2016-05

Standardized Assessment of Hereditary Ataxia Patients in Clinical Studies

Paap, BK

10.1002/mdc3.12315
Movement Disorders Clinical Practice
Wiley

Movement Disorders
CLINICAL PRACTICE

REVIEW

Standardized Assessment of Hereditary Ataxia Patients in Clinical Studies

Brigitte K. Paap, PhD,[1,] Sandra Roeske, PhD,[1] Alexandra Durr, MD, PhD,[2,3] Ludger Schöls, MD,[4,5] Tetsuo Ashizawa, MD,[6] Sylvia Boesch, MD, MSc,[7] Lisa M. Bunn, PhD,[8] Martin B. Delatycki, MBBS, FRACP, PhD,[9,10] Paola Giunti, MD, PhD,[11] Stéphane Lehéricy, MD, PhD,[3,12,13] Caterina Mariotti, MD,[14] Jörg Melegh, MD, PhD, DSc,[15] Massimo Pandolfo, MD, PhD,[16] Chantal M.E. Tallaksen, MD,[17,18] Dagmar Timmann, MD,[19] Shoji Tsuji, MD, PhD,[20] Jörg Bela Schulz, MD,[21] Bart P. van de Warrenburg, MD PhD,[22] Thomas Klockgether, MD[1,23]*

Abstract: **Background:** Hereditary ataxias are a heterogeneous group of degenerative diseases of the cerebellum, brainstem, and spinal cord. They may present with isolated ataxia or with additional symptoms going beyond cerebellar deficits. There are an increasing number of clinical studies with the goal to define the natural history of these disorders, develop biomarkers, and investigate therapeutic interventions. Especially, early and preclinical disease stages are currently of particular interest.

Methods and Results: Evidence-based, we review standards for sampling and storage of biomaterials, clinical and neuropsychological assessment, as well as neurophysiology and neuroimaging and recommendations for standardized assessment of ataxia patients in multicenter studies.

Conclusions: DNA, RNA, serum, and, if possible, cerebrospinal fluid samples should be processed following established standards. Clinical assessment in ataxia studies must include use of a validated clinical ataxia scale. There are several validated clinical ataxia scales available. There are no instruments that were specifically designed for assessing neuropsychological and psychiatric symptoms in ataxia disorders. We provide a list of tests that may prove valuable. Quantitative performance tests have the potential to supplement clinical scales. They provide additional objective and quantitative information. Posturography and quantitative movement analysis—despite valid approaches—require standardization before implemented in multicenter studies. Standardization of neurophysiological tools, as required for multicenter interventional trials, is still lacking. Future multicenter neuroimaging studies in ataxias should implement quality assurance measures as defined by the ADNI or other consortia. MRI protocols should allow morphometric analyses.

[1]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; [2]APHP Department of Genetics, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [3]Institut du Cerveau et de la Moelle, INSERM U1127, CNRS UMR7225, Sorbonne Universités–UPMC Université Paris VI UMR_S1127, Paris, France; [4]Department of Neurology and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany; [5]German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany; [6]Department of Neurology and Neuroscience Research Program, Methodist Hospital Research Institute, Houston, Texas, USA; [7]Department of Neurology, Medical University Innsbruck, Innsbruck, Austria; [8]School of Health Professions, Peninsula Allied Health Center, University of Plymouth, United Kingdom; [9]Murdoch Children's Research Institute, Melbourne, Australia; [10]Clinical Genetics, Austin Health, Heidelberg, Victoria, Australia; [11]Ataxia Centre Department of Molecularneuroscience, UCL Institute of Neurology, London, United Kingdom; [12]Institut du Cerveau et de la Moelle (ICM) epiniere, Centre de NeuroImagerie de Recherche (CENIR), Paris, France; [13]Service de Neuroradiologie, Groupe Hospitalier Pitie-Salpetriere, Paris, France; [14]Unit of Genetics of Neurodegenerative and Metabolic Disorders, Fondazione IRCCS-Istituto Neurologico Carlo Besta, Milan, Italy; [15]Department of Medical Genetics and Szentagothai Research Center, University of Pécs, Pécs, Hungary; [16]Université Libre de Bruxelles, Brussels, Belgium; [17]Department of Neurology, Oslo University Hospital, Oslo, Norway; [18]Faculty of Medicine, Oslo University, Oslo, Norway; [19]Department of Neurology, Essen University Hospital, University of Duisburg-Essen, Essen, Germany; [20]Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [21]Department of Neurology and JARA Brain, University Hospital, RWTH Aachen, Aachen, Germany; [22]Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition, and Behavior, Nijmegen, The Netherlands; [23]Department of Neurology, University Hospital of Bonn, Bonn, Germany

***Correspondence to:** Dr. Brigitte K. Paap, German Center for Neurodegenerative Diseases e.V. (DZNE), Clinical Research, Ernst-Robert-Curtius-Straße 12, D53117 Bonn, Germany; E-mail: brigitte.paap@dzne.de

Keywords: ataxia, clinical assessment, rating scales, quantitative performance tests, biomaterial.
Relevant disclosures and conflicts of interest are listed at the end of this article.
This article was published online on 11 February 2016. After online publication, some headings in text were revised. This notice is included to indicate that it has been corrected on 23 February 2016.
Received 11 August 2015; revised 12 October 2015; accepted 2 November 2015.
Published online 11 February 2016 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12315

doi:10.1002/mdc3.12315

Hereditary ataxias are a clinically and genetically heterogeneous group of degenerative diseases of the cerebellum, brainstem, and spinal cord. Their prominent clinical features are progressive ataxia comprising impairment of gait, balance, and limb coordination, as well as disturbances of speech swallowing and oculomotor control. Hereditary ataxias may present as purer forms with more isolated ataxia or as complicated forms with additional neurological symptoms.

Hereditary ataxias are subdivided into the autosomal-recessive ataxias with Friedreich's ataxia (FRDA) as the most prevalent entity -except East Asia-, the autosomal-dominant ataxias designated as spinocerebellar ataxias (SCAs), and X-linked ataxias with fragile X-associated tremor ataxia syndrome (FXTAS) as the most common form. Currently, more than 50 recessive ataxias (http://neuromuscular.wustl.edu/ataxia/recatax.html), and approximately 40 SCAs, have been genetically delineated (http://neuromuscular.wustl.edu/ataxia/domatax.html). Additionally, ataxias can be caused by mitochondrial DNA mutations as well. A subgroup of potentially hereditary ataxias are the sporadic adult-onset degenerative disorders with no identified etiology share many clinical features with the hereditary ataxias, but the causes of these ataxias are unknown. An overview of hereditary ataxias and causative gene mutations can be found online (http://neuromuscular.wustl.edu/).

With the genetic classification of hereditary ataxias, an increasing number of clinical studies aim to define the natural history of these disorders, develop biomarkers, and investigate therapeutic interventions. Early and preclinical disease stages are currently attracting particular interest. For such studies, generally accepted standards for sampling and storage of biomaterials, clinical and neuropsychological assessment, quantitative performance tests, as well as neuroimaging are highly needed. In this article, we review the available evidence and give recommendations for standardized assessment of ataxia patients in multicenter studies.

