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Age of Onset: Can We Rely on Essential Tremor Patients to Report This? Data from a Prospective, Longitudinal Study

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Abstract

Background—Essential tremor (ET) is among the most prevalent neurological diseases. Age of onset, a key variable in neuroepidemiological and genetic research, is chiefly assessed by self-report rather than medical record review; the latter may be of little use. As a researcher, one wonders about the quality of this self-report. Is age of onset something which can be reproducibly self-reported by patients? There are few published data to aid researchers.

Methods—Age of onset was self-reported at two time points (baseline and follow-up) in 86 ET cases in a longitudinal epidemiological study in New York.

Results—The mean follow-up interval was 5.7 ± 2.5 (maximum = 14) years. Overall, agreement between the baseline and follow-up reports was high ($\rho = 0.85$, $p < 0.001$). Yet the difference (age of onset_{baseline} – age of onset_{follow-up}) ranged widely (from –47 to 32 years), and in one fifth of cases was ≥ 10 years. Greater agreement was associated with several clinical factors including age, medication use, embarrassment, depressive symptoms, cognitive test score and disease duration.

Conclusions—Differences in reported age of onset in ET may vary widely, and in up to one fifth of patients may be substantial. Investigators should approach these self-reports with caution.

Keywords

Essential tremor; Epidemiology; Age of onset; Clinical factors; Genetics

Introduction

Essential tremor (ET) is among the most common neurological diseases [1, 2]. In epidemiological studies, disease incidence and prevalence both increase with age [1–3].

Age, and more specifically age of onset, is important in numerous fundamental respects. First, in the ET literature, age of onset is at the center of a debate as to whether individuals who develop tremor in their seventh decade represent a group with a completely distinct disease entity sometimes referred to as ‘senile tremor’ or merely a group with older-onset ET [4, 5]. Second, in ET and other neurological disorders, age of onset is a major determinant of rate of progression, prognosis and risk of mortality [6–9]. Third, a wide range of genetic studies on neurological disorders stratify genetic risk based on age of onset, classifying patients as ‘early onset/younger onset’ versus ‘older onset’ [10–12]; thus an accurate appraisal of age of onset is critical. Finally, in neuroepidemiological research, in order to assess and then quantify the role of genetic and environmental risk factors which may influence disease risk or age of onset, one must ensure that age of onset itself is accurately reported [12, 13].

Age of onset in ET is chiefly assessed by self-report rather than medical record review; the latter may be of little use. As a researcher, one then wonders about the quality of this self-report. Is age of onset something that can be reproducibly self-reported by patients? The current analyses capitalize on a prospective, epidemiological study in which ET cases were assessed at two time points, and data on age of onset were collected at each time. We know of only one other pilot study that has addressed this reliability issue in ET [14]. There are no other published data to aid neuroepidemiologists.

Methods

Study Design and Subject Selection

ET cases were enrolled in a research study of the environmental epidemiology of ET at Columbia University Medical Center (CUMC). Baseline assessments took place between 2000 and 2009 [15, 16]. By design, ET cases were identified from several sources, the major ones being a computerized billing database of all ET patients who were seen once or more at the Neurological Institute of New York (CUMC), and advertisements to ET patients who were members of the International Essential Tremor Foundation. All cases had received a diagnosis of ET from their treating neurologist and were confined to a geographic area that was within 2 h driving distance of CUMC in New York, New Jersey and Connecticut [15, 16].

With their enrollment, each case signed a written informed consent form, approved by the CUMC Internal Review Board. Cases completed demographic and clinical questionnaires and underwent a standardized videotaped tremor examination, which included assessments of postural and kinetic tremors [17]. Each videotape was reviewed by a senior neurologist specializing in movement disorders (E.D.L.), who rated the severity of the arm tremor, and assigned a total tremor score (TTS, 0–36, maximum) [18] and confirmed the ET diagnosis in each case using published diagnostic criteria (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor, in the absence of Parkinson’s disease) [17, 19].

