI-ARSACS was not significant.

Discussion

ARSACS results in manifestations than can be classified into 3 main components according to the neurologic system impaired: pyramidal, cerebellar, and neuropathic. It is not

Figure 1 Distribution of the disease-specific severity index for autosomal recessive spastic ataxia of Charlevoix-Saguenay total score

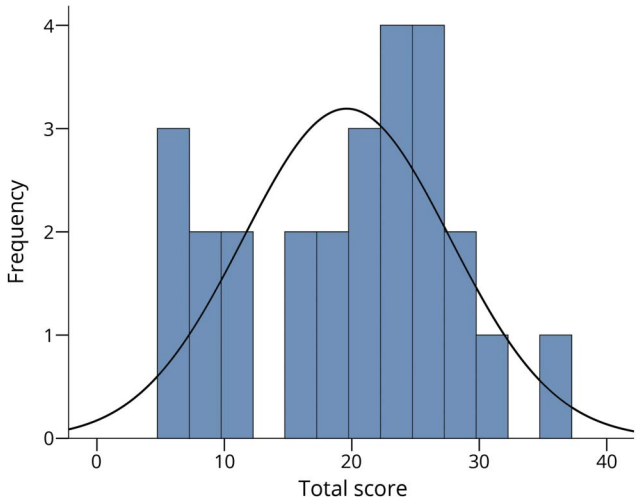
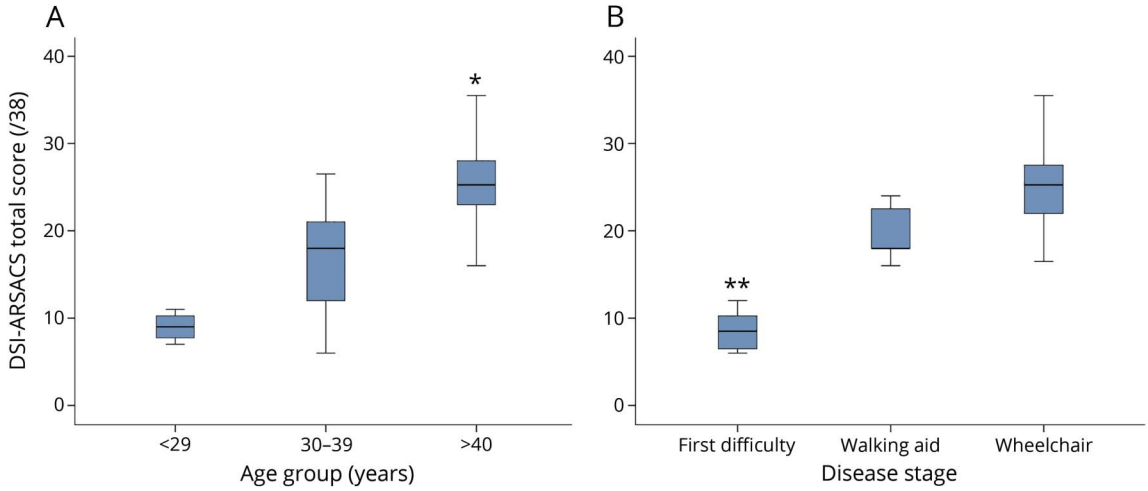


Figure 2 Disease-specific severity index for autosomal recessive spastic ataxia of Charlevoix-Saguenay (DSI-ARSACS) total score distribution



DSI-ARSACS total score distribution according to (A) age groups and (B) disease stages. * Post hoc analyses showed a significant difference between the >40 years group and the 2 others ($p \leq 0.002$) and ** between the first difficulty group and the 2 others ($p < 0.003$).

possible to capture these 3 components by using existing scales. The DSI-ARSACS was specifically developed to address the condition of patients with ARSACS. The final version of the scale has been deposited in the SAVOIRS UdeS repository with the complete administration guide that includes detailed instructions for all items. Note that permission from the first author (C.G.) is required for any use of the scale.

The final index includes 8 items reflecting the 3 main components of the disease and matches the desirable criteria. Impairments of cerebellar origin are predominant in ARSACS and affect several functions, which explain the number of items in the disease-specific severity index for this component.

Despite the small number of participants included in this study, scores are normally distributed; skewness and kurtosis values indicate that although many participants obtained a score in the extremes (negative kurtosis value, flattened distribution), scores are not clustered in one side of the distribution. Selected participants were therefore representative of a wide range of disease severity level, which increases our confidence in the results. Results confirm the construct validity of the DSI-ARSACS according to its capacity to distinguish between patients based on the disease stage or disease duration, and the significant correlations with outcome measures reflecting the main activity limitations. A strong correlation was found with the 6MWT but did not reach statistical significance. This can probably be explained by the

Table 3 Participant scores for all outcome measures and correlations with the disease-specific severity index for autosomal recessive spastic ataxia of Charlevoix-Saguenay total score

Outcome measures	Mean (SD), min–max	Correlation, ρ	*p* Value
SARA	23.4 (8.8), 7–35	0.955	<0.001
BBS	19.0 (20.9), 0–55	−0.933	<0.001
Barthel	80.0 (18.6), 35–100	−0.903	<0.001
9HPT, s	56.0 (27.5), 22.6–133.2	0.865	<0.001
10MWT maximum speed, m/s (n = 10)	1.16 (0.430), 0.270–1.54	−0.827	0.003
10MWT comfortable speed, m/s (n = 10)	0.961 (0.391), 0.260–1.34	−0.754	0.012
6MWT, m (n = 8)	357.6 (105.6), 188.5–480.0	−0.611	0.108
SF-12 physical component	44.4 (7.3), 29.2–58.4	−0.410	0.038
SF-12 mental component	55.4 (6.6), 43.5–73.5	0.237	0.244

Abbreviations: 6MWT = 6-Minute Walk Test; 9HPT = 9-Hole Peg Test; 10MWT = 10-Meter Walk Test; BBS = Berg Balance Scale; SARA = Scale for the Assessment and Rating of Ataxia; SF-12 = 12-Item Short-Form Health Survey.

small number of participants (n = 8) who were able to perform the test. Also, as no item addresses the psychological aspects of the disease, the lack of correlation between the mental component of the SF-12 and the DSI-ARSACS score was expected.

The final item selection has been made based on criteria stated above but it is important to note that even if some of them have been removed, they can be interesting for the follow-up of patients with ARSACS. Among them is the LEMOCOT,[25] which is a measure of lower limb coordination. In addition to being easy and requiring simple material, its validity and reliability has been demonstrated in the ARSACS population.[26]

The number of participants is small for a validation study. The next step will thus be to conduct a multicenter study to increase the sample size to further document the validity of the DSI-ARSACS. Since we have designed this tool keeping future clinical trials in mind, it could be used in 2 ways: first for initial patient classification to help case selection and second to measure the efficacy of the treatment. For this, the reliability and responsiveness of the DSI-ARSACS will have to be assessed, to determine its capacity to detect changes over time, and to chart the progression of the disease.

However, results obtained in this study showed strong preliminary validity, and demonstrated the potential of using this new disease-specific scale for the classification and the selection of patients in the context of clinical trials.

Study funding

Study funded by the Canadian Institutes of Health Research (Emerging Team Grant TR2-119189), in partnership with Fondation de l'Ataxie Charlevoix-Saguenay and Muscular Dystrophy Canada. C.G. holds a career-grant funding from Fonds de Recherche du Québec-Santé (31011).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* November 23, 2018. Accepted in final form May 15, 2019.

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