Methods

Searches were conducted in the MEDLINE, EFNS Guidelines, and EMQN databases. The review period was from January 1990 to 2014. Original articles, review articles, and guideline recommendations were reviewed. Search terms were hereditary ataxia, cerebellar ataxia, autosomal-recessive ataxia, Friedreich's ataxia, spinocerebellar ataxia, autosomal-dominant cerebellar ataxia, and Machado-Joseph disease and were used in various combinations with terms like clinical assessment scales, functional score, MRI, PET, gait analysis, genotyping, biomarker, biomaterial, morpho*, and neuropsycho*. In the next step, the identified assessments tools, such as "Scale for the Assessment and rating of Ataxia" ("SARA"), "International Cooperative Ataxia Rating Scale" ("ICARS"), "Composite Cerebellar Functional Severity Score" ("CCFS"), were used as search terms in combination with disease terms. Reference lists of publications of interest were screened for other relevant studies. B.P. performed the literature search and wrote the first draft. T.K. reviewed all versions. A preliminary version of the manuscript was then circulated among all authors. This version was discussed and consented by conference calls, before the final version was drafted and circulated.

Ataxia Research Consortia and Study Groups

In recent years, a number of large national and international research consortia have received public funding to perform clinical research in hereditary ataxias. SPATAX is a consortium of European and North African investigators under French leadership that focuses on clinical and genetic studies in recessive ataxias and hereditary spastic paraplegias (HSPs) (http://spatax.wordpress.com/). The EUROSCA Clinical Network that was funded by the European Union (EU) between 2004 and 2008 developed clinical assessment tools for ataxia, established an electronic database, and initiated a natural history study of dominantly inherited spinocerebellar ataxias (SCAs) (http://www.eurosca.org). To continue clinical research activities, investigators of the EUROSCA Clinical Network in 2008 founded the Ataxia Study Group (ASG) (http://www.ataxia-study-group.net/html/about). Currently, there are two large EU-funded consortia involved in clinical ataxia and HSP research. Major initiatives to study FRDA are performed by EFACTS (http://www.e-facts.eu) in Europe and the Cooperative Clinical Research Network (CCRN) in the United States, Canada, Brazil, and Australia. NeurOmics is using -omics methods to find disease causing genes, improve diagnostics, and develop novel therapies for 10 rare neurodegenerative and neuromuscular disease groups, including ataxia (http://rd-neuromics.eu/). The Cerebellar Ataxia Group (CAG), which has evolved into the Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA), comprises North American ataxia investigators. Clinical studies initiated by the CRC-SCA received funding from the National Institutes of Health (NIH). The Japanese Ataxia Study Group receives funding from the Japanese government. It is running a large patient registry.

Common Data Elements

Starting in 2006, the National Institute of Neurological Disorders and Stroke (NINDS) and other federal agencies and international organizations have the common mission of developing data standards for clinical research. On their webpage (http://www.commondataelements.ninds.nih.gov/ProjReview.aspx#tab=Introduction), common as well as disease-specific data elements are published as a resource to build study specific common data element (CDE) data collection sheets. General CDEs include medical history data; scores on neurological assessments; demographic information (e.g., date of birth/age, race, and ethnicity); and details about medications used by participants throughout a study. For FRDA, disease-specific recommendations of tools and CDEs are given by NINDS (http://www.commondataelements.ninds.nih.gov/Doc/

doi:10.1002/mdc3.12315

FA/FA_CDE_Highlight_Summary.pdf).[1] CDEs for other forms of ataxias are not available yet.

Biomaterial Sampling and Storage

Availability of biomaterials is an essential prerequisite for progress in the understanding of neurodegenerative diseases.

Genetic testing is performed for genetic classification of study participants. On http://www.scabase.eu, information about ataxia genetics regarding current best practices protocols for molecular genetic testing, lists of repeat sequences, primers, and normal and pathogenic repeat sizes on the main loci are maintained.

Orphanet and—in Europe—EuroGenTest are data sources for genetic tests and relevant laboratories.

DNA is needed for the proper classification of study subjects with known diseases and for identification of novel disease genes and genetic modifiers.

Fibroblast or peripheral blood mononuclear cell (PBMC) samples are valuable sources for various experiments, in particular, generation of induced pluripotent stem cells (iPSC). Because sampling of PBMCs is less invasive and easier than that of fibroblasts, PBMCs are the currently recommended source of iPSCs.[2] Given the enormous potential of research with iPSCs, routine sampling of PBMCs in clinical studies, if feasible, is highly recommended.[3]

There are several systematic efforts for brain collections under standardized protocol. Here as well, effort and money are limiting factors. Additionally, the trust of potential donors and their families plays an important role in the success of building up brain collections.

Biomaterials, such as blood samples, urine, and cerebrospinal fluid (CSF), are required for the development of fluid biomarkers, which—other than in common neurodegenerative diseases, such as Alzheimer's disease (AD)—are currently not available in ataxia.

Usefulness of biomaterials critically depends on the clinical information on the subjects from whom the materials are derived. Biomaterial collections that are not linked to reliable clinical data are therefore of limited use. Another important aspect that is critical for the usefulness of biomaterials is the biophysical quality of the samples.[4] All procedures, including acquisition, handling, and preprocessing before final storage, storage, and retrieval, strongly influence the composition and stability of the samples. These steps should be therefore performed following standard operation procedures, as are generally recommended for biomaterial banking.[3,5,6] Furthermore, a documentation of the biomaterial quality is necessary and should be performed as detailed and internationally comprehensive as possible. An example of such documentation is the standard preanalytical (SPREC) code (http://www.isber.org/?page=SPREC).[7] For further information see supplemental material.

Overall, DNA, RNA, serum, and—whenever possible—CSF and PBMC samples comprise a set of biomaterials that should be taken.

Clinical Scales

Clinical scales are the most important component of assessment in clinical studies. They serve as outcome measures in clinical interventional trials and are therefore key instruments that have a strong impact on future research and patient care. Clinical ataxia scales have been recently reviewed in detail.[8] We will describe here the most widely used scales and comment on their properties with respect to use in multicenter and longitudinal studies. Their basic psychometric properties are summarized in Table 1.

ICARS[9]

The ICARS was the first ataxia scale and is widely used in observational studies as well as in interventional trials. It consists of 19 items grouped into four subscales that contribute to a total score of 100 points. Subdivisions of different ataxia components are postural and gait disturbance, limb ataxia, dysarthria, and oculomotor disorders.[9]

ICARS has been evaluated in six published studies in MSA, SCA, and FRDA patients.[10] Standard psychometric variables, such as total Crohnbach's α, inter-rater reliability, and test-retest reliability, were reported to be good to very good. However, several investigators observed interdependencies between several items. Furthermore, principal component analysis showed that the ICARS score is determined by four different factors that do not coincide with the subscales. The ICARS also lacked linearity and showed floor and ceiling effects.[11] However, ICARS shows good sensitivity to change.

