Quantifiable evaluation of cerebellar signs in children

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ABSTRACT

Objective: To validate, examine the internal validity, and adapt to children the electronic version of the composite cerebellar functional severity (CCFS) score.

Methods: In this multicenter study, we compared the validated manual device with the new electronic version (n = 46) and analyzed its kinetics in 146 patients with Friedreich ataxia through the EFACTS (European Friedreich's Ataxia Consortium for Translational Studies) network, 77 patients with spinocerebellar ataxia, and 48 controls. We validated the CCFS in cerebellar ataxias in healthy children (n = 120) and children with Friedreich ataxia through the EFACTS network (n = 33).

Results: We showed that the electronic CCFS is a reliable replacement for the manual version (intraclass correlation coefficient: 0.98 [0.97–0.99]), and that the electronic CCFS is consistent when performed several times (0.92 [0.84–0.97]). Analysis of kinetics data showed an acceleration and irregularity that is not relevant compared with total speed. The CCFS was tested after modification in a population of patients with Friedreich ataxia between 8 and 19 years old, and showed similar values as adult patients with Friedreich ataxia (1.203 ± 0.125 vs 1.228 ± 0.167) and significantly higher values than controls of the same age (0.863 ± 0.042).

Conclusions: The electronic CCFS is a quantified measurement of cerebellar ataxia independent of age, usable in individuals aged from 7 to 80 years. The automated nature of the electronic test device makes it reproducible between operators and centers, as well as easy to use. ***Neurology*® 2015;84:1–8**

GLOSSARY

CCFS = composite cerebellar functional severity; **EFACTS** = European Friedreich's Ataxia Consortium for Translational Studies; **FRDA** = Friedreich ataxia; **SARA** = Scale for the Assessment and Rating of Ataxias; **SCA** = spinocerebellar ataxia.

The composite cerebellar functional severity (CCFS) score was developed as a quantitative tool to measure cerebellar severity independently from age[1] and has demonstrated its usefulness in epidemiologic studies, clinical trials, and patient follow-up.[2,3] It was validated in adults, and there are currently no quantifiable assessments of cerebellar signs available for children.

The CCFS is a combination of the time to perform 2 tasks, a 9-hole pegboard and a click test. Both tasks include a series of alternative movements: placing dowels and finger-pointing cycles. Since the first publication, the CCFS has undergone significant changes. An electronic version has been developed to facilitate administration and increase reliability and reproducibility. Using the electronic device, we can analyze the evolution of performance during the task with 3 main expected profiles of kinetics: slowing down due to fatigue, acceleration due to learning, or stable performance. In addition, the variability of

Supplemental data at Neurology.org

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performance during the task can be analyzed. These data allow us to assess the internal validity of the CCFS.

The objectives of the study were to validate the electronic CCFS, to examine its internal validity by analyzing the kinetics, and to extend its validity to children.

METHODS

Participants. Four different groups of individuals were enrolled from January 2011 to December 2012.

Group I: Validation of the electronic CCFS. We recruited 46 individuals in the genetics department of the Salpêtrière University Hospital and performed CCFS on both manual and electronic devices. There were 16 control subjects and 30 patients, including 25 patients with autosomal dominant spinocerebellar ataxia (SCA), 2 patients with familial spastic paraplegia, 2 patients with autosomal recessive cerebellar ataxia, and 1 patient with an unknown diagnosis.

Group II: CCFS kinetics. We used raw CCFS data from 271 adult individuals. We included 146 patients with Friedreich ataxia (FRDA) from university hospitals within the EFACTS (European Friedreich's Ataxia Consortium for Translational Studies) network,[4] 77 patients with SCA from the Genetics Department in the Salpêtrière University Hospital, and 48 controls (16 of them also participated in group I). Two or more measurements were available for 21 individuals.

Group III: CCFS in children. To evaluate the device in children, we included 120 healthy participants younger than 20 years in Milan and Paris in 2012.

Group IV: CCFS in patients with FRDA younger than 20 years. EFACTS recruited 33 children with FRDA from May 2011 to May 2012.

Standard protocol approvals, registrations, and patient consents. We obtained written informed consent according to the guidelines of ethical committees in each country from all patients in the EFACTS networks and through a longitudinal follow-up study, AOM 03059.

