The Cerebellum
https://doi.org/10.1007/s12311-022-01399-z

LETTER TO THE EDITOR

Remote Measurement of Functional Status in Pre-symptomatic and Symptomatic Individuals with Machado-Joseph Disease

Elaine Cristina Miglorini[1,2] · Victor Henrique Ignácio de Souza[2,3] · Camila Maria de Oliveira[1,2] · Gabriela Bolzan[2,4] · Maria Luiza Saraiva-Pereira[2,4,5,6] · Vanessa Bielefeldt Leotti[7,8] · Laura Bannach Jardim[1,2,3,4,6,9]

Accepted: 24 March 2022

The COVID-19 pandemic disrupted countless human activities since 2020. In most places, face-to-face visits for research projects were interrupted for months; some studies were adapted to use remote methods. One challenge was to find an instrument prone to remote application that could detect a reduction in functional status among carriers of spinocerebellar ataxias. The most used criterion is the cutoff of 3 points in the Scale for Assessment and Rating of Ataxia (SARA) [1]. The remote SARAhome version was recently proposed [2], but the technology needed was not available in research centers like ours yet.

As an alternative, we studied the Friedreich Ataxia Rating Scale/activities of daily living (FARS-ADL) [3], a patient-reported outcome designed to evaluate limitations in functional status of ataxic subjects.

We aimed to test if FARS-ADL could distinguish subjects with SARA score > = 3 (ataxics) among persons belonging to families with spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD). Confirmed carriers and their relatives at 50% risk were evaluated during July and August 2021. FARS-ADL was administered as a structured interview by telephone; SARA and DNA samples were collected simultaneously in our institution within 15 days after FARS-ADL. Participants at 50% risk and examiners were kept blinded to their genetic results.

Nineteen ataxic (with SARA > = 3) and 13 pre-ataxic (with SARA < 3) SCA3/MJD carriers, and 13 related controls were included, with median (IQR) ages of 44.01 (19.00), 29.00 (8.00), and 40.00 (13.75) years. Ataxic and pre-ataxic subjects carried 75 (4) and 75 (4) CAG repeats in their expanded alleles; age at onset of gait ataxia was 43 (19) in ataxics. Two alternatives were used to define FARS-ADL cutoffs between ataxic and pre-ataxic. According to a maximum-accuracy cut-point, FARS-ADL values less than 4 detected persons with SARA < 3, while values greater than 8 detected persons with SARA > = 3 (Fig. 1A). According to the ROC curve and Youden's index, a FARS-ADL score larger than 4 points detected presence of SARA > = 3 (Fig. 1B), with 7.7% and 5.6% of false-positives and false-negatives, and with sensitivity and specificity of 0.94 and 0.92.

Former reports on simultaneous FARS-ADL and SARA data were obtained in Friedreich's Ataxia (FRDA) subjects with SARA larger than 3 [4, 5], where 57 out of 594 subjects

✉ Laura Bannach Jardim
ljardim@hcpa.edu.br

1 Programa de Pós-Graduação em Ciências Médicas, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2400, Porto Alegre 90035-003, Brazil

2 Centros de Pesquisa Clínica e Experimental, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, Porto Alegre 90035-003, Brazil

3 Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2400, Porto Alegre 90035-003, Brazil

4 Programa de Pós-Graduação em Genética e Biologia Molecular, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves, 9500, Building 43312, Porto Alegre 91501-970, Brazil

5 Departamento de Bioquímica, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2600-Prédio Anexo, 90.035-003, Porto Alegre, Brazil

6 Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, Porto Alegre 90035-003, Brazil

7 Departamento de Estatística, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves, 9500, Building 43-111, Porto Alegre 91501-900, Brazil

8 Grupo de Pesquisa e Pós-Graduação, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, Porto Alegre 90035-003, Brazil

9 Departamento de Medicina Interna, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2350, Porto Alegre 90035-003, Brazil