In April 2009, we began conducting follow-up assessments on ET cases, trying to give preference to the oldest cases first (i.e. those with the highest likelihood of loss to follow-up

due to mortality), and then using a random selection strategy. Upon reassessment, each case signed an informed consent form approved by the CUMC Internal Review Board. To date, we have reenrolled 86 of 376 ET cases. These 86 enrollees are similar to the larger group of 376 from which they were drawn in terms of baseline tremor severity (TTS, 17.9 ± 7.0 vs. 18.9 ± 7.2 , $t = 1.17$, $p = 0.24$), baseline tremor duration (23.2 ± 17.9 vs. 22.8 ± 18.6 years, $t = 0.18$, $p = 0.86$) and baseline age (65.3 ± 12.6 vs. 67.4 ± 15.4 years, $t = 1.18$, $p = 0.24$). During the follow-up assessment, ET cases again completed the baseline assessment, which on average had been performed 5.7 ± 2.5 (range = 2–14) years previously.

Study Evaluation

During the baseline and follow-up assessments, ET cases completed the same demographic and clinical questionnaires, which solicited demographic data (age, gender, race, years of education), clinical information regarding tremor (including duration, medication usage, the question ‘Do other people often tell you that you have a tremor’) and family history information. ET cases were classified as having a family history of tremor if they reported at least one first- or second-degree relative with ET or tremor. Patients were also asked, ‘How old were you when you first noticed the tremor?’

Tremor-related motor disability was evaluated with a brief 10-item version of a 36-item, validated tremor disability questionnaire [20]; self-reported ability to perform a range of motor activities was assessed (signing name, carrying a cup, dialing a telephone, using a key), with the possible score range from 0–100 (maximum disability). The Folstein Mini-Mental State Exam (MMSE) [21] was administered (range = 0–30, no impairment). Medical comorbidity was assessed using the Cumulative Illness Rating Scale (CIRS), in which the severity of medical problems (0 = none to 3 = severe) was rated in 14 body systems (e.g. cardiac, respiratory, renal) and a CIRS score was assigned (range = 0–42, maximal comorbidity) to each subject [22].

For the follow-up assessment, two additional assessments were added. First, the Center for Epidemiological Studies Depression Scale (CESD-10), a self-report 10-item screening questionnaire for depressive symptoms (range = 0–30, greater depressive symptoms) [23] was added. The CESD-10 has been shown to have good reliability and excellent sensitivity and specificity using a diagnosis of major depressive disorder as diagnosed using the *Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised, as the gold standard [24, 25].

In 2010, during the follow-up assessment period, the Essential Tremor Embarrassment Assessment (ETEA), a 14-item self-assessment scale for tremor-related embarrassment, was created [26] and then added to the follow-up assessment. The ETEA items are structured as a series of 14 statements, and the participant is asked to first provide a simple response (disagree or agree) and then to provide a more nuanced response (0- to 5-point Likert scale ranging from disagree = 0 to agree strongly = 5). The ETEA is administered by a health care provider or researcher, yet it collects data on the patient’s self-assessment of embarrassment. The sum of the simple responses yields an initial score (score A, range = 0–14) and the sum of the nuanced responses yields a second score (score B, range = 0–70), with higher scores indicating greater embarrassment [26].

At each evaluation, a standardized videotaped tremor examination, which included assessments of postural and kinetic tremors [17, 27], was performed. Each videotape was reviewed by a senior neurologist specializing in movement disorders (E.D.L.), who rated the arm tremor and assigned a TTS (0–36) [18].

Statistical Analyses

Statistical analyses were carried out using SPSS (version 18.0.2; Chicago, Illinois, Ill., USA).

The follow-up interval was calculated as the time that had elapsed in years between the baseline and follow-up assessments. The variable ‘age of onset difference’ was the difference in years between the age of onset reported at baseline and the age of onset reported at follow-up ($\text{age of onset}_{\text{baseline}} - \text{age of onset}_{\text{follow-up}}$); positive values indicated that the age of onset_{baseline} was higher than age of onset_{follow-up}, and negative values indicated the converse. A value of zero indicated that the same age of onset was reported at the two time intervals. The age of onset difference was also expressed as an absolute value: $|\text{age of onset difference}|$. Parametric tests were used, unless variables were not normally distributed (e.g. age of onset difference, $|\text{age of onset difference}|$). For completeness, agreement between age of onset_{baseline} and age of onset_{follow-up} was assessed using both Pearson’s correlation coefficient (ρ) and an intraclass correlation coefficient (ICC). For ICC, absolute agreement was assessed rather than consistency. We also examined whether any demographic or clinical variables were correlated with $|\text{age of onset difference}|$. Since the $|\text{age of onset difference}|$ was not normally distributed (Kolmogorov-Smirnov test = 2.18, $p < 0.001$), and the ICC assumes a normal distribution, a nonparametric approach (Spearman’s correlation coefficient, ρ) was used to assess this correlation.