Data available. Age at examination, electronic CCFS scores, and clinical diagnosis were available for all participants. Manual CCFS scores were available for all participants from group I. Disease duration and clinical score (SARA: Scale for the Assessment and Rating of Ataxias) were available for all patients in group II and most patients in group IV. Raw CCFS data were available from all participants in groups II, III, and IV.

CCFS. The CCFS is a quantitative assessment initially developed and validated for use in SCA. It includes 2 functional tests for the dominant hand: the 9-hole pegboard test (the time needed to place dowels in 9 holes) and the click test (time needed to perform 10 finger-pointing cycles).[1] The time to perform each test is adjusted for the age of the individual to compute a score. Then both scores are combined to compute the CCFS score (see details in supplemental data on the *Neurology*® Web site at Neurology.org).

The manual CCFS consists of a wooden 9-hole pegboard and of a click test device, 2 switches separated by a distance of 39 cm. An attendant monitors the time to complete each test with the help of a stopwatch. The electronic CCFS is similar, but both pegboard and click test device are equipped with electronic sensors. These sensors automate the measurement of the time it takes to complete the entire task as well as the time between clicks and the time between the placements of 2 dowels (supplemental data).

The manual version of the CCFS, referred as "manual CCFS" was only analyzed for group I. In all other groups, the data are from the electronic device. In addition, we updated the formula to account for ages before 20 years. The expression "updated CCFS" refers to this updated version.

SARA. The SARA is a semiquantitative scale developed to assess functional impairments caused by ataxia, with values ranging from 0 (no ataxia) to 40 (most severe ataxia).[5]

CCFS kinetic data. We studied the kinetics of the electronic CCFS trials by computing a linear regression of the time between 2 clicks or dowel placements (period) in function of the number of clicks or dowel placements per trial per patient. The slope of that model, in milliseconds per click or per dowel placement, represented either acceleration (negative slope) or increased fatigue (positive slope). The residual variance, in milliseconds squared, represented period irregularities. The intercept, in milliseconds, represented the starting period.

Statistical analysis. We validated the electronic CCFS by calculating an intraclass correlation coefficient between the manual and the electronic CCFS in participants from group I.

We compared the CCFS kinetics between diagnostic groups using analysis of variance test, followed by pairwise t tests for significant analysis of variance. The slopes were compared to 0 using 1-sample t tests. We tested whether CCFS kinetic parameters were associated with disease duration and clinical severity using Pearson correlation coefficients. We assessed the consistency of measurements by calculating an intraclass correlation coefficient when several measurements were available for one participant.

To check the validity of the CCFS in children (younger than 20 years), we performed a regression model of the CCFS score against age. Because the CCFS is normalized for age, the slope should, in theory, be equal to 0. Since this was not the case, we computed new normalization algorithms for the click test and the pegboard test. We tested the slope of this updated CCFS against the age of the subjects, to check for independence between the updated CCFS and age.

Results were reported as mean ± SD, and regression analysis coefficients were reported as mean ± SE. All tests were 2-sided, and results were considered significant at the 5% threshold. The p values for pairwise t tests were corrected for multiple testing using the Holm method. Confidence intervals of the intraclass correlation coefficients were computed using a nonparametric bootstrap with the BCa (bias-corrected and accelerated) method (10,000 replicates). All analyses were performed in the R programming language, version 3.1.1, with the RStudio Integrated Development Environment.

RESULTS

Electronic CCFS validation. For the validation of the electronic CCFS, we included 46 individuals, 16 controls aged 24 to 64 years and 30 patients with various diseases aged 19 to 69 years (table 1, group I). The CCFS scores were normal for the controls (0.811 ± 0.033) for the manual CCFS and increased for the patients (1.056 ± 0.164). The differences between the electronic and the manual measures were small (0.005 [−0.017 to 0.028], paired t test, $p = 0.63$, for controls; −0.006

