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Familial vs. Sporadic Essential Tremor: What Patterns Can One Decipher in Age of Onset?

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Abstract

Background—Essential tremor (ET) is a very prevalent neurological disease. Although familial and sporadic ET are assumed to have different age at onset distributions, no detailed study of this question has been carried out.

Methods—Using a carefully-characterized sample of 376 ET cases (232 [61.7%] familial) enrolled in a clinical-epidemiological study, we contrasted the age of onset distributions in familial vs. sporadic ET.

Results—Familial ET had a lower age at onset distribution, regardless of current age. The majority (71 [86.6%] of 82) childhood onset ET cases were familial rather than sporadic. Additionally, onset of ET occurred after age 40 in a majority of cases (125 [53.9%] of 232 with

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Competing Interests

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familial ET and 118 [81.9%] of 144 with sporadic ET), and in approximately one-quarter to one-half of cases, after age 60 years.

Conclusions—The age of onset of ET differs between familial and sporadic ET and furthermore, is variable within each of these groups. Childhood onset ET is usually familial, and the small number of identified exceptions could be due to *de novo* mutations. Understanding the heterogeneity in onset age will provide insights into the nature of underlying etiological and patho-biological processes, about which little is presently known.

Keywords

essential tremor; epidemiology; genetics; familial; sporadic; age of onset

Introduction

Although essential tremor (ET) is highly heritable [1-4], numerous ET cases do not have an identified family history [1, 2]. This observation, as well as others, indicates that environmental factors are also likely to play a role in the etiology of this disease [5-9]. Surprisingly, few if any clinical differences between familial and sporadic ET have been identified. One possible exception is age of onset: the two forms of ET are commonly assumed to differ with respect to age of onset, with earlier onset in the familial than in the sporadic form [10-12]. However, no detailed study has been carried out of the age of onset distributions in the familial vs. sporadic ET. Using a carefully-characterized sample of nearly 400 ET cases enrolled in a clinical epidemiological study, we contrasted the distributions of age of onset in familial vs. sporadic ET, to identify distinct patterns of age of onset. Understanding the heterogeneity in age of onset will provide insights into the nature of the underlying etiological and patho-biological processes, about which so little is presently known.

Methods

Participants

ET cases were enrolled in a study of environmental risk factors for ET at Columbia University Medical Center (CUMC) [13]. Hence, they were not enrolled based on the presence vs. absence of family history of ET. Upon enrollment, a trained tester obtained written informed consent, approved by the CUMC Institutional Review Board, from all participants. ET cases were identified from two primary sources: a computerized billing database of all ET patients who were seen at least once at the Center for Parkinson's Disease and Other Movement Disorders at CUMC over the past 5 years, and the International Essential Tremor Foundation (IETF) [13]. IETF members who lived in the New York metropolitan area were mailed advertisements and volunteered as participants [13, 14]. All enrollees had received diagnoses of ET from their treating neurologists and lived within a 2-hour driving distance of CUMC [13, 14]. After enrollment, all diagnoses were confirmed using published diagnostic criteria, as outlined below [13, 14].

Clinical Evaluation

Each case underwent an in-person evaluation that included a series of demographic and clinical questionnaires. Age of onset was defined as the self-reported age at which the individual first noted tremor. A prior study indicated that this age is reliably reported by ET cases [15]. Each case was asked whether he or she had one or more relatives with ET or tremor and, if so, to provide additional demographic and clinical information on each affected relative.

Each case also underwent a 20-minute videotaped neurological examination, which included an assessment of postural tremor, five tests of kinetic tremor, and assessments of head (neck), voice and jaw tremors [13]. Each videotaped examination was reviewed by E.D.L., who rated the severity of postural and kinetic arm tremors (range = 0 – 3) using a reliable and valid clinical rating scale, assigning a total tremor score (range 0 - 36) [13]. Diagnoses of ET were re-confirmed by E.D.L. based on the available data using Washington Heights Inwood Genetic Study of Essential Tremor (WHIGET) criteria (moderate or greater amplitude kinetic tremor [tremor rating ≥ 2] during three or more tests or a head tremor, in the absence of Parkinson's disease, dystonia or another cause) [13]. These diagnostic criteria for ET were developed for a population-based genetic study and, based on data from approximately 2,000 normal (non-diseased controls), the criteria carefully specify the specific examination maneuvers during which tremor should be present and the severity of tremor that should be evident during these maneuvers to distinguish normal from ET. The WHIGET criteria have been shown to be both reliable [16] and valid [17], have been used by tremor investigators in the United States and internationally [18-27].

Definitions

Familial ET (ET_F) was defined using both liberal and conservative criteria. Using liberal criteria, ET_F was the presence, by the proband's report, of at least one first- or second-degree relative with "ET" or "tremor"; sporadic ET (ET_S) was defined as the absence of at least one such relative. Using conservative criteria, ET_F was the presence, by the proband's report, of at least one first- or second-degree relative with "ET"; sporadic ET (ET_S) was defined as the absence of at least one such relative.