Published online: 29 March 2022

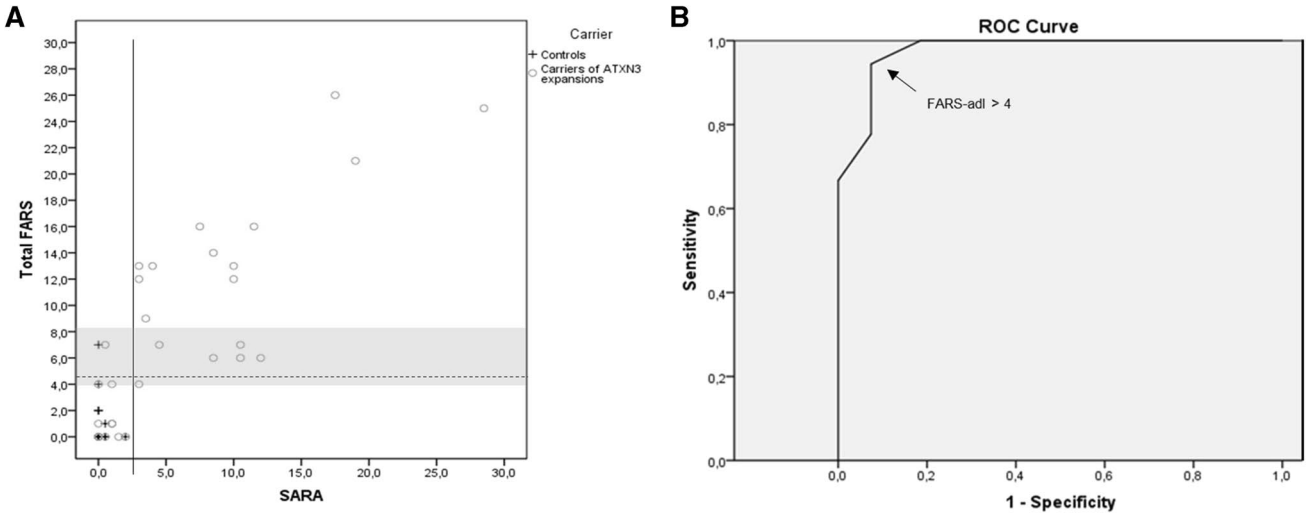

Fig. 1 **A** Correlation between the Scale for Assessment and Rating of Ataxia (SARA) and Friedreich Ataxia Rating Scale-activities of daily living (FARS-ADL) scores. Circles and crosses represent carriers of ATXN3 expansions and non-carriers (controls). The grey zone represents the limits outside the accuracy maximization model, while the hatched line represents the cutoff according to the ROC curve. **B** The receiver operating characteristic (ROC) curve of FARS-ADL as predictor of SARA scores equal or larger than 3 points

showed FARS-ADL scores of 4 or less (Reetz, personal communication). This would be equivalent to 9.6% false-negatives if FARS-ADL larger than 4 was used to classify FRDA subjects as ataxic.

Remote evaluations of persons at risk for ataxia might continue to be a demand for the near future. FARS-ADL is an easy to perform questionnaire through online interfaces or telephone calls. FARS-ADL does not detect ataxia, but in this population at risk for ataxia, it might help investigators to assume which subjects are already ataxic in the temporary impossibility of using the gold-standard method SARA. The specificity was high in SCA3/MJD, but not sufficient for FRDA. Therefore, it will be important to study more pre-ataxic and ataxic carriers to confirm the usefulness of FARS-ADL as a remote predictor of the symptomatic/ataxic status in SCA3/MJD and in other forms of ataxia.

Acknowledgements We thank all the subjects and families who contributed to this study.

Authors' Contributions ECM contributed to the conception, organization, and execution of research project; helped in review and critique statistical analysis and critically revised the manuscript; and helped in manuscript review and critique. VHIS, CMO, and GB contributed to the research project execution, statistical analysis review and critique, and manuscript review and critique. MLSP contributed to the research project execution and manuscript review and critique. VLT contributed to the research project conception and execution, statistical analysis design and execution, and manuscript review and critique. LBJ contributed to the research project conception and organization; helped in the design, and review and critique of the statistical analysis; helped in the writing, review, and critique of the first draft of the manuscript. All authors read and approved the final manuscript.

Funding This study was supported by Fundação do Amparo à Pesquisa do Rio Grande do Sul (FAPERGS) (grant numbers 17/2551–0001 035–3 and 17/2551–0001 1463–4), Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre (FIPE-HCPA) (grant numbers 20–0026). MLSP and LBJ were supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil.

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

Declarations

Ethics Approval This study was approved by the Institutional Ethics Committee (Comissao de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre) (CAAE 28002720.4.0000.5327).

Conflict of Interest All authors declare that there are no financial disclosures or any conflicts of interest.

References

1. Schmitz-Hübsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, Giunti P, Globas C, Infante J, Kang JS, Kremer B, Mariotti C, Melegh B, Pandolfo M, Rakowicz M, Ribai P, Rola R, Schöls L, Szymanski S, van de Warrenburg BP, Dürr A, Klockgether T, Fancellu R. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology. 2006;66(11):1717–20. https://doi.org/10.1212/01.wnl.0000219042.60538.92.
2. Grobe-Einsler M, Taheri Amin A, Faber J, Schaprian T, Jacobi H, Schmitz-Hübsch T, Diallo A, Tezenas du Montcel S, Klockgether T. Development of SARAhome, a new video-based tool for the assessment of ataxia at home. Mov Disord. 2021;36(5):1242–6. https://doi.org/10.1002/mds.28478.

3. Subramony SH, May W, Lynch D, Gomez C, Fischbeck K, Hallett M, Taylor P, Wilson R, Ashizawa T, Cooperative Ataxia Group. Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale. Neurology. 2005;64(7):1261–2. https://doi.org/10.1212/01.WNL.0000156802.15466.79.
4. Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, Parkinson MH, Sweeney MG, Mariotti C, Panzeri M, Nanetti L, Arpa J, Sanz-Gallego I, Durr A, Charles P, Boesch S, Nachbauer W, Klopstock T, Karin I, Depondt C, vom Hagen JM, Schöls L, Giordano IA, Klockgether T, Bürk K, Pandolfo M, Schulz JB. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 2015;14(2):174–82. https://doi.org/10.1016/S1474-4422(14)70321-7.
5. Reetz K, Dogan I, Hilgers RD, Giunti P, Parkinson MH, Mariotti C, Nanetti L, Durr A, Ewenczyk C, Boesch S, Nachbauer W, Klopstock T, Stendel C, de Rivera Rodríguez, Garrido FJ, Rummey C, Schöls L, Hayer SN, Klockgether T, Giordano I, Didszun C, Rai M, Pandolfo M, Schulz JB, EFACTS study group. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 4-year cohort study. Lancet Neurol. 2021;20(5):362–72. https://doi.org/10.1016/S1474-4422(21)00027-2.