There are two modified versions of the ICARS, the Brief Ataxia Rating Scale (BARS) for use by movement disorder specialists and general neurologists, and the modified ICARS (MICARS), in which further items were added.[12] Both scales lack further validation. Recently, the effect of age on ICARS, BARS, and SARA scores has been assessed in healthy children.

SARA[13]

The SARA is a clinical scale based on a semiquantitative assessment of cerebellar ataxia. It has eight unequally weighted items evaluating to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test. Oculomotor functions are not included in the SARA.

The SARA was initially validated in two studies of 167 and 119 SCA patients.[13,14] Subsequent evaluation studies were done in mixed populations of ataxia patients[15] and in FRDA.[16] The SARA has been translated into Iberia-Brazilian, Japanese, and Chinese versions, and the translated versions were also validated. Recently, the SARA was also tested in healthy children of various age groups.[10]

Overall, psychometric properties were shown to be as good as for the ICARS. In contrast to the ICARS, the SARA behaves linearly without ceiling or floor effects. In FRDA

doi:10.1002/mdc3.12315

TABLE 1 Psychometric features of ataxia rating scales and functional performance scores

Name	Internal Consistency (Crohnbach's α)	Inter-rater Reliability (ICC)	Test-Retest Reliability (ICC)	Sensitivity to Change	Scale	References
Generic ataxia scales						
ICARS	0.94 (FRDA), 0.95 (SCA)	0.95	0.93 (FRDA), 0.97 (SCA)	ES: 0.26	0–100 points	8,10–12
SARA	0.94	0.98	0.90	ES: =<0.2; SRM: 0.5	0–40 points	13,14
Disease-specific ataxia scales						
FARS	0.86	0.95	0.95	Part I–III: ES: 0.34 ES: 0.34; SRM: 0.53	Part I: 0–6 points; Part II: 0–36 points; Part III: 0–117 points	15
NESSCA	0.77	0.97	n/a	ES: 0.22	0–40	16
Nonataxia symptoms inventory						
INAS	n/a	0.88	0.65	SRM: 0.26	0–16 points	17
Functional performance tests						
ACFS	n/a	0.92 (PATA), 0.93 (9HPT, T25FW)	n/a	SRM: 9HPT: 0.43, T25FW: 0.26; LCLA: 0.19; PATA: no change; z2 score: 0.37; z3 score: 0.39; ES: 0.34; SRM: 0.53	Continuous; arithmetic mean across all three z scores	15,18
SCAFI	0.72	n/a	n/a	SRM: 0.48	Continuous; arithmetic mean across all three z scores	19
CCFS	n/a	n/a	0.92 [0.84, 0.97]	CCFS ES: <0.2, SRM: 0.32CCFSw: ES: <0,2, SRM:.0 40	Continuous; $\log_{10}$ z score, electronic, validated in children	20,21

ICC, intraclass correlation; ES, effect size; SRM, standard response mean; n/a, not available; T25FW, timed 25 feet walk; LCVA, low-contrast visual acuity.

patients, sensitivity to change of SARA was greater than that of the Friedreich Ataxia Rating Scale (FARS) and ICARS.[17] In addition, clinically relevant changes were defined, and it was demonstrated that SARA is a major determinant of health-related quality of life in SCA patients. From the practical point of view, SARA has less repetitive items, is less time-consuming to administer, and easier to use than ICARS.

FARS[18]

The FARS comprises neurological signs that specifically reflect FRDA symptoms assessed in three functional domains: (1) functional staging (overall mobility); (2) activity of daily living (ADL); (3) neurological assessments (bulbar, upper and lower limbs, peripheral nerve, upright stability, and gait functions). The FARS has been validated in two studies of 14 and 155 FRDA patients, respectively.[18] Regner et al. discussed that for longitudinal measurement in unselected cohorts, a 2-year period may be the minimum period to gain reasonable power.[19]

Psychometric properties were good and comparable to ICARS and SARA. However, ceiling effects were observed. FARS meets essential criteria for validity for the measurement of disease progression. As a measure of sensitivity, FARS has greater effect size in FARDA patients than ICARS.[16,17]

Neurological Examination Score for Spinocerebellar Ataxia[20]

The Neurological Examination Score for Spinocerebellar Ataxia (NESSCA) was developed specifically for SCA3 patients based on a standardized neurological examination. Thus, the 18 items selected comprise a global inventory of general neurological signs and of signs specific for SCA3. It has been validated in a cross-sectional study of 99 SCA3 patients. Inter-rater reliability (20 patients) was high. Scores correlated with SARA scores. Sensitivity to change was not investigated.

Scales for the Assessment and Rating of Nonataxia Features

Inventory of Non Ataxia Signs[21]

The Inventory of Non Ataxia Signs (INAS) comprises a list of various nonataxia signs that often occur in ataxia patients and of cerebellar oculomotor signs that are not considered in the SARA. INAS has 30 items related to neurological signs, such as spasticity, and to reported abnormalities, such as dysphagia. The items are grouped into functional categories, reflecting 16 nonataxia and cerebellar oculomotor signs.[21] As a simple quantitative measure, the INAS count reflects the presence or absence of

doi:10.1002/mdc3.12315

nonataxia signs, when at least one item related to a nonataxia sign is present.

The INAS performed very well in terms of inter-rater and test-retest reliability. There were mild floor and no ceiling effects. Responsiveness and sensitivity, however, were less satisfactory. Another limitation is that the INAS lacks precise definitions and instructions for investigators, which may cause variability in judgments of symptom severity. However, the INAS is an inventory —not a rating—scale, so the score depends on the presence, not on the severity of symptoms and signs. The INAS is easy to use, only requiring tests or procedures that are routinely performed in the neurological examination. Overall, it has proved to be a useful supplement to the SARA, but it is not an appropriate primary outcome measure in interventional trials in ataxia.

Other Scales

In some types of ataxias, specific symptoms are frequently encountered. Examples are spasticity in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) and autonomic dysfunction in SCA3. In these instances, it is useful to apply other scales that assess specific symptoms more accurately than the INAS. In SCA3 patients, the Unified Multiple System Atrophy Rating Scale (UMSARS) has been validated.[22] In ARSACS and other spastic ataxias, the Spastic Paraplegia Rating Scale (SPRS), which has been developed for hereditary spastic paraplegia patients,[23] can be applied. However, further validation is desirable.

Patient-Reported Measures

Outcome measures that are patient reported may be valuable for complementing physician-based outcomes. Examples for generic health status measurement tools or disease-specific tools are Short Form Health Survey version 2 (SF-36 V2)[24] or the Friedreich Ataxia Impact Scale (FAIS).[25] The SF-36 is a general measurement of quality of life. Quality of life is an important secondary endpoint in clinical interventional trials. The SF-36 does not address many ataxia-related issues, though. The FAIS contains 126 items covering eight functional areas. It was developed and validated in over 400 FRDA patients grouped into different levels of disease severity. In a recent longitudinal study, the FAIS was found to provide valuable insight into the perspective of individuals with FRDA on their health status and morbidity. However, responsiveness to change appears limited and its use in intervention studies is questionable.