Analyses

Analyses were initially performed using the liberal definition for ET_F and then repeated using the conservative definition of ET. As in prior studies, childhood onset ET was defined as age 18 or younger [28]. As age of onset was not normally distributed (Kolmogorov-Smirnov test, p-value <0.001), a non-parametric test (Mann-Whitney test) was used when comparing groups by age of onset. Several of our analyses/tables also took current age into consideration, as current age and age of onset are highly correlated.

Results

There were 388 ET cases, of whom 376 (97%) provided information on age of onset and were included in the analysis (Table 1). ET_F was identified in 232 (61.7%) cases using the liberal definition and 117 (31.1%) cases using the conservative definition. The current age of

ET_F was similar to that of ET_S: median = 71.0 for ET_F using liberal definition vs. 71.0 for ET_S (Mann-Whitney test = 1.24, p = 0.22), and median = 71.0 for ET_F using conservative definition vs. 71.0 for ET_S (Mann-Whitney test = 0.09, p = 0.93).

We plotted age by age of onset, comparing ET_F (liberal definition) to ET_S (Figure 1). Several patterns were evident:

1. Overall, the age of onset of ET_F cases was younger than that of ET_S (i.e., note the downward shift in the distribution of red squares relative to blue circles in Figure 1). The mean ± standard deviation age of onset was 39.1 ± 22.2 [median = 40.0 years] for ET_F vs. 53.9 ± 19.8 [59.0 years] for ET_S (Mann-Whitney z = 6.13, p < 0.001).
2. In general, at each current age, the mean age of onset of ET_F cases was lower than that of ET_S cases (Table 2 and Figure 2).
3. Among all childhood onset (age of onset ≤18 years, N = 82) cases, 71 (86.6%) had familial as opposed to sporadic ET (Figure 1, Table 3).
4. Childhood onset ET was not always familial – 11 (13.4%) of 82 cases with onset ≤18 years had ET_S (Figure 1, Table 3). Conversely, 11 (7.6%) of 144 ET_S cases had an age of onset that was ≤18 years.
5. Age at onset occurred ≥40 years in majority of both familial (54%, N = 125) and sporadic (82%, N = 118) cases (Figure 1, Table 3).
6. ET_F seemed to have two peaks in age of onset (see Table 3 and two clusters of red squares in Figure 1): a childhood peak (≤18 years) that comprised 71 (30.6%) cases and an older peak (≥ 40 years) that comprised 125 (53.9%) cases (Figure 1). The remaining 36 (15.5%) cases were between ages 19 and 39 years.
7. Age at onset occurred at age 60 or older in a significant proportion of both familial (22.8%, N = 53) and sporadic (48.6%, N = 70) cases (Figure 1, Table 3).

The findings using the conservative definition of ET_F were similar to those presented above, with similar patterns as noted above in 1 – 7 (data not shown).

One possible explanation for apparently younger age at onset in familial ET is that ET_F cases are more aware of their own tremor than are sporadic cases, because they have relatives with tremor. That is, even if the actual age at onset is the same in both groups, familial ET cases may report a younger age of onset because of greater awareness of their tremor. To explore this possibility, we performed a secondary analysis in which we stratified ET_F cases into those who reported having affected relatives in preceding generations (e.g., grandparents, parents, aunts, or uncles) vs. those who reported affected relatives only in the same or younger generations (e.g., siblings, children) (Figure 3). In general, at each current age, the age of onset of ET_F cases in the latter group (with affected relatives only in the same or younger generations) remained younger than that of ET_S cases (Figure 3). This suggests that the observed difference in age of onset between ET_F and ET_S is not solely the result of reporting bias.

Discussion

Familial ET is widely believed to have an earlier age onset than sporadic ET, but no detailed analysis of the distributions of age of onset has been done. In this study, we found a number of patterns.

Age of onset varied widely within both forms of ET; however, in general, the age of onset of ET_F cases was statistically significantly younger than that of ET_S cases. Curiously, childhood onset was rare in ET_S but was common in ET_F. Yet this dearth of childhood onset ET_S cases did not account entirely for the observed younger age of onset of ET_F cases than ET_S cases. On closer inspection (Figure 2, Table 2), one can see that at each current age, the age of onset of ET_F cases was lower than that of ET_S cases. Hence, having a genetic predisposition for ET not only increases disease risk [1], but it also seems to lower the age of disease onset.

In ET_F but not ET_S, there seemed to be two peaks in age of onset, a young peak and an older peak. In ET_S, by contrast, while there were some young-onset cases, there was no young onset peak. This suggests that the genetic predisposition results in an early onset form of disease during childhood. Thus, the genetic predisposition not only increases disease risk, and lowers age of onset at each age across the age spectrum, as discussed above, but it also results in a childhood onset form of the disease. Why some cases of ET_F begin in childhood whereas others do not begin until elderly life, is not clear, but could be related to the nature of the underlying susceptibility gene or genes as well as their combination with environmental factors.

A small number, 7.6%, of ET_S cases had childhood onset ET. These cases had no apparent family history. One explanation is that they did not correctly recall their age of onset, misattributing it to a younger age