Results

There were 86 ET cases (table 1). The mean age at the time of the baseline assessment was 65.3 ± 12.6 years. The mean follow-up interval was 5.7 ± 2.5 years (range = 2–14 years).

The age of onset_{baseline} ranged from 6 to 75 years (mean = 41.9 ± 18.7 years, median = 45 years). The age of onset_{follow-up} ranged from 6 to 80 years (mean = 41.5 ± 17.4 years, median = 45 years).

The age of onset difference ranged from –47 to 32 years (mean = -0.34 ± 10.18 years, median = 0.0 years) (fig. 1). The $|\text{age of onset difference}|$ ranged from 0 to 47 years (mean = 5.95 ± 8.24 years, median = 3.0 years). The $|\text{age of onset difference}|$ was 0 years in 19 (22.1%) cases, 1 year in 10 (11.6%) cases, 2 years in 11 (12.8%) cases and 5 years in a total of 57 (66.2%) of 86 cases. The $|\text{age of onset difference}|$ was 10 years in 18 (20.9%) cases.

Agreement between age of onset baseline and age of on-set_{follow-up} was assessed using both Pearson’s correlation coefficient (ρ) and an ICC; the respective values were $\rho = 0.85$ ($p < 0.001$) and ICC = 0.84 ($p < 0.001$), indicating a high level of agreement (fig. 2).

We examined whether any demographic or clinical variables were correlated with | age of onset difference | (table 2). These analyses revealed that greater | age of onset difference | was associated with a number of variables: older baseline age, answering ‘no’ to the question ‘has a doctor ever prescribed medication for your tremor’, lower Folstein MMSE score (i.e. more cognitive difficulty), lower CESD-10 score (i.e. fewer depressive symptoms) and lower ETEA scores (i.e. less embarrassment) (table 2). There was no correlation between the time that had elapsed in years between the baseline and follow-up assessments and the | age of onset difference | ($\rho = 0.03$, $p = 0.80$). We also examined whether any demographic or clinical variables were associated with age of onset difference rather than | age of onset difference |, and the results were similar, except that greater age of onset difference was found in cases with disease of longer baseline duration ($\rho = 0.33$, $p = 0.002$). In summary, greater reproducibility was found in ET cases who were (1) younger; (2) had been prescribed ET medications; (3) were more embarrassed by their ET; (4) had greater depressive symptoms; (5) had fewer cognitive issues and, possibly, (6) had ET of shorter duration.

Discussion

In this study of 86 ET cases, the follow-up interval was as long as 14 years in some cases; on average it was nearly 6 years. Overall, agreement between the age of onset reported at baseline and at follow-up was high ($\rho = 0.85$, $p < 0.001$). However, the difference (age of onset_{baseline} – age of onset_{follow-up}) ranged widely (from –47 to 32 years), and in 18 (20.9%) cases was ≥ 10 years. Some subgroups of patients may be more reliable than others: greater reproducibility was associated with several clinical factors including age, medication use, embarrassment, depressive symptoms, cognitive test score and disease duration.

Age of onset is a key determinant in genetic and epidemiological studies of neurological disorders. Age of onset in ET is chiefly assessed by the patient’s self-report rather than medical record review; the latter may be of little documentary value. As a researcher, one then wonders about the quality of this self-report. Our data, while showing a high level of overall reproducibility, also show that investigators should approach these self-reports with caution; differences in reported age of onset in ET may vary widely, and in up to one fifth of patients may be substantial. What other strategies may investigators use? One approach would be to examine handwriting samples (e.g. signatures, letters) retrospectively, as an objective record of the possible onset and development of tremor. Yet this approach would be challenging and would not determine onset in ET cases with preserved handwriting (e.g. cases with tremor while pouring and eating but not while writing) or in ET cases whose main sign is head rather than arm tremor. Another approach would be to use collateral history from family members. Both approaches serve to supplement the data collected by self-report with other forms of data and underscore the limitations of self-report data.