Table 1 Characteristics of the controls and patients included in the 4 groups

	Group							
	I		II			III	IV	
	Controls	Patients	Controls	SCA	FRDA	Controls	FRDA	
No.	16	30	48	77	146	120	33	
Age, y	38.2 ± 11.3 (24–64)	43.7 ± 15.3 (19–69)	44.7 ± 13.4 (19–74)	50.3 ± 13.1 (18–77)	35.8 ± 13.2 (18–76)	12.0 ± 3.1 (7.0–18.0)	15.6 ± 3.1 (8–19)	
Sex, F, n (%)	—	—	30 (63)	40 (52)	82 (56)	73 (61)	15 (45)	
e-CCFS	0.806 ± 0.045 (0.699–0.876)	1.062 ± 0.174 (0.768–1.450)	0.834 ± 0.048 (0.706–0.953)	1.112 ± 0.160 (0.839–1.588)	1.228 ± 0.167 (0.932–1.700)	0.863 ± 0.042 (0.782–0.990)[a]	1.203 ± 0.125 (0.969–1.504)[a]	
m-CCFS	0.811 ± 0.033 (0.745–0.868)	1.056 ± 0.164 (0.787–1.452)	—	—	—	—		
Disease duration, y	—	—	—	11.8 ± 7.6 (0–36)	15.6 ± 8.6 (2–49)	—	7.4 ± 3.3 (2–14)[b]	
SARA	—	—	—	16.4 ± 7.4 (4.5–36)	19.2 ± 8.6 (1.5–36)	—	16.5 ± 7.9 (5–31)	

Abbreviations: e-CCFS = composite cerebellar functional severity from the electronic device; FRDA = Friedreich ataxia; m-CCFS = composite cerebellar functional severity from the manual device; SARA = Scale for the Assessment and Rating of Ataxias; SCA = spinocerebellar ataxia.
Data are given as mean ± SD (minimum–maximum) unless otherwise indicated.
[a] Updated CCFS score.
[b] Data available for 27 patients.

[−0.015 to 0.003], paired t test, $p = 0.20$, for patients). The intraclass correlation coefficient between the manual and electronic CCFS was very good (0.98 [0.97–0.99]).

CCFS kinetics study (electronic device). For the study of CCFS kinetics, we included 271 individuals, 48 controls aged 19 to 74 years, 77 patients with SCA aged 18 to 77 years, and 146 patients with FRDA aged 18 to 76 years (table 1, group II). The CCFS scores were between 0.706 and 0.953 for the controls (0.834 ± 0.048) and increased for both patients with SCA (1.112 ± 0.160) and patients with FRDA (1.228 ± 0.167). SARA scores were also increased in patients with SCA (16 ± 7) and patients with FRDA (19 ± 9). Disease duration was 12 ± 8 years for patients with SCA and 16 ± 9 years for patients with FRDA.

We assessed differences in CCFS kinetics between diagnostic groups (table 2). Starting period given by the intercept was higher for patients with SCA and FRDA than for controls, for the click test ($p < 0.001$) and for the pegboard test ($p < 0.001$). Starting period was also higher in patients with FRDA than in patients with SCA for the click test ($p < 0.001$) and for the pegboard test ($p < 0.001$).

For the click test, acceleration, given by the slope, was significantly different from 0 and was negative, indicating an acceleration during the task, in controls and FRDA ($p < 0.001$) but not in SCA ($p = 0.27$). For the pegboard test, acceleration was significantly different from 0 for controls and patients with SCA ($p < 0.001$ and $p = 0.016$, respectively) but not for patients with FRDA ($p = 0.08$). However, this acceleration was not significantly different between diagnostic groups for click and pegboard tests. Acceleration (slope values) remained negligible compared with the starting period (intercept) values: from 250 to 750 times smaller for the click test and from 36 to 90 times smaller for the pegboard test.

Period irregularity, given by the residual variance, was higher for patients with SCA and FRDA than for controls, for the click test ($p < 0.001$) and for the pegboard test ($p = 0.015$ and $p < 0.001$, respectively). Period irregularity did not differ between FRDA and SCA for the click test ($p = 0.07$) but it was higher for patients with FRDA for the pegboard test ($p < 0.001$).

