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SHORT COMMUNICATION

Scale for the assessment and rating of ataxia: Age-dependent performance of healthy adults

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Abstract

Background and purpose: The Scale for Assessment and Rating of Ataxia (SARA) is a widely used clinical scale. The objective was to study the age dependence of SARA in healthy adults and to define age-specific cut-off values to differentiate healthy from ataxic individuals.

Methods: Data from 390 healthy individuals and 119 spinocerebellar ataxia patients were analyzed. SARA scores were mapped on functional SARA (fSARA). Age-adjusted cut-off values were determined by receiver operating characteristic curve analysis.

Results: The cut-off value was 3 for SARA and 1.5 for fSARA. Older patients had higher SARA cut-off values (4.5 for 60–69 years and 6.5 for 70–79 years). Age-adjusted cut-off values for fSARA are 1 for 18–29, 30–39 and 50–59 years, 2 for 40–49 and 60–69 years and 3 for 70–79 years. Sensitivity and specificity were higher for SARA than for fSARA.

Conclusion: In this study, age-dependent cut-off values were defined for SARA and fSARA. The results may be relevant for the design of future preventive trials in spinocerebellar ataxias that use conversion to ataxia as an outcome.

KEYWORDS
ataxia, cut-off, fSARA, SARA

INTRODUCTION

Clinical scales are considered essential prerequisites for observational studies and interventional trials but are also important for monitoring clinical course and therapy effects of patients in clinical routine and during rehabilitation. The currently most widely used ataxia scale is the Scale for Assessment and Rating of Ataxia (SARA) [1] SARA consists of the following items: 1, gait; 2, stance; 3, sitting; 4, speech disturbance; 5, finger chase; 6, nose–finger test; 7, fast alternating hand movements; and 8, heel–shin slide. SARA item 1 has nine, items 2 and 4 seven, and item 3 five response categories. The SARA sum score ranges from 0 to 40, with 0 indicating absence of ataxia and 40 being the most severe degree of ataxia.

Following requests of the US Food and Drug Administration, an ongoing drug trial with spinocerebellar ataxia (SCA) patients registered with ClinicalTrials.gov as NCT03701399 used the functional SARA (fSARA), a shortened and modified version of the SARA. The fSARA consists of only SARA items 1–4, each with five response categories yielding a maximum score of 16 points. Although fSARA was designed for prospective assessment, fSARA scores can be retrospectively reconstructed from SARA scores. To date, there are no published validation studies of fSARA.

The initial SARA validation study included a control group of 110 healthy individuals with a mean age of 47.1 ± 15.0 years and a SARA score of 0.4 ± 1.1. One participant had a score of 7.5, and 21% had a sum score greater than 0. Currently, there is an increasing number of observational studies of pre-ataxic SCA mutation carriers. In these studies, a SARA cut-off value of 3 is often used to distinguish pre-ataxic from ataxic individuals. This cut-off was defined as the lowest possible score greater than the mean + 2SD of the control group of the SARA validation study which amounts to 2.6. In future, preventive trials in pre-ataxic mutation carriers will be a realistic option. In such trials, the number of patients converting to manifest disease could serve as a primary outcome [2]. As an objective indicator of conversion, the availability of a valid and reliable SARA cut-off is essential.

In this study, SARA data of 390 healthy adults and 110 SCA patients were analyzed. Specifically, the intention was to study the age dependence of SARA performance in healthy adults and to define age-specific cut-off values. Given the potential usefulness of fSARA for interventional trials, our study was extended to fSARA.

PATIENTS AND METHODS

Study population

The study analyzed data from 390 healthy individuals and 119 patients with SCAs (Table 1).

The group of healthy individuals included 110 controls from the SARA validation study [1] 149 non-mutation carriers from the RISCA study [3]. 10 non-mutation carriers from the ESMI study [4]. 55 individuals from control cohorts of the DZNE and 66 healthy individuals who were enrolled for the present study. Inclusion criteria for inclusion in the healthy individuals group were (i) age ≥ 18 years and (ii) absence of any disease interfering with performing SARA according to clinical judgement.