The ADL part of FARS is another quality-of-life measure, which is used frequently. As an outcome in the EFACTS study, it showed effect sizes comparable to those of the SARA.[26]

Assessment of Neuropsychological and Psychiatric Symptoms

Because the cerebellum has a prominent role in motor control, ataxia patients mainly present with motor symptoms. The cerebellum plays a role also in nonmotor functions. Neuropsychological and psychiatric symptoms of variable severity are encountered in a number of ataxias.[27] The reasons for this are 3-fold: (1) Because of cerebellar connections to nonmotor cortical areas, cerebellar disease can be associated with neuropsychological symptoms, mainly disturbances of executive function; (2) in many ataxias, neurodegeneration extends beyond the sites that result in ataxia by involving forebrain structures. This results in intellectual impact and cognitive decline; (3) furthermore, as with many other chronic brain diseases, ataxia can be associated with depression.[28, 29]

There are no instruments that were specifically designed for assessment of neuropsychological and psychiatric symptoms in ataxia. Thus, in studies of ataxia patients, various instruments are used that have been previously developed and validated in other populations. A comprehensive overview of such studies is given by Almeida-Silva et al.[30]

Although neuropsychological and psychiatric abnormalities have been investigated in numerous studies, there are only a few multicenter and longitudinal studies.[31, 32] A major problem in the use of timed neuropsychological tests in ataxia patients is their motor slowness, which is a confounding factor in assessing cognitive function. This should be taken into account when selecting specific tests. Neuropsychological tests recommended in order to minimize motor skills' interference with special emphasis on covering executive, visuospatial, and verbal domains are given in Table 2.

Quantitative Performance Tests

For ataxia, a number of tests are in use that measure performance in specific coordinative tasks in a quantitative way. These tests yield metric, continuous data that facilitate analysis. In addition, inter-rater reliability is usually higher than in clinical scales. Assessments range from simple time measurements, for example, the time needed to complete a 25-foot (ft) walk, syllable repetition rate, and pegboard tests, to complex assessments that require specific equipment, for example, stride length variability measured with the GAITRite system, acoustic speech analysis systems,[33] and systems to analyse the kinematics and forces of reaching and grasping movements.[34] Each of the obtained measures reflects only performance in the respective task. But the results of various tests can be combined to composite measures that are thought to provide a more comprehensive account of disease severity.

Ataxia Functional Composite[35]

The Ataxia Functional Composite (AFCS) was specifically designed for FRDA. It is derived from the Multiple Sclerosis Functional Composite (MSFC) and composed of a timed 25-ft walk, the 9-hole pegboard test (9HPT), and low-contrast visual acuity (LCVA). It has been validated in 20 hereditary ataxia patients, showing a strong correlation to ICARS. Test results are given as calculated Z scores.

doi:10.1002/mdc3.12315

TABLE 2 Recommended neuropsychological tests for assessing cognitive functions in ataxia patients*

Domain	Function	Test	Abbreviation	References
Global cognitive status	General cognitive functioning	Mini–Mental State Examination	MMSE	64
	General cognitive functioning	Montreal Cognitive Assessment	MoCA	65
	General intellectual ability	2 Subtests of the Wechsler Abbreviated Scale of Intelligence: Vocabulary and Matrix Reasoning	WASI	66
Memory	Verbal memory	California Verbal Learning Test	CVLT	67
	Verbal memory	Auditory-Verbal Learning Test	AVLT	68
	Visual memory	Continous Visual Memory Test	CVMT	69
Executive functions/attention	Working memory	Digit-Span (Wechsler Adult Intelligence Scale)	WAIS-IV	70
	Interference	STROOP Color and Word Test	STROOP	71
	Verbal fluency (lexical and semantic)	Controlled Oral Word Association Test	COWAT	72
	Set shifting	Wisconsin Card Sorting Test	WCST	73
	Selective Attention, Sustained Attention, Divided Attention	Test of Everyday Attention	TEA	74
Verbal functions and language skills	Naming	Boston Naming Test	BNT	75
	Aphasia	Bedside Form of the Western Aphasia Battery-R	WAB-R	76
Reasoning	Sequencing	Picture Arrangement (Wechsler Adult Intelligence Scale)	WAIS-R	77
Visuoperceptive Functions	Visual recognition	Judgment of Line Orientation	JLO	78
Depression	Severity of depressive symptoms	Beck Depression Inventory	BDI	79

*Considering to minimizing the need for manual response and ataxia as a confounding factor.

SCA Functional Index[14, 36]

The SCA Functional Index (SCAFI) is very similar to the AFCS, but the LCVA was replaced by a speech test (PATA repetition rate). The walking test is designated as an 8-m walk, but is essentially identical to the 25-ft walk of the AFCS. The SCAFI score is derived from the arithmetic mean of the Z scores of the three tests. The SCAFI reached the criterion for retest reliability and showed, in general, favorable measurement precision. However, in longitudinal tests, SCAFI deteriorates within the stable group of patients during the follow-up period. The clinical relevance of the longitudinal SCAFI changes seeks further investigation.

Composite Cerebellar Functional Severity Score[37]

The Composite Cerebellar Functional Severity Score (CCFS) is a performance-based scale that combines two tests of upper limb function, the 9HPT and the click test. Measurements are adjusted for age and can be used for both for dominant and recessive ataxias and are adapted for children.[38] A version of the CCFS includes a handwriting test (CCFSw).[39, 40] However, patients with a SARA score of 30 or above may not be able to perform the CCFS(w).

Posturography[41]

Posturography is a technique that quantifies postural control in upright stance in either static or dynamic conditions. It is widely used for diagnosis of balance disorders. Posturography using gold-standard laboratory (Codamotion 3D motion analysis system with Visual 3D offline processing software) has been used to quantitatively investigate balance (static conditions) in adults with SCA6. Measures of overall sway speeds as well as pitch and roll directional components of sway have been used to comprehensively describe overall and directional components of instability. Quantitative reports of mean sway speeds correlate with same-day measures of disease severity (using the SARA), where an increase in SARA is associated with linear increases in sway speed. Posturography was additionally used to explore levels of axial instability. Laboratory investigations of sensory mechanisms of balance control (dynamic conditions) have incorporated the use of posturography in order to determine sensorimotor abnormalities in adults with SCA6.[42] Posturography requires careful control of sensory conditions to ensure reliability of highly sensitive measures, but, when achieved, is feasible as a measure to either track disease progression or to evaluate the treatment effect of therapies in both clinical and home settings.[43] In addition to standardization of stance width, foot splay angle, and underfoot surface, standardization of the visual environment is of considerable importance during testing given that hypermetric balance responses and increased overall measures of instability are notable when patients observe moving scenery in their visual environment.[42, 43] Validated portable measures of posturography (body sway speeds and directional velocities) include the XSens MTx monitor,[43] but posturographic methods, incorporating other accelerometry-containing devices, are similarly possible.

