

Rating scales for rare neurological diseases

What are we learning from Friedreich ataxia?

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We are living in exciting times. Effective treatments are emerging for devastating disorders that were completely intractable until the very recent past, including a growing number of the thousands of mostly genetic rare diseases that overall account for a significant portion of neurology and child neurology. This has been made possible by spectacular advances in genetics, the generation of relevant animal and cellular models, progress in molecular and cell biology leading to the identification of therapeutic targets, and the development of novel therapeutic agents, including small molecules, oligonucleotides, monoclonal antibodies, and gene therapy.

Although exciting, moving to the therapeutic era for rare neurologic diseases has created new challenges in the clinic. The design of clinical trials for these conditions requires knowledge of their natural history and the use of appropriate clinical assessment tools and biomarkers. The article by Rummey et al.¹ in this issue of *Neurology Genetics* describes the psychometric properties of the modified Friedreich Ataxia Rating Scale (mFARS). The mFARS is an adaptation of the FARS, a rating scale that was developed to quantitatively assess the severity of the neurologic features of Friedreich ataxia (FRDA), with the goal of providing a progression-sensitive clinical assessment tool that could be used in natural history studies and as an outcome measure in clinical trials.²

FRDA, the most common inherited ataxia in white populations but still a rare disease with a birth incidence of 2–3 in 100,000, is an autosomal recessive multisystem disorder characterized by neurologic impairment, hypertrophic cardiomyopathy, skeletal abnormalities, and carbohydrate intolerance.³ FRDA is due to insufficient levels of frataxin (FXN), a mitochondrial protein involved in iron-sulfur cluster biogenesis, caused by expanded guanine-adenosine-adenosine repeats in the *FXN* gene that suppress its transcription via an epigenetic mechanism. Advances in understanding FRDA pathogenesis are leading to new therapeutic strategies, aiming to restore FXN levels or targeting the downstream consequences of its deficiency, such as altered iron metabolism, impaired mitochondrial function, and oxidative damage.⁴ This has already led to clinical trials, and more are expected in the coming years.

The FARS was originally designed to capture the whole spectrum of neurologic features of FRDA. In addition to a neurologic examination, it includes a functional staging for ataxia, an assessment of activities of daily living, and 2 instrumental tests, the PATA rate for dysarthria and the Nine-Hole Peg Test for upper limb dexterity. These components may be also used separately from the FARS neurologic examination (FARS_n), which assesses gait and limb ataxia, dysarthria, sensory loss, weakness, and amyotrophy. The FARS is a clinical assessment tool used by the Friedreich Ataxia-Clinical Outcome Measures (FA-COMS) collaborative study, an ongoing prospective investigation of FRDA clinical features and progression involving multiple sites in the United States, Canada, Brazil, and Australia, whose results have already made the object of several publications.⁵ The mFARS is the product of a reassessment of the FARS_n, aiming to improve its psychometric characteristics.

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Rummey et al. studied the psychometric properties of the mFARS in the FA-COMS cohort, which includes patients with FRDA of all ages, age of onset, severities, and disease durations. As the authors state, this makes this cohort ideal for the analysis of a rating scale. They conclude that their study confirms the validity and structure of the FARSn but also endorses the modifications leading to the mFARS, which eliminate “weak” items that correlate poorly and progress differently from the rest of the scale.

Some considerations are prompted by this well-conceived and well-conducted study. First, the mFARS, by excluding FARSn items assessing tongue and facial atrophy plus all peripheral nervous system items including weakness, amyotrophy, sensory loss, and deep tendon reflexes, essentially becomes an ataxia rating scale. The European Friedreich Ataxia Consortium for Translational Studies (EFACTS), a similar European initiative to FA-COMS, uses the Scale for the Assessment and Rating of Ataxia (SARA)⁶ as a primary measure of neurologic progression in FRDA. The SARA was initially validated in autosomal dominant spinocerebellar ataxias, and, as its name says, it was conceived from the beginning as a general rather than a disease-specific ataxia rating scale. Remarkably, published results from the EFACTS⁷ and FA-COMS⁵ show a very similar behavior of the SARA and the mFARS, essentially showing the same sensitivity to progression and providing overlapping results in power calculations for clinical trials. The SARA has the distinct advantage of being a more compact scale, and because of simpler training, being easier to use in a multicenter context. Rummey et al. suggested that the mFARS may nevertheless prove superior in more complex studies because it provides a more detailed evaluation of overall patient status and a more complex yet valid construct. It is important that the mFARS has been accepted as a primary outcome for FRDA clinical trials by the US Food and Drug Administration. The recently completed a randomized, double blind, placebo-controlled study of the safety and efficacy of omaveloxolone in FRDA (MOXIe), had the mFARS as a primary end point.⁸ Remarkably, MOXIe was the first positive randomized controlled trial in FRDA, showing a significant divergence in the mFARS score between placebo- and omaveloxone-treated patients after 48 weeks (Reata press release, October 14, 2019). This very recent result confirms the validity of the mFARS in a clinical trial context. The SARA is currently used in 2 ongoing European FRDA trials: a clinical study to evaluate the effect of MIN-102 on the progression of Friederich ataxia in male and female patients (FRAMES), assessing the pioglitazone derivative MIN-102 to boost mitochondrial biogenesis and

function, and a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of nicotinamide in patients With Friedreich ataxia (NICOFa), assessing nicotinamide to inhibit Class III histone deacetylases that contribute to the guanine-adenosine-adenosine expansion-triggered repression of *FXN* expression.

While only future experience will establish whether these scales are equally effective in FRDA clinical trials or if one proves superior, the point that they are both ataxia rating scales rather than comprehensive assessments of all FRDA neurologic features remains. Can we generalize this conclusion and say that rating scales assessing specific neurologic features are to be preferred to disease-specific scales in rare neurologic disorders? This is an open and controversial question. There have been and there are continuing efforts to develop and validate disease-specific scales for rare and even ultra-rare diseases, with the goal of disposing of robust, sensitive outcome measures for clinical trials, capturing as much as possible of the complexities of each of these conditions. Whether the same goal can be attained by appropriately combining general scales for neurologic impairments as weakness, spasticity, ataxia, and dystonia remains to be determined, but, in the light of our experience with a disease with as complex a neurologic picture as FRDA, this approach may be a viable and possibly even a preferable option.

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Disclosure

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References

1. Rummey C, Corben LA, Delatycki MB, et al. Psychometric properties of the Friedreich Ataxia Rating Scale. *Neurol Genet* 2019;5:e371. doi: 10.1212/NXG.0000000000000371.
2. Lynch D, Farmer J, Tsou A, et al. Measuring Friedreich ataxia. *Neurology* 2006;66:1711–1716.
3. Pandolfo M, Manto M. Cerebellar and afferent ataxias. *Continuum (Minneapolis)* 2013;19(5 Movement Disorders):1312–1343.
4. Pandolfo M. Treatment of Friedreich's ataxia. *Expert Opin Orphan D*. 2013;1:221–234.
5. Patel M, Isaacs CJ, Seyer L, et al. Progression of Friedreich ataxia: quantitative characterization over 5 years. *Ann Clin Transl Neurol* 2016;3:684–694.
6. Schmitz-Hübsch T, du Montcel TS, Baliko L, et al. Scale for the assessment and rating of ataxia. *Neurology* 2006;66:1717–1720.
7. Reetz K, Dogan I, Hilgers RD, et al. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. *Lancet Neurol* 2016;15:1346–1354.
8. Lynch DR, Farmer J, Hauser L, et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. *Ann Clin Transl Neurol* 2019;6:15–26.