Starting period (intercept) and period irregularity (residual) were closely related ($r = 0.82$ [0.78, 0.86], $p < 0.001$, for click test; and $r = 0.76$ [0.71, 0.81], $p < 0.001$, for pegboard test), with participants with a longer starting period being more irregular (figure 1, A and B). Acceleration was significantly inversely associated with starting period ($r = -0.33$ [−0.44, −0.22], $p < 0.001$, for the click test; and $r = -0.50$ [−0.59, −0.41], $p < 0.001$, for the pegboard test); participants

Table 2 Electronic CCFS kinetics (group II)

Measure	Controls	SCA	FRDA	p Value[a]
Click test				
Intercept, ms	506 ± 108 (474-537); $p < 0.001$	1,198 ± 572 (1,068-1,328); $p < 0.001$	1,535 ± 748 (1,413-1,658); $p < 0.001$	<0.001
Slope, ms/click	−2.1 ± 3.8 (−3.2 to −1.0); $p < 0.001$	−1.6 ± 12.8 (−4.5 to 1.3); $p = 0.27$	−5.7 ± 16.9 (−8.5 to −3.0); $p < 0.001$	0.08
Residual variance, ms^2	61 ± 48 (47-75); $p < 0.001$	225 ± 174 (185-264); $p < 0.001$	274 ± 226 (237-311); $p < 0.001$	<0.001
Pegboard test				
Intercept, ms	1,319 ± 230 (1,252-1,386); $p < 0.001$	3,392 ± 2,392 (2,849-3,935); $p < 0.001$	5,437 ± 4,205 (4,749-6,125); $p < 0.001$	<0.001
Slope, ms/placement	−19 ± 33 (−28 to −9); $p < 0.001$	−66 ± 235 (−119 to −12); $p = 0.016$	−71 ± 498 (−153 to 10); $p = 0.08$	0.71
Residual variance, ms^2	287 ± 223 (222-352); $p < 0.001$	894 ± 1,126 (638-1,149); $p < 0.001$	1,584 ± 1,633 (1,317-1,852); $p < 0.001$	<0.001

Abbreviations: CCFS = composite cerebellar functional severity; FRDA = Friedreich ataxia; SCA = spinocerebellar ataxia.
Data are given as mean ± SE (95% confidence interval); p value for the 1-sample t test testing to 0 the parameter.
[a] The p value for the analysis of variance comparing the 3 groups.

with a longer starting period accelerated more during the test (figure 1, C and D). Acceleration was slightly associated with period irregularity for the click test ($r = -0.15$ [−0.26, −0.03], $p = 0.013$) but not for the pegboard test ($r = -0.05$ [−0.17, 0.07], $p = 0.39$) (figure 1, E and F).

Relations with clinical characteristics. For patients with SCA and FRDA, starting period was correlated with SARA score for both the click test and pegboard test ($r = 0.71$ [0.64, 0.76], $p < 0.001$, and $r = 0.63$ [0.55, 0.70], $p < 0.001$, respectively) and disease duration ($r = 0.41$ [0.29, 0.51], $p < 0.001$, and $r = 0.31$ [0.19, 0.43], $p < 0.001$). Period irregularity was also associated with disease duration and SARA score for both the click test ($r = 0.28$ [0.15, 0.39], $p < 0.001$, and $r = 0.58$ [0.48, 0.65], $p < 0.001$, respectively) and the pegboard test ($r = 0.36$ [0.24, 0.47], $p < 0.001$, and $r = 0.55$ [0.45, 0.63], $p < 0.001$, respectively). Acceleration was not significantly associated with either SARA score or disease duration, for both click test and pegboard test.