doi:10.1002/mdc3.12315

Quantitative Movement Analysis

Computerized gait analyses systems offer an objective and quantitative measure of gait as well as directed movements. It has been used in ataxia as an outcome measure in several nonpharmacological interventional studies. A spatiotemporal gait analysis system based on infrared diode recording (Vicon) has been shown to pick-up changes in movement performance and scores correlate with clinical ataxia scales and with relevance for everyday life.[44] GAITRite is a portable, instrumented electronics carpet system that allows recording of stride length and variability during short walking sequences. GAITRite was validated in study of 25 healthy adults and showed strong concurrent validity and high test-retest reliability.[45] In ataxia, it was used in only a few single-center studies. One study showed that dynamic properties of locomotion in cerebellar ataxia patients were markedly impaired and that shifting walking speed away from preferred walking speed resulted in a loss of dynamic stability.[46] The other study showed that discrete gait abnormalities precede manifest ataxia in SCA6 mutation carriers compared to manifest SCA6 patients.[47] In FRDA, the sensitivity in measuring disease severity was investigated.[48] There are no studies that validate Vicon or GAITRite as an assessment instrument in multicenter studies of ataxia patients. However, the feasibility of quantitative gait analysis as an outcome measure for clinical trials in SCAs has been assessed in a small monocentric study on a total of 20 SCA1, 2, 3, and 6 patients at two time points, and data indicated that a high test-retest reliability was demonstrated. Vicon would also allow quantifying the kinematics of reaching and grasping movements.

Easy-to-apply hand-held objects that allow measurement of grip forces, an objective parameter of manual performance, have been used in single-center trials of patients with mixed cerebellar pathology.[49] They need to be validated in multicenter studies. The same is true for automatic speech analysis systems.[49]

Electrophysiology (Nerve Conduction Studies, Evoked Potentials)

Peripheral nerves, dorsal columns, and pyramidal tracts are frequently affected in degenerative ataxias and can be quantitatively assessed by neurophysiological tools, such as nerve conductions studies, somatosensory evoked potentials, and motor evoked potentials. Neurophysiological tests show characteristic findings in different subtypes of SCA, being present even in preclinical stages of SCA2.[50, 51] In FRDA, nerve conduction and evoked potential studies demonstrate the sensory neuronopathy, dorsal column degeneration, and pyramidal tract involvement that characterize the disease. Nerve conduction studies, by revealing the presence of a peripheral neuropathy and its type, provide an important support to the differential diagnosis of recessively inherited ataxias.[52] However, multicenter approaches[53] and longitudinal studies in ataxias[54, 55] are rare and face major challenges in standardization to assure reproducibility and intercenter comparability of quantitative neurophysiological measures, as required for multicenter interventional trials.

Eye Movement Tracking

Oculomotor disturbances are a common and often early sign in most hereditary ataxias. Specific oculomotor abnormalities, such as saccade slowing, are helpful in the diagnosis of hereditary atxias.[56] Presence or absence of oculomotor signs is recorded by the INAS together with nonataxia signs. Quantitative recording of eye movements has been performed in several monocentre studies. However, multicenter and longitudinal approaches face major challenges in standardization to assure reproducibility and intercenter comparability. However, given the potential of oculomotor recording for detection of early or even preclinical abnomalities, efforts to establish reliable multicenter recording techniques are strongly encouraged.

Neuroimaging

Neuroimaging allows assessment of the morphological and functional alterations of the brain and spinal cord in ataxia patients. Most neuroimaging studies in ataxia use MRI, but there are also molecular imaging studies with radiotracers. A recent consensus paper discussed application of these neuroimaging methods in ataxia.[57]

Magnetic Resonance Imaging (MRI)

Numerous MRI studies have been performed in ataxia patients, most of which were cross-sectional and done in a single center. Multicenter longitudinal studies, on the other hand, face numerous methodological problems, which require rigorous measures of quality assurance and control. These issues have been carefully addressed by large consortia investigating patients with common neurodegenerative diseases, mainly AD, but the respective standards and recommendations have not yet been applied to ataxia studies.[58]

Structural T1-weighted MRI enables quantification of focal brain atrophy, in particular, of the cerebellum, but also of other parts of the brain. Images have been analyzed with region of interest–based volumetry and voxel-based morphometry. A multicenter study of SCA1, 3, and 6 patients showed brain tissue loss in the cerebellum and brainstem with a genotype-specific pattern. In a 2-year longitudinal study of this cohort, the rate of tissue loss in these structures and basal ganglia nuclei was significantly greater in patients compared to controls. Some of the volumetric measures had larger effect sizes than the SARA clinical scale.[59] Similarly, there was progressive gray and white matter loss in a single-center longitudinal study of SCA2 patients.

Diffusion imaging is the method of choice to study white matter abnormalities, either with diffusion tensor imaging (DTI) or with more recent mathematical models, for example,

doi:10.1002/mdc3.12315

high-angular resolution diffusion imaging (HARDI), that describe the 3D displacement distribution of water diffusion. Although multicenter DTI studies are feasible and there is evidence for white matter involvement in ataxias, DTI has not yet been assessed in larger ataxia studies. Quantitative MRI techniques have also potential interest to study tissue properties, including myelin and iron content with relaxometry and susceptibility-weighted imaging.[60–62] Similarly, functional MRI in ataxia has been limited to small, single-center, cross-sectional studies. The challenge for multicenter studies lies in the experimental paradigms used in most functional MRI studies. MR spectroscopy allows measurement of brain metabolites.[63] Its usefulness is limited by the large voxel size in which measurements are made and the difficulty to standardize acquisitions across sites. Again, multicenter studies are lacking. Such studies will also need to account and correct for different scanner types.

Molecular Imaging

In molecular imaging, radiotracers are used to assess brain metabolic activity or label neurotransmitter receptors. Binding and distribution of the radiotracers in the brain are detected with PET or single-photon emission computed tomography (SPECT). PET and SPECT have been used to study glucose metabolism, dopamine receptors, dopamine transporters, benzodiazepine receptors, and acetylcholine esterase activity in ataxia patients. Although these studies provided important insights into the neurobiology of ataxia disorders,[63] standardization and validation of the molecular imaging methods as assessment tools in multicenter ataxia studies is lacking. However, for AD, a framework for multicenter fluorodeoxyglucose (FDG) PET studies has been defined and applied by the ADNI consortium.[64]

Conclusions and Recommendations

Biomaterials

Given the importance of availability of biomaterials for the development of biomarkers, biomaterial sampling should take place in all ataxia patient studies. DNA, RNA, and serum or plasma and—if possible—PBMC samples should be taken for analysis of molecular processes and alterations on several molecular levels. Although there are not many publications on molecular properties of CSF samples from ataxia patients, we suggest CSF sampling for future investigations as well.

To be able to compare biomaterials from different studies, it is recommended that acquisition, handling, and storage be performed according to generally accepted standards of biobanking, as outlined above. This includes documentation of biomaterial quality. The value of biomaterial samples critically depends on the availability of standardized clinical data.