We previously wrote a short report on test-retest reliability of age of onset in ET [14], but that report differs from the current one in a number of substantive ways. First, the prior report sampled only 24 patients, who were evaluated after 2 years [14]. The current sample size, $n = 86$, is approximately 4 times larger. Second, the prior study sampled cases only after 2 years [14], thereby increasing the likelihood of high test-retest reliability. The current

study resamples cases up to 14 years later (mean = 5.7 years, median = 5.0 years). Perhaps most important is that the prior study sampled ET cases who were primarily of low education (mean = 10 years) in a socioeconomically disadvantaged setting [14], whereas the current sample is a group of ET cases of higher educational attainment seen in a typical treatment setting. Finally, the prior study examined only a limited number of factors that were correlated with reliability of reported age of onset [14], whereas the current study examines a full complement of such factors; it is the sample size of the current study that allows for such analyses. To date, we have conducted follow-up assessments in 86 ET cases. It will be interesting to see whether the trends noted here are maintained in a larger follow-up sample of ET cases.

Reliability of reported age of onset has been examined in Parkinson's disease, comparing the subject's medical records, a family history questionnaire and a subject history questionnaire [28]; the findings report high reliability ($r = 0.94$), but the test-retest reliability has not been examined. Medical records would not be of much value in ET, as the issue of tremor often does not become part of the clinical dialogue [3].

In summary, differences in reported age of onset in ET may vary widely, and in up to one fifth of patients may be substantial. Investigators should approach these patient reports with caution. Some subgroups of patients may be more reliable than others.

References

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord.* 2010; 25:534–541. [PubMed: 20175185]
2. Benito-Leon J, Bermejo-Pareja F, Morales JM, Vega S, Molina JA. Prevalence of essential tremor in three elderly populations of central Spain. *Mov Disord.* 2003; 18:389–394. [PubMed: 12671944]
3. Benito-Leon J, Bermejo-Pareja F, Louis ED. Incidence of essential tremor in three elderly populations of central Spain. *Neurology.* 2005; 64:1721–1725. [PubMed: 15911798]
4. Louis ED, Wendt KJ, Ford B. Senile tremor. What is the prevalence and severity of tremor in older adults? *Gerontology.* 2000; 46:12–16. [PubMed: 11111223]
5. Deuschl G, Elble R. Essential tremor – neurodegenerative or nondegenerative disease towards a working definition of ET. *Mov Disord.* 2009; 24:2033–2041. [PubMed: 19750493]
6. Hely MA, Morris JG, Reid WG, O'Sullivan DJ, Williamson PM, Broe GA, Adena MA. Age at onset: the major determinant of outcome in Parkinson's disease. *Acta Neurol Scand.* 1995; 92:455–463. [PubMed: 8750110]
7. Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muentner MD. Effect of age at onset on progression and mortality in Parkinson's disease. *Neurology.* 1989; 39:1187–1190. [PubMed: 2771070]
8. Louis ED, Agnew A, Gillman A, Gerbin M, Viner AS. Estimating annual rate of decline: prospective, longitudinal data on arm tremor severity in two groups of essential tremor cases. *J Neurol Neurosurg Psychiatry.* 2011; 82:761–765. [PubMed: 21436230]
9. Louis ED, Benito-Leon J, Ottman R, Bermejo-Pareja F. A population-based study of mortality in essential tremor. *Neurology.* 2007; 69:1982–1989. [PubMed: 18025392]
10. Kamboh MI, Barmada MM, Demirci FY, Minster RL, Carrasquillo MM, Pankratz VS, Younkin SG, Saykin AJ, Sweet RA, Feingold E, Dekosky ST, Lopez OL. Genome-wide association analysis of age-at-onset in Alzheimer's disease. *Mol Psychiatry.* 2011 E-pub ahead of print.
11. Gan-Or Z, Bar-Shira A, Mirelman A, Gurevich T, Giladi N, Orr-Urtreger A. The age at motor symptoms onset in LRRK2-associated Parkinson's disease is affected by a variation in the MAPT locus: a possible interaction. *J Mol Neurosci.* 2012; 46:541–544. [PubMed: 21898123]