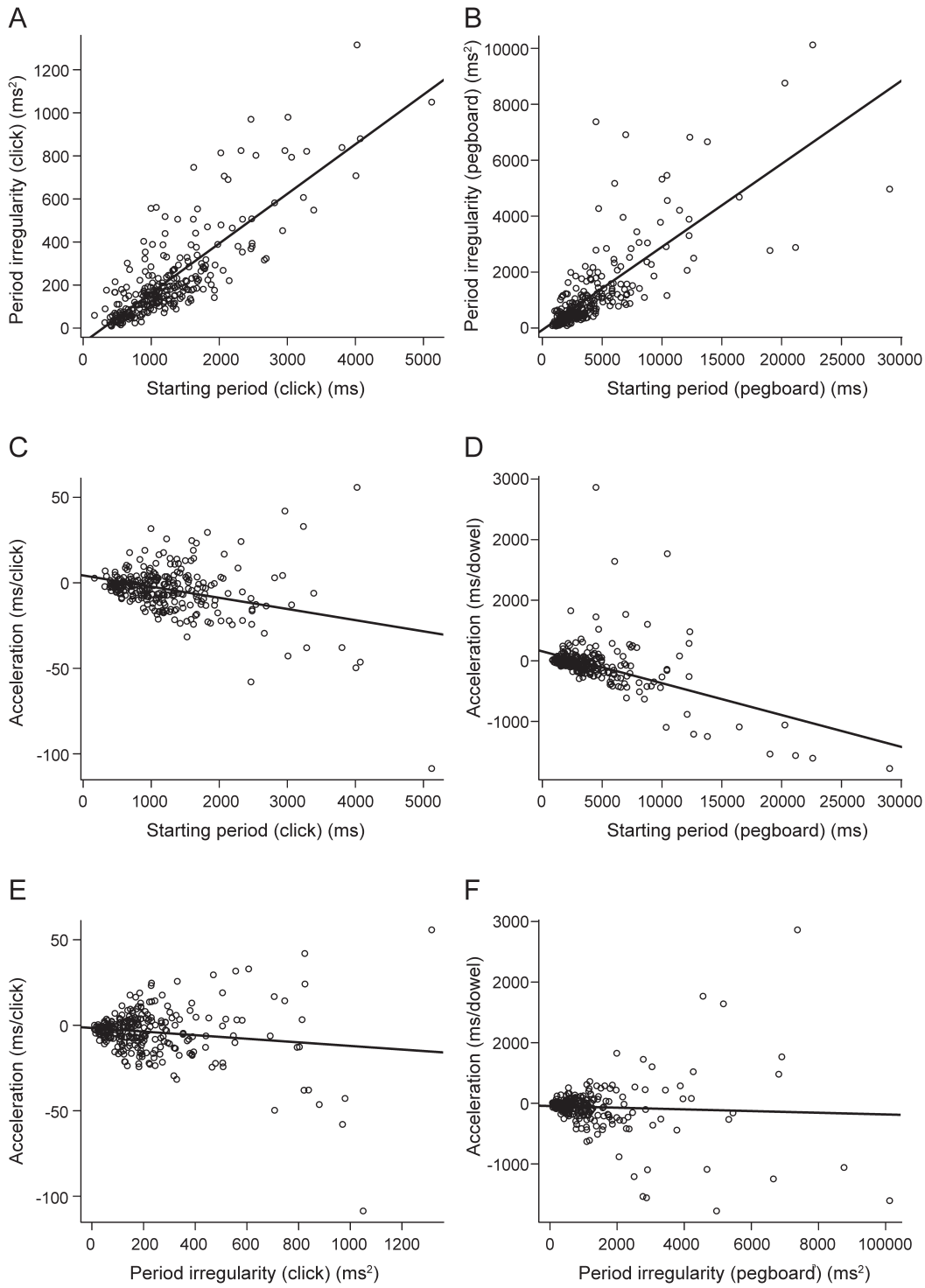
Test–retest reliability. Intraclass correlation coefficients, calculated for the 21 participants with at least 2 measurements, were high for click test starting period (0.85 [0.60, 0.99]), low for pegboard test starting period (0.33 [0.18, 0.45]), moderate for click test period irregularity (0.51 [0.27, 0.81]), low for pegboard test period irregularity (0.49 [0.21, 0.87]), and poor for click test and pegboard test acceleration (−0.65 [−0.91, −0.32] and −0.55 [−0.81, −0.25], respectively). The intraclass correlation coefficient for the CCFS was high (0.92 [0.84, 0.97]).

CCFS in children (electronic device). For the study of CCFS in individuals younger than 20 years, we included 120 controls aged 7 to 18 years (table 1, group III). CCFS scores ranged from 0.766 to 1.051 (0.890 ± 0.048). CCFS scores were significantly higher in children than in adult controls (children: 0.890 ± 0.048 vs adults: 0.834 ± 0.048, $p < 0.001$).