Data of the 119 SCA patients were taken from the SARA validation study [1]. Inclusion criteria were (i) age ≥ 18 years, (ii) progressive ataxia and (iii) positive genetic testing for any SCA mutation or linkage to any SCA locus or clinical evidence of autosomal dominant inheritance. All study participants underwent a SARA assessment performed by an experienced clinical examiner.

The study was approved by the responsible ethics committees, and all patients signed informed consent prior to participation.

Mapping of SARA on fSARA

Functional SARA is a shortened and modified version of SARA that consists only of items 1–4, each with five response categories. Collapsing SARA response categories into a single fSARA category allowed an unequivocal transformation of SARA to fSARA scores. Details of the mapping are given in Table S1.

TABLE 1 Characteristics of patients and healthy individuals

	Patients[a]	Healthy individuals[b]						
Age (years)	**Total 22–81**	**18–29**	**30–39**	**40–49**	**50–59**	**60–69**	**70–79**	**Total 18–79**
n	119	84	66	62	53	69	56	390
Mean age, SD (years)	50.3, 13.2	24.1, 3.5	34.5, 2.7	43.8, 2.8	54.2, 2.9	64.7, 3.0	74.3, 2.9	47.5, 17.9
F/M (*n*)	61/58	50/34	47/19	35/27	34/19	35/34	29/27	230/160
SARA								
Mean	15.9	0.2	0.3	0.4	0.3	0.8	1.8	0.6
SD	8.5	0.5	0.7	0.6	0.6	1.1	2.0	1.1
Range	1.5–40	0–2	0–2.5	0–2.5	0–2.5	0–4.5	0–7.5	0–7
Median	13.5	0	0	0	0	0.5	1	0
IQR	12.5	0	0	0.9	0.5	1	3	1
fSARA								
Mean	5.6	0	0	0.1	0.1	0.3	0.6	0.2
SD	3.9	0.1	0.2	0.2	0.4	0.5	0.8	0.5
Range	0–16	0–1	0–1	0–1	0–2	0–2	0–2	0–2
Median	4	0	0	0	0	0	0	0
IQR	5	0	0	0	0	0	1	0

Abbreviations: F, female; fSARA, functional SARA; IQR, interquartile range; M, male; *n*, number; SARA, Scale for Assessment and Rating of Ataxia.

[a]From the SARA validation study. Diagnoses: SCA1, *n* = 15; SCA2, *n* = 28; SCA3, *n* = 26; SCA6, *n* = 19; SCA7, *n* = 8; SCA14, *n* = 1; SCA17, *n* = 3; SCA23, *n* = 1; unknown mutation, *n* = 18.

[b]110 healthy controls from the SARA validation study, controls from observational studies with the same assessments (RISCA, *n* = 149; ESMI, *n* = 10; control cohorts of the DZNE, *n* = 55) and an additional 66 healthy individuals recruited for this study.

Statistical analysis

Healthy individuals were divided into six age groups: 18–29, 30–39, 40–49, 50–59, 60–69 and 70–79 years. To compare the age groups, the Kruskal–Wallis test followed by Dunn's test with Bonferroni correction for multiple testing was used. *p* values smaller than 0.05 were considered significant. Receiver operating characteristic (ROC) curve analysis with maximization of the Youden index (*J*) in 1000 boot runs was performed to determine the optimal, age-adjusted SARA and fSARA cut-off values to differentiate between healthy individuals and SCA patients. Values greater than or equal to the cut-off value define the clinical diagnosis of ataxia. Results are presented as Youden index, sensitivity (SE), specificity (SP) and area under the curve (AUC). All analyses were performed using R Software for Statistical Computing, version 4.1.2.