12. Tan EK, Peng R, Wu YR, Wu RM, Wu-Chou YH, Tan LC, An XK, Chen CM, Fook-Chong S, Lu CS. LRRK2 g2385r modulates age at onset in Parkinson's disease: a multi-center pooled analysis. *Am J Med Genet B Neuropsychiatr Genet.* 2009; 150B:1022–1023. [PubMed: 19152345]
13. Harwood DG, Kalechstein A, Barker WW, Strauman S, St George-Hyslop P, Iglesias C, Loewenstein D, Duara R. The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the age of onset in Alzheimer's disease. *Int J Geriatr Psychiatry.* 2010; 25:511–518. [PubMed: 19750560]
14. Louis ED, Schonberger RB, Parides M, Ford B, Barnes LF. Test-retest reliability of patient information on age of onset in essential tremor. *Mov Disord.* 2000; 15:738–741. [PubMed: 10928590]
15. Louis ED, Zheng W, Jurewicz EC, Watner D, Chen J, Factor-Litvak P, Parides M. Elevation of blood beta-carboline alkaloids in essential tremor. *Neurology.* 2002; 59:1940–1944. [PubMed: 12499487]
16. Louis ED, Jiang W, Pellegrino KM, Rios E, Factor-Litvak P, Henchcliffe C, Zheng W. Elevated blood harmaline (1-methyl-9H-pyrido[3,4-b]indole) concentrations in essential tremor. *Neurotoxicology.* 2008; 29:294–300. [PubMed: 18242711]
17. Louis ED, Ottman R, Ford B, Pullman S, Martinez M, Fahn S, Hauser WA. The Washington Heights-Inwood Genetic Study Of Essential Tremor: methodologic issues in essential-tremor research. *Neuroepidemiology.* 1997; 16:124–133. [PubMed: 9159767]
18. Louis ED, Ford B, Bismuth B. Reliability between two observers using a protocol for diagnosing essential tremor. *Mov Disord.* 1998; 13:287–293. [PubMed: 9539343]
19. Louis ED, Ford B, Lee H, Andrews H, Cameron G. Diagnostic criteria for essential tremor: a population perspective. *Arch Neurol.* 1998; 55:823–828. [PubMed: 9626774]
20. Louis ED, Barnes LF, Wendt KJ, Albert SM, Pullman SL, Yu Q, Schneier FR. Validity and test-retest reliability of a disability questionnaire for essential tremor. *Mov Disord.* 2000; 15:516–523. [PubMed: 10830418]
21. Folstein MF, Folstein S, McHugh PR. 'Minimental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:129–138. [PubMed: 1202204]
22. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc.* 1968; 16:622–626. [PubMed: 5646906]
23. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med.* 1994; 10:77–84. [PubMed: 8037935]
24. Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies – Depression Scale and the Geriatric Depression Scale. *Arch Intern Med.* 1997; 157:449–454. [PubMed: 9046897]
25. Irwin M, Artin KH, Oxman MN. Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). *Arch Intern Med.* 1999; 159:1701–1704. [PubMed: 10448771]
26. Traub RE, Gerbin M, Mullaney MM, Louis ED. Development of an essential tremor embarrassment assessment. *Parkinsonism Relat Disord.* 2010; 16:661–665. [PubMed: 20869901]
27. Louis ED, Agnew A, Gillman A, Gerbin M, Viner AS. Estimating annual rate of decline: prospective, longitudinal data on arm tremor severity in two groups of essential tremor cases. *J Neurol Neurosurg Psychiatry.* 2011; 82:761–765. [PubMed: 21436230]
28. Reider CR, Halter CA, Castelluccio PF, Oakes D, Nichols WC, Foroud T. Reliability of reported age at onset for Parkinson's disease. *Mov Disord.* 2003; 18:275–279. [PubMed: 12621630]

Fig. 1.