Clinical Assessment

Clinical assessment in ataxia studies must include application of a validated clinical ataxia scale (see Table 1). To facilitate comparability between studies, generic ataxia scales, such as SARA and ICARS, are preferable to scales that are applicable only to one specific ataxia disease, unless there are particular reasons to choose a disease-specific scale. In many ataxia disorders, ataxia is accompanied by additional nonataxia symptoms. Currently, INAS is the only available instrument to assess these symptoms comprehensively.

Patient-Reported Measures

Quality of life and the perspective of individuals on their health status are important outcomes in clinical trials. FAIS or the ADL part of FARS may be suitable tools.

Assessment of Neuropsychological and Psychiatric Symptoms

There are no instruments that were specifically designed for assessment of neuropsychological and psychiatric symptoms in ataxia. Thus, in studies of ataxia patients, various instruments are used that have been previously developed and validated in other populations. A list of tests that may be valuable in monitoring ataxia patients is given in Table 2. For ataxia, these instruments need validation in longitudinal and multicenter studies.

Quantitative Performance Tests

Quantitative performance tests have a great potential to serve as supplementary outcome measures in addition to clinical scales because they provide objective and quantitative information. It is therefore hoped that they are more sensitive than clinical scales. AFCS, SCAFI, and CCFS are each sets of simple timed tests that do not require expensive equipment or extensive training. Although they have been sufficiently validated so that they can be used in multicenter longitudinal studies, there is currently no evidence that they are more sensitive than clinical scales. Validated posturographic approaches using gold-standard laboratory methods or portable home-based devices are feasible options with the potential to be sensitive continuous outcome measures for use in multicentered studies. Associated with disease severity and balance impairment, sway speeds as measures of instability require careful standardization of sensory conditions to ensure short- and long-term test-retest reliability. Oculomotor readings have a great potential for detection of early abnormalities. Efforts to establish reliable multicenter recording techniques are encouraged.

Neuroimaging

Future multicenter neuroimaging studies in ataxias should implement quality assurance measures following standards, as

doi:10.1002/mdc3.12315

TABLE 3 Summarized recommendations for the use of clinical assessment tools

Type of Assessment	Methods	Usage in Longitudinal Multicenter Ataxia Studies
Biomaterial sampling	Cell, blood, and CSF draw, processing, storage, and analysis	Must have: DNA, RNA, serum; if possible: CSF and PBMC; follow standardized protocols
Clinical rating scales	Generic ataxia scales: ICARS, SARA	Important outcome measure
	Disease-specific ataxia rating scale: FARS, NESSCA	May be useful to assess specific ataxias
Nonataxia Inventory	INAS	Supplementary outcome measure; only instrument for nonataxia sign assessment
Nonataxia scales	SPRS, UMSARS	May be useful to assess specific symptoms (e.g., spasticity, autonomic dysfunctions); further validation needed
Neuropsychology and psychiatry	Tests for cognitive functions and depression	Supplementary outcome measure; no ataxia specific tests; further validation needed
Functional performance tests	ACFS, SCAFI, CCFS	Supplementary outcome measure; not proven to be more sensitive than clinical scales
	Posturography	Not yet undergone standardization and validation in multicenter studies
	Quantitative movement analysis	Not yet undergone standardization and validation in multicenter studies
	Oculomotor recording	Not yet undergone standardization and validation in multicenter studies
Neuroimaging	MRI: T1-weighted MP-RAGE sequences	Great potential as supplementary outcome measure; follow ADNI consortium protocols
	Molecular imaging: PET, SPECT	Not yet undergone standardization and validation in multicenter studies
Electrophysiology	Nerve conduction studies, evoked potentials	Not yet undergone standardization and validation in multicenter studies
Patient-reported measures	FAIS, ADL, SF-36 V2	Supplementary outcome measure

defined by the ADNI consortium or comparable consortia. Given that MRI morphometric studies in ataxia yielded robust results, MRI protocols should include T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequences that allow morphometric analyses. Because multicenter studies using other imaging modalities are lacking, no recommendations concerning specific sequences or protocols can be given. As an outlook, multimodal integration could be the way to generate significant makers for follow-up combing several imaging and clinical tools.

Electrophysiology

Effects on peripheral nerves, dorsal columns, and pyramidal tracts can be quantitatively assessed by neurophysiological tools, such as nerve conductions studies, somatosensory evoked potentials, and motor evoked potentials. Multicenter approaches to longitudinal studies in ataxias are rare and face major challenges in standardization to assure reproducibility and intercenter comparability.

A brief summary of all conclusions is given in Table 3.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

B.K.P.: 1A, 1B, 1C, 3A, 3B
S.R.: 1B, 1C, 3B
A.D.: 1C, 3B
L.S.: 1C, 3B
T.A.: 1C, 3B
S.B.: 1C, 3B
L.M.B.: 1C, 3B
M.B.D.: 1C, 3B
P.G.: 1C, 3B
S.L.: 1C, 3B
C.M.: 1C, 3B
B.M.: 1C, 3B
M.P.: 1C, 3B
C.M.E.T.: 1C, 3B
D.T.: 1C, 3B
S.T.: 1C, 3B
J.B.S.: 1C, 3B
B.P.v.d.W.: 1C, 3B
T.K.: 1A, 3B

Disclosures

Funding Sources and Conflicts of Interest: The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 2012-305121 "Integrated European –omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases (NEURO-

doi:10.1002/mdc3.12315

MICS)." P.G. is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Center. The authors report no sources of funding and no conflicts of interest. S.L is supported by ANR grants Investissements d'Avenir (IHU-A-ICM ANR-10-IAIHU-06 and ANR-11-INBS-006)

Financial Disclosures for previous 12 months: A.D., L.S., and T.K. have recieved funding through NeurOmics, FP7 grant from the European Commission (no. 2012-305121). A.D. declares a pending patent: EP14187649 : « Quantitative assessment of cerebellar impairments » Sophie Tezenas du Montcel, Alexandra Durr (2 Octobre 2014). P.G. is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Center. P.G., C.M. received research funding from the European integrated project on spinocerebellar ataxias; European Union's FP6 Contract number LSHM-CT-2004-503304 (Project EFACTS: European Friedreich's Ataxia Consortium for Translational Studies); and from the Italian Ministry of Health (Grant RF-2011-02347420). S.B. recieved honoraria from Ipsen, Allergan, AbbVie, Novartis, and Licher and grants from the Jubiläumsfonds ÖNBTiroler ZukunftsstiftungFWF (translational). J.B.S., M.P., P.G, and S.B. received funding through EFACTS, FP7 grant from the European Commission (HEALTH-F2-2010- 242193). M.D. has received grants from the National Health and Medical Research Council, the Friedreich Ataxia Research Association, and the Friedreich Ataxia Research Alliance. M.D. is a consultant to Healthscope Pathology.