A regression analysis showed that before the age of 20 years, the CCFS was associated with age (slope = −0.009 [−0.011, −0.006], $p < 0.001$) (figure 2A). An analysis of the subscores of the CCFS showed that both the total click time and the total pegboard time were associated with age (slope = −0.29 [−0.38, −0.19], $p < 0.001$, and slope = −0.25 [−0.35, −0.15], $p < 0.001$, respectively).

By design, the CCFS is supposed to be independent of age. To correct this problem, we calculated the formula to normalize the click test and the

Figure 1 Relationship between kinetic measures for the click and pegboard tests

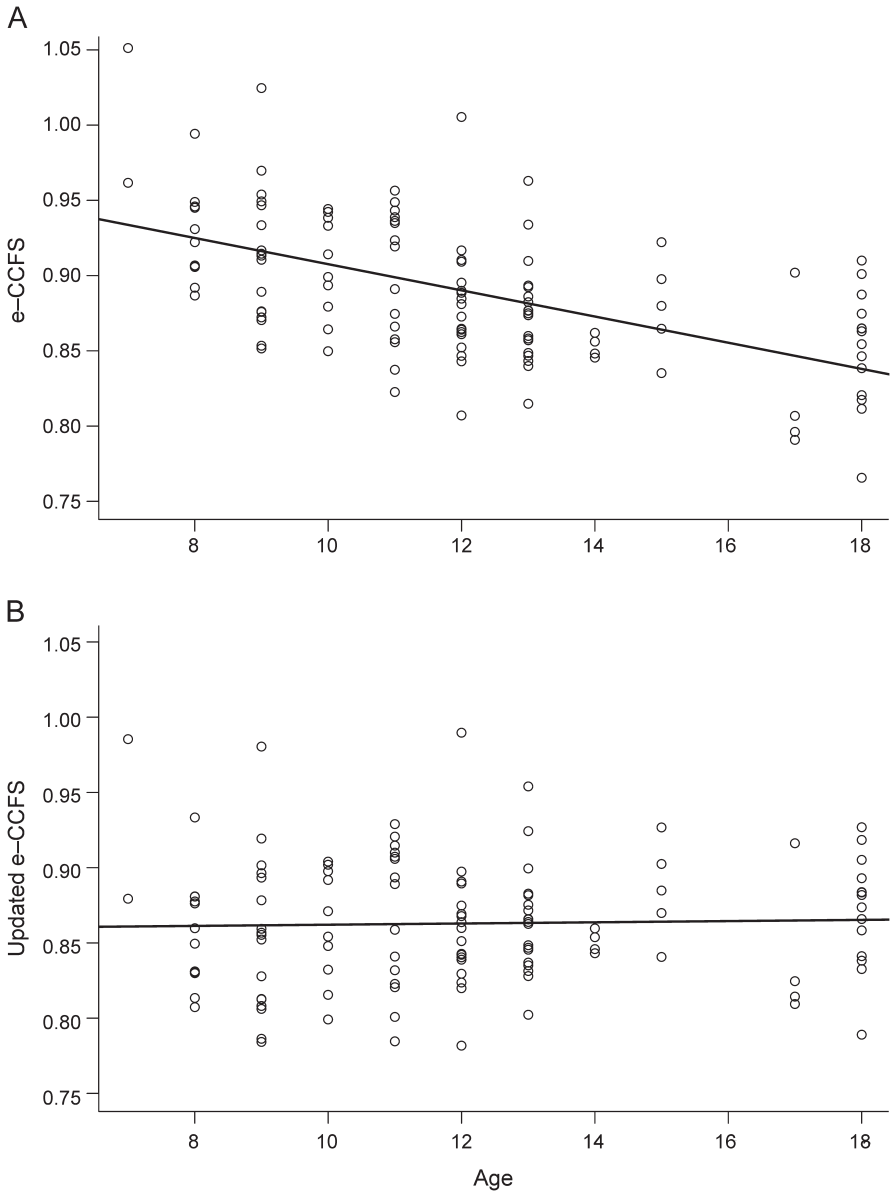


The click test data are given in panels A, C, and E, and the pegboard test data in panels B, D, and F.

pegboard test time below 20, with the 2 following constraints: (1) the updated CCFS should not change for individuals older than 20 to maintain comparability with previous studies; and (2) there should not be a strong difference in the normalization formula used just before or just after 20 to avoid artificial "jumps" in CCFS values around that age.