RESULTS

Healthy individuals had a SARA score of 0.6 ± 1.1 (mean ± SD) and an fSARA score of 0.2 ± 0.5 (Table 1). Both scores differed between age groups (SARA, df = 5, $\chi^2 = 71$, $p < 0.0001$; fSARA, df = 5, $\chi^2 = 78$, $p < 0.0001$; Kruskal–Wallis test).

Pairwise comparisons (Dunn's test) showed higher SARA scores of the 60–69 years group compared to those of the 18–29 years ($p < 0.0001$), the 30–39 years ($p = 0.014$) and the 50–59 years group ($p = 0.022$). The SARA scores of the 70–79 years group were higher than those of the 18–29 years ($p < 0.0001$), the 30–39 years ($p < 0.0001$), the 40–49 years ($p < 0.0001$) and the 50–59 years group ($p < 0.0001$).

The fSARA scores of the 60–69 years group were higher than those of the 18–29 years ($p < 0.001$), the 30–39 years ($p = 0.009$) and the 40–49 years group ($p = 0.031$). The fSARA scores of the 70–79 years group were higher than those of all other age groups (18–29 years, 30–39 years, 40–49 years, 50–59 years, $p < 0.0001$; 60–69 years, $p = 0.004$).

An ROC analysis of the SCA patients ($n = 119$) and healthy individuals of the SARA validation study ($n = 110$) yielded a SARA cut-off value of 3 ($J = 0.96$, SE = 0.99, SP = 0.96, AUC = 0.99). Using the entire dataset of 390 healthy individuals, the same SARA cut-off value of 3 was determined for the 18–29, 30–39, 40–49 and 50–59 years groups ($J = 0.99$, SE = 0.99, SP = 1, AUC = 0.99). The cut-off value for the 60–69 years group was 4.5 ($J = 0.95$, SE = 0.97, SP = 0.99, AUC = 0.99) and that of the 70–79 years group 6.5 ($J = 0.88$, SE = 0.93, SP = 0.96, AUC = 0.98) (Figure 1 and Table S2).

The fSARA cut-off value from ROC analysis of SCA patients ($n = 119$) and healthy individuals of the SARA validation study ($n = 110$) was 1.5 ($J = 0.91$, SE = 0.95, SP = 0.96, AUC = 0.99). The age-specific values from the entire dataset of healthy individuals ($n = 390$) were 1 for the 18–29 years group ($J = 0.98$, SE = 0.99, SP = 0.99, AUC = 0.99), 1 for the 30–39 years group ($J = 0.96$, SE = 0.99, SP = 0.97, AUC = 0.99), 2 for the 40–49 years group ($J = 0.95$, SE = 0.95, SP = 1, AUC = 0.99), 1 for the 50–59 years group ($J = 0.91$, SE = 0.99, SP = 0.92, AUC = 0.99), 2 for the 60–69 years group ($J = 0.90$, SE = 0.95, SP = 0.96, AUC = 0.99) and 3 for the 70–79 years group ($J = 0.79$, SE = 0.79, SP = 1, AUC = 0.97) (Figure 1 and Table S2).

Item-specific SARA cut-off values determined in the entire dataset without consideration of age were 2 for item 1, 1 for items 2–4 and 1 for SARA items 5–8. The respective fSARA values were 1 for items 1–4.

DISCUSSION

In this study, SARA data of a large group of healthy adult individuals were analyzed. SARA performance significantly worsened in individuals beyond the age of 60 years. This was also reflected in a SARA cut-off value higher than the currently used value of 3 for individuals older than 60 years. For individuals younger than 60 years, the cut-off value of 3 was confirmed. The analysis of the fSARA data of healthy individuals yielded corresponding results, but sensitivity and specificity of fSARA to distinguish non-ataxic from ataxic individuals—although excellent—were lower than those of SARA. Unlike SARA, age-dependent fSARA cut-off values are not uniform across all age groups younger than 60 years with a higher cut-off for patients between 40 and 49 years. This anomaly may be caused by lower discriminatory power of fSARA due to reduction to 0–4 points in gait and stance assessment.