References

1. Lynch DR, Pandolfo M, Schulz JB, et al. Common data elements for clinical research in Friedreich's ataxia. *Mov Disord* 2013;28:190–195.
2. Kamlage B, Maldonado SG, Bethan B, et al. Quality markers addressing preanalytical variations of blood and plasma processing identified by broad and targeted metabolite profiling. *Clin Chem* 2014;60:399–412.
3. Teunissen CE, Tumani H, Bennett JL, et al. Consensus guidelines for CSF and blood biobanking for CNS biomarker studies. *Mult Scler Int* 2011;2011:246412.
4. Baker M. Biorepositories: building better biobanks. *Nature* 2012;486:141–146.
5. Vaught JB, Henderson MK. Biological sample collection, processing, storage and information management. *IARC Sci Pub*. 2011;163:23–42.
6. Betsou F, Lehmann S, Ashton G, et al. International Society for Biological and Environmental Repositories (ISBER) Working Group on Biospecimen Science. Standard preanalytical coding for biospecimens: defining the sample PREanalytical code. *Cancer Epidemiol Biomarkers Prev* 2010;19:1004–1011.
7. Saute JA, Donis KC, Serrano-Munuera C, et al. Ataxia rating scales—psychometric profiles, natural history and their application in clinical trials. *Cerebellum* 2012;11:488–504.
8. Trouillas P, Takayanagi T, Hallett M, et al. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. *J Neurol Sci* 1997;145:205–211.
9. Brandsma R, Spits AH, Kuiper MJ, et al. Childhood Ataxia and Cerebellar Group. Ataxia rating scales are age-dependent in healthy children. *Dev Med Child Neurol* 2014;56:556–563.
10. Schmitz-Hubsch T, Tezenas du Montcel S, Baliko L, et al. Reliability and validity of the International Cooperative Ataxia Rating Scale: a study in 156 spinocerebellar ataxia patients. *Mov Disord* 2006;21:699–704.
11. Cano SJ, Hobart JC, Hart PE, Korlipara LV, Schapira AH, Cooper JM. International Cooperative Ataxia Rating Scale (ICARS): appropriate for studies of Friedreich's ataxia? *Mov Disord* 2005;20:1585–1591.
12. Storey E, Tuck K, Hester R, Hughes A, Churchyard A. Inter-rater reliability of the International Cooperative Ataxia Rating Scale (ICARS). *Mov Disord* 2004;19:190–192.
13. Schmitz-Hubsch T, du Montcel S, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006;66:1717–1720.
14. Schmitz-Hubsch T, Fimmers R, Rakowicz M, et al. Responsiveness of different rating instruments in spinocerebellar ataxia patients. *Neurology* 2010;74:678–684.
15. Subramony SH, May W, Lynch D, et al. Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale. *Neurology* 2005; 64:1261–1262.
16. Kieling C, Rieder CR, Silva AC, et al. A neurological examination score for the assessment of spinocerebellar ataxia 3 (SCA3). *Eur J Neurol* 2008;15:371–376.
17. Jacobi H, Rakowicz M, Rola R, et al. Inventory of Non-Ataxia Signs (INAS): validation of a new clinical assessment instrument. *Cerebellum* 2013;12:418–428.
18. Assadi M, Leone P, Veloski JJ, Schwartzman RJ, Janson CG, Campellone JV. Validating an Ataxia Functional Composite Scale in spinocerebellar ataxia. *J Neurol Sci* 2008;268:136–139.
19. Schmitz-Hubsch T, Giunti P, Stephenson DA, et al. SCA Functional Index: a useful compound performance measure for spinocerebellar ataxia. *Neurology* 2008;71:486–492.
20. du Montcel ST, Charles P, Ribai P, et al. Composite cerebellar functional severity score: validation of a quantitative score of cerebellar impairment. *Brain* 2008;131(Pt 5):1352–1361.
21. Filipovic Pierucci A, Mariotti C, Panzeri M, et al.; EFACTS Study Group. Quantifiable evaluation of cerebellar signs in children. *Neurology*. 2015;84:1225–1232.
22. Schmahmann JD, Gardner R, MacMore J, Vangel MG. Development of a brief ataxia rating scale (BARS) based on a modified form of the ICARS. *Mov Disord* 2009;24:1820–1828.
23. Schule R, Holland-Letz T, Klimpe S, et al. The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. *Neurology* 2006;67(3):430–434.
24. Weyer A, Abele M, Schmitz-Hubsch T, et al. Reliability and validity of the scale for the assessment and rating of ataxia: a study in 64 ataxia patients. *Mov Disord* 2007;22:1633–1637.
25. Burk K, Malzig U, Wolf S, et al. Comparison of three clinical rating scales in Friedreich ataxia (FRDA). *Mov Disord* 2009;24:1779–1784.
26. Burk K, Schulz SR, Schulz JB. Monitoring progression in Friedreich ataxia (FRDA): the use of clinical scales. *J Neurochem* 2013;126(Suppl 1):118–124.
27. Friedman LS, Farmer JM, Perlman S, et al. Measuring the rate of progression in Friedreich ataxia: implications for clinical trial design. *Mov Disord* 2010;25:426–432.
28. Wilson CL, Fahey MC, Corben LA, et al. Quality of life in Friedreich ataxia: what clinical, social and demographic factors are important? *Eur J Neurol* 2007;14:1040–1047.
29. Cano SJ, Riazi A, Schapira AH, Cooper JM, Hobart JC. Friedreich's ataxia impact scale: a new measure striving to provide the flexibility required by today's studies. *Mov Disord* 2009;24:984–992.
30. Reetz K, Dogan I, Costa AS, et al. 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;14:174–182.
31. Burk K. Cognition in hereditary ataxia. *Cerebellum* 2007;6:280–286.
32. Hoche F, Seidel K, Brunt ER, et al. Involvement of the auditory brainstem system in spinocerebellar ataxia type 2 (SCA2), type 3 (SCA3) and type 7 (SCA7). *Neuropathol Appl Neurobiol* 2008;34:479–491.
33. Rub U, Farrag K, Seidel K, et al. Involvement of the cholinergic basal forebrain nuclei in spinocerebellar ataxia type 2 (SCA2). *Neuropathol Appl Neurobiol* 2013;39:634–643.
34. Almeida-Silva UC, Hallak JE, Junior WM, Osorio Fde L. Association between spinocerebellar ataxias caused by glutamine expansion and

doi:10.1002/mdc3.12315

psychiatric and neuropsychological signals—a literature review. *Am J Neurodegener Dis* 2013;2:57–69.