We performed a regression analysis on the sample of controls younger than 20 years to obtain the new normalization formula for the click test and the pegboard test, and constrained normalization at exactly 20 years

Figure 2 Relationship between age and the CCFS for children



Scatterplots of age and e-CCFS (A) and the updated e-CCFS (B) are presented with the linear regression line. In the updated version, independence between age and score is obtained. CCFS = composite cerebellar functional severity; e-CCFS = CCFS from the electronic device.

to be the same in the formula used before and after this age. The new normalization formulas were as follows:

$$\text{Z click} = \text{click time} - \left(0.03 \times \text{age}^2 - 1.14 \times \text{age} + 18.89\right) \text{ if age} < 20,$$

$$\text{Z click} = \text{click time} - \left(0.05 \times \text{age} + 8\right) \text{ if age} \geq 20,$$

$$\text{Z peg} = \text{pegboard time} - \left(-0.08 \times \text{age} + 12.62\right) \text{ if age} < 20,$$

$$\text{Z peg} = \text{pegboard time} - \left(0.002 \times \text{age}^2 - 0.16 \times \text{age} + 13.4\right) \text{ if age} \geq 20.$$

The published formula was then used to compute the CCFS (supplemental data).

After applying this updated formula, the CCFS was independent of age before 20 years (slope = 0.0004 [−0.002, 0.003], $p = 0.73$) (figure 2B) as already shown for adults. The updated CCFS score ranged from 0.782 to 0.990 (0.863 ± 0.042).

CCFS in children with FRDA. We used the updated formula to compute the CCFS score in a population of patients with FRDA aged 8 to 19 years (table 1, group IV). Updated CCFS scores ranged from 0.969 to 1.504 (1.203 ± 0.125), SARA scores from 5 to 31 (16.5 ± 7.9), and disease duration from 2 to 14 years

(7.4 ± 3.3). The updated CCFS scores were significantly higher than for young controls (group III) (1.203 vs 0.863, $p < 0.001$), but not significantly different from adult patients with FRDA (1.203 vs 1.228, $p = 0.43$).

DISCUSSION We demonstrated in this study that (1) the electronic CCFS is a reliable replacement for the manual version; (2) the CCFS is internally valid since the analysis of the kinetics data did not add additional information compared with the previously published CCFS data; (3) the CCFS can be used in children older than 7 years with minor corrections of the formula; and (4) the updated CCFS is valid in children with FRDA.

The existence of an electronic version of the CCFS facilitates the use of this test in a multicenter setting. The similarity of devices between centers may decrease a center effect that would be greater if the examinations were administrated by different staff personnel. Since the collection of data is automated, the test is reproducible and can be used by nonmedical investigators such as clinical trial assistants. Finally, the automated collection of data permits better transparency and reduces the risk of transcription errors. However, because we have shown concordance between the manual and the electronic CCFS, the manual CCFS can be performed in absence of the electronic device.

With the analysis of kinetic data, we obtained detailed insight into the measurements collected by the CCFS. Acceleration was negligible and not clinically relevant. Period irregularity seems to be nothing more than a proxy of starting period, and is of no interest on its own. It is thus justified to use the total test time as a whole, without considering kinetic factors.

In light of these new findings, the necessity for performing 10 finger-pointing cycles may be questioned, since all pertinent information may be captured with a single cycle. However, repetition of finger-pointing cycles decreases measurement variability, and thus gives a better approximation of a "true" patient score. This is especially important for patients with more severe disease, because we showed that variability increased when patients were slower.