A limitation of our study is the lack of participants older than 80 years. This limits the use of SARA in individuals of this age, for

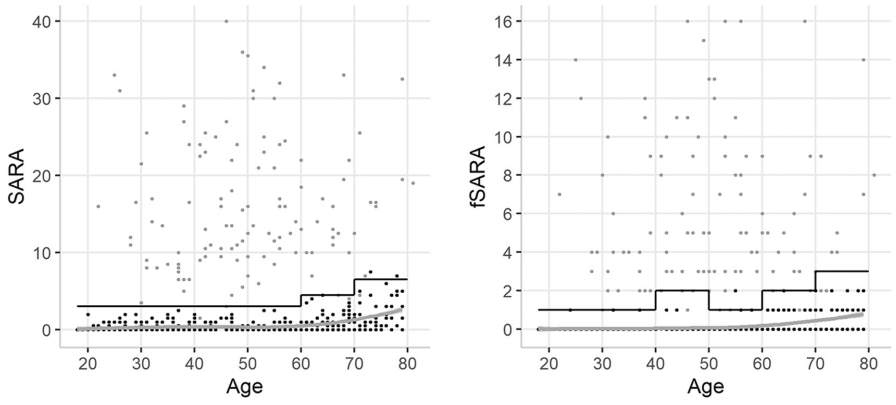

FIGURE 1 Scatter plot of SARA (left) and fSARA (right) by age from healthy individuals (black dots) and patients (grey dots). The black line shows the cut-off values from ROC analyses (receiver operating characteristic). The grey line shows locally weighted scatterplot smoothing (LOESS, local polynomial regression fitting) and 95% confidence band for healthy controls.

example in rehabilitation and follow-up of old patients with ataxia due to cerebellar stroke. This shortcoming is less relevant for the design of future preventive trials in genetic ataxias because such trials will be performed in younger individuals. There are no published validation studies for fSARA, and the score neglects impaired coordination of extremities, which is an important limitation to the score. Nevertheless, fSARA is currently being applied in an increasing number of clinical trials. Another limitation of this study is the retrospective reconstruction of fSARA data. As a mapping of SARA on fSARA is almost unequivocally possible, our analysis nevertheless gives useful information on the properties of fSARA.

Our study confirms previous findings that balance and coordination deteriorate with age [5–7]. The novel finding is that this decline can be captured with a relatively simple clinical scale, such as SARA. Inspection of the data and the statistical analysis revealed that this decline does not take a linear course, but that there is a threshold age of 60 years after which balance and coordination get worse.

The main benefit of our study is the definition of age-dependent cut-off values that clearly distinguish between healthy individuals and ataxic patients. Given the increasing number of studies that are focusing on the pre-ataxia or early ataxia stages, precise knowledge of the features defining the transition between these stages is mandatory. For the interpretation of the results of such studies, it will be necessary to carefully compare the subjective report on the time of ataxia onset by patients and the clinically observed onset defined by a SARA score beyond the cut-off value.

AUTHOR CONTRIBUTIONS

Conceptualization: Marcus Grobe-Einsler, Ina R. Vogt, Thomas Klockgether. Methodology: Marcus Grobe-Einsler, Alina Schmnidt, Ina R. Vogt, Tamara Schaprian. Formal analysis and investigation: Marcus Grobe-Einsler, Alina Schmidt, Ina R. Vogt, Tamara Schaprian. Writing—original draft preparation: Marcus Grobe-Einsler. Writing—review and editing: Thomas Klockgether, Tamara Schaprian, Ina R. Vogt, Alina Schmidt. Supervision: Thomas Klockgether, Marcus Grobe-Einsler, Ina R. Vogt.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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