35. Klinke I, Minnerop M, Schmitz-Hubsch T, et al. Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3, and 6. *Cerebellum* 2010;9:433–442.
36. Schmitz-Hubsch T, Coudert M, Tezenas du Montcel S, et al. Depression comorbidity in spinocerebellar ataxia. *Mov Disord* 2011; 26:870–876.
37. Merk M, Ziegler W. MoDiaS—a PC-based system for routine acoustic speech analysis of neurogenic speech disorders. In: Maassen B, Groenen P, ed. *Pathologies of Speech and Language. Advances in Clinical Phonetics and Linguistics*. London: Whurr; 1999:315–321.
38. Brandauer B, Hermsdorfer J, Beck A, et al. Impairments of prehension kinematics and grasping forces in patients with cerebellar degeneration and the relationship to cerebellar atrophy. *Clin Neurophysiol* 2008;119:2528–2537.
39. Chan E, Charles P, Ribai P, et al. Quantitative assessment of the evolution of cerebellar signs in spinocerebellar ataxias. *Mov Disord* 2011;26:534–538.
40. Tezenas du Montcel S, Charles P, Goizet C, et al. Factors influencing disease progression in autosomal dominant cerebellar ataxia and spastic paraplegia. *Arch Neurol* 2012;69:500–508.
41. Diener HC, Dichgans J. Applications and uses of static and dynamic measurement of posture (posturography) [in German]. *Fortschr Neurol Psychiatr* 1988;56:249–258.
42. Bunn LM, Marsden JF, Voyce DC, Giunti P, Day BL. Sensorimotor processing for balance in spinocerebellar ataxia type 6. *Mov Disord* 2015;30:1259–1266.
43. Bunn LM, Marsden JF, Giunti P, Day BL. Training balance with opto-kinetic stimuli in the home: a randomized controlled feasibility study in people with pure cerebellar disease. *Clin Rehabil* 2015;29:143–153.
44. Ilg W, Synofzik M, Brotz D, Burkard S, Giese MA, Schols L. Intensive coordinative training improves motor performance in degenerative cerebellar disease. *Neurology* 2009;73:1823–1830.
45. Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. *Gait Posture* 2003;17:68–74.
46. Schniepp R, Wuehr M, Neuhaeusser M, et al. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. *Mov Disord* 2012;27:125–131.
47. Rochester L, Galna B, Lord S, Mhiripiri D, Eglon G, Chinnery PF. Gait impairment precedes clinical symptoms in spinocerebellar ataxia type 6. *Mov Disord* 2014;29:252–255.
48. Milne SC, Hocking DR, Georgiou-Karistianis N, Murphy A, Delatycki MB, Corben LA. Sensitivity of spatiotemporal gait parameters in measuring disease severity in Friedreich ataxia. *Cerebellum* 2014; 13:677–688.
49. Wessel K, Hermsdorfer J, Deger K, et al. Double-blind crossover study with levorotatory form of hydroxytryptophan in patients with degenerative cerebellar diseases. *Arch Neurol* 1995;52:451–455.
50. Velazquez Perez L, Sanchez Cruz G, Canales Ochoa N, et al. Electrophysiological features in patients and presymptomatic relatives with spinocerebellar ataxia type 2. *J Neurol Sci*. 2007;263:158–164.
51. Linnemann C, Tezenas du Montcel S, Rakowicz M, et al. Peripheral neuropathy in spinocerebellar ataxia type 1, 2, 3, and 6. The Cerebellum. 2015:1–9.
52. Anheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. *N Engl J Med* 2012;366:636–646.
53. Klockgether T, Schols L, Abele M, et al. Age related axonal neuropathy in spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD). *J Neurol Neurosurg Psychiatry* 1999;66:222–224.
54. Velazquez-Perez L, Rodriguez-Labrada R, Canales-Ochoa N, et al. Progression of early features of spinocerebellar ataxia type 2 in individuals at risk: a longitudinal study. *Lancet Neurol* 2014;13:482–489.
55. Velazquez-Perez L, Rodriguez-Labrada R, Canales-Ochoa N, et al. Progression markers of Spinocerebellar ataxia 2. A twenty years neurophysiological follow up study. *J Neurol Sci* 2010;290:22–26.
56. Baldarcara L, Currie S, Hadjivassiliou M, et al. Consensus paper: radiological biomarkers of cerebellar diseases. *Cerebellum* 2015;14:175–196.
57. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging* 2008;27:685–691.
58. Reetz K, Costa AS, Mirzazade S, et al.; axia Study Group Investigators. Genotype-specific patterns of atrophy progression are more sensitive than clinical decline in SCA1, SCA3 and SCA6. *Brain*. 2013;136 (Pt 3):905–917.
59. Guimaraes RP, D'Abreu A, Yasuda CL, et al. A multimodal evaluation of microstructural white matter damage in spinocerebellar ataxia type 3. *Mov Disord* 2013;28:1125–1132.
60. Bonilha da Silva C, Bergo FP, D'Abreu A, Cendes F, Lopes-Cendes I, Franca MC Jr. Dentate nuclei T2 relaxometry is a reliable neuroimaging marker in Friedreich's ataxia. *Eur J Neurol*. 2014;21:1131–1136.
61. Solbach K, Kraff O, Minnerop M, et al. Cerebellar pathology in Friedreich's ataxia: atrophied dentate nuclei with normal iron content. *Neuroimage Clin* 2014;6:93–99.
62. Adanyeguh IM, Henry PG, Nguyen TM, et al. In vivo neurometabolic profiling in patients with spinocerebellar ataxia types 1, 2, 3, and 7. *Mov Disord* 2015;30:662–670.
63. Jagust WJ, Bandy D, Chen K, et al. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement* 2010;6:221–229.
64. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
65. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–699.
66. Wechsler D. *Wechsler Abbreviated Scale of Intelligence*. New York: The Psychological Corporation (Harcourt Brace & Company); 1999.
67. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test: Second Edition*, 2nd ed. San Antonio, TX: Psychological Corporation; 2000.
68. Schmidt M. *Rey Auditory and Verbal Learning Test: A Handbook*. Los Angeles, CA: Western Psychology Services; 1996.
69. Trahan DE, Larrabee GJ. *Continuous Visual Memory Test: Professional Manual*. Odessa, FL: Psychological Assessment Resources; 1988.
70. Wechsler D. *Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV)*. San Antonio, TX: NCS Pearson; 2008.
71. Golden C, Freshwater S. *A Manual for the Stroop Color and Word Test*. Chicago, IL: Stoelting; 2002.
72. Patterson J. Controlled oral word association test. In: Kreutzer J, DeLuca J, Caplan B, eds. *Encyclopedia of Clinical Neuropsychology*. New York: Springer New York; 2011:703–706.
73. Heaton RK. *Wisconsin Card Sorting Test Manual*. Odessa, FL: Psychological Assessment Resources; 1981.
74. Ward T, Ridgeway V, Nimmo-Smith I. *The Test of Everyday Attention*. Bury St. Edmunds, UK: Thames Valley Test Company; 1994.
75. Kaplan EF, Goodglass H, Weintraub S. *The Boston Naming Test*. Boston, MA: E. Kaplan, H. Goodglass; 1978.
76. Kertesz A. *Western Aphasia Battery Revised*. San Antonio, TX: Harcourt Assessment; 2006.
77. Wechsler D. *WAIS-R Manual: Wechsler Adult Intelligence Scale—Revised*. New York: Psychological Corporation; 1981.
78. Benton AL, Hamsher KD, Varney NR, Spreen O. *Judgment of Line Orientation*. New York: Oxford University Press; 1983.
79. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory-II*. San Antonio TX: Psychological Corporation; 1996.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: SPREC Code Data elements (http://www.isber.org/?page=SPREC)

Examples of data elements describing the workflow of solid and fluidic sample processing.

doi:10.1002/mdc3.12315