Since many inherited as well as isolated cases of cerebellar ataxias can start in childhood, there has been a need for a tool to be used with this particular population in epidemiologic studies and in clinical trials. The other quantitative score developed for patients with dominant ataxia, SCAFI (SCA Functional Index), has been validated only in adults and its validity in patients with FRDA has not been tested.[6] Other ataxia rating scales, such as FARS (Friedreich's Ataxia Rating Scale)[7] and ICARS (International Cooperative Ataxia Rating Scale),[8] have already been widely used in children with FRDA.[9–15] However, these scales do not take into account that scores can change over time in healthy subjects during normal development. The updated CCFS is particularly valuable for use with children because it is independent from the age of the individuals. It could thus measure changes caused by the disease independently from changes caused by maturation of the cerebellar system.

The main limitation of the CCFS is the ability of the patient to perform the task. Patients with the most severe disease are not able to perform the tasks at all and thus cannot be evaluated using the CCFS.

The electronic CCFS is a measurement scale of ataxia independent of age that has good internal validity and is usable for individuals aged 7 to 80 years. It has proven to be a useful tool to evaluate and follow cerebellar signs in patients with dominant SCA and FRDA. The automated nature of the electronic test device makes it reproducible between operators and centers, and facilitates its use.

AUTHOR CONTRIBUTIONS

Antoine Filipovic Pierucci: conceptualized study, analyzed data, interpreted data, drafted manuscript, revised manuscript. Caterina Mariotti: conceptualized study, revised manuscript. Marta Panzeri: revised manuscript. Paola Giunti: revised manuscript. Sylvia Boesch: revised manuscript. Jörg Schulz: revised manuscript. Massimo Pandolfo: contribution of vital reagents/tools/patents, study coordination, obtaining funding, revised manuscript. Alexandra Durr: conceptualized study, interpreted data, drafted manuscript, revised manuscript. Sophie Tezenas du Montcel: designed study, analyzed data, interpreted data, drafted manuscript, revised manuscript.

ACKNOWLEDGMENT

The authors thank all participants for their patience, Fabien Lesne and Sandra Benaich for the technical assistance, and Sarah Boster for critical reading of the manuscript.

STUDY FUNDING

Supported by European Community grant FP7-HEALTH-F2-2010-242193: Patient Registry of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS); European Community grant FP6-2002-Lifeschihealth: European Integrated Project on Spinocerebellar Ataxias (EUROSCA): pathogenesis, genetics, animal models and therapy; and national French funding, Hospital Clinical Research Program (PHRC): Natural history, genetic bases and phenotype-genotype correlations in autosomal dominant spinocerebellar degenerations.

DISCLOSURE

A. Filipovic Pierucci reports no disclosures relevant to the manuscript. C. Mariotti received research support from the European Community grant FP7-HEALTH-F2-2010-242193 (EFACTS) and from the Associazione Italiana Sindromi Atassiche (AISA). M. Panzeri received research support from the European Community grant FP7-HEALTH-F2-2010-242193 (EFACTS). P. Giunti reports that this study was funded by EC FP7 (EFACTS) and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. S. Boesch received research support from the European Community grant FP7-HEALTH-F2-2010-242193 (EFACTS). J. Schulz has received funding for travel and/or speaker honoraria from GlaxoSmithKline, Merz Pharmaceuticals, Lilly, Novartis, Santhera Pharmaceuticals, Lundbeck Inc., Pfizer Inc., and Takeda Pharmaceutical Company Limited; serves as editor-in-chief for the *Journal of Neurochemistry* and an editorial board member of the *Journal of Neuroscience*, *Synapse*, and

eNeuro; and has received research support from the BMBF, EU (EFACTS), and the DFG. M. Pandolfo received research support from the European Community grant FP7-HEALTH-F2-2010-242193 (EFACTS), from the Friedreich's Ataxia Research Alliance (FARA), and from Repligen Corporation; has received honoraria from BioMarin and Voyager Therapeutics; and has received royalties from Athena Diagnostics. A. Durr received support from the European Community grants FP7-HEALTH-F2-2010-242193 (EFACTS) and FP6-2002-Lifescihealth (EUROSCA), and from French national funding (PHRC), RBM01-29; and reports a pending patent: Quantitative assessment of cerebellar impairments (EP14187649). S. Tezenas du Montcel reports a pending patent: Quantitative assessment of cerebellar impairments (EP14187649). Go to Neurology.org for full disclosures.

Received September 17, 2014. Accepted in final form December 1, 2014.

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