The variable 'age of onset difference' was the difference in years between the age of onset reported at baseline and the age of onset reported at follow-up ($\text{age of onset}_{\text{baseline}} - \text{age of onset}_{\text{follow-up}}$); positive values indicated that the age of onset_{baseline} was higher than age of onset_{follow-up}, and negative values indicated the converse. A value of zero indicated that the same age of onset was reported at the two time intervals. The age of onset difference ranged from -47 to 32 years (mean = -0.34 ± 10.18 years, median = 0.0 years).

Fig. 2.
Scatter plot of age of onset_{baseline} vs. age of onset_{follow-up}.

Table 1

Baseline demographic and clinical characteristics of 86 ET cases

Age, years	65.3±12.6
Female	43 (50.0)
White race	82 (95.3)
Education, years	16.2±2.6
Age of tremor onset, years	41.9±18.7
Tremor duration, years	23.2±17.9
TTS	17.9±7.0
Has a doctor ever prescribed medication for your tremor?	
Yes	52 (60.5)
No	34 (39.5)
Daily ET medication	38 (44.2)
Do other people often tell you that you have a tremor?	
Yes	65 (75.6)
No	21 (24.4)
Family history of ET or tremor	53 (61.6)
Tremor disability questionnaire score	48.0 (25.8)
Folstein MMSE score	28.8±1.5
CESD-10 score ^a	6.4±4.5
ETEA ^{a,b}	
Score A	5.9±3.7
Score B	19.6±16.1
CIRS score	5.3±3.5

Values are either means ± standard deviation or numbers with percentages in parentheses.

^aEvaluation performed at follow-up rather than baseline.

^bBased on n = 60 rather than 86.

Table 2

| Age of onset difference |: association with baseline clinical characteristics in 86 ET cases

Characteristics	Correlation (ρ) between clinical characteristic and age of onset difference or age of onset difference within strata defined by the clinical characteristic ^a
Age, years	$\rho = 0.33$, $p = 0.002$
Sex	
Male	6.7 ± 7.0 (3.0)
Female	6.2 ± 9.4 (2.0)
	Mann-Whitney = 0.44, $p = 0.66$
Race	
White	6.0 ± 8.4 (3.0)
Nonwhite	5.8 ± 3.9 (5.5)
	Mann-Whitney = 0.86, $p = 0.39$
Education, years	$\rho = -0.08$, $p = 0.50$
Age of tremor onset, years	$\rho = 0.14$, $p = 0.19$
Tremor duration, years	$\rho = 0.10$, $p = 0.34$
TTS	$\rho = -0.02$, $p = 0.87$
Has a doctor ever prescribed medication for your tremor?	
Yes	4.9 ± 7.1 (2.0)
No	7.5 ± 9.6 (5.0)
	Mann-Whitney = 2.12, $p = 0.03$
Daily ET medication	
Yes	6.7 ± 8.3 (3.5)
No	5.3 ± 8.2 (3.0)
	Mann-Whitney = 1.14, $p = 0.26$
Do other people often tell you that you have a tremor?	
Yes	5.5 ± 7.0 (3.0)
No	7.2 ± 11.4 (4.0)
	Mann-Whitney = 0.58, $p = 0.56$
Family history of ET or tremor	
Yes	6.0 ± 8.9 (3.0)
No	5.9 ± 7.2 (3.0)
	Mann-Whitney = 0.35, $p = 0.72$
Tremor disability questionnaire score	$\rho = -0.15$, $p = 0.18$
Folstein MMSE score	$\rho = -0.34$, $p = 0.002$
CESD-10 score ^b	$\rho = -0.24$, $p = 0.029$
ETEA ^{b,c}	
Score A	$\rho = -0.34$, $p = 0.009$
Score B	$\rho = -0.34$, $p = 0.009$
CIRS score	$\rho = 0.04$, $p = 0.72$

^a This column shows the correlation (Spearman's ρ) between a clinical characteristic (e.g. CIRS score) and | age of onset difference |, or the mean $\pm$ SD (median) | age of onset difference | in strata defined by the clinical characteristic (e.g. | age of onset difference | in males vs. females).

^b Evaluation performed at follow-up rather than baseline.

^c Based on n = 60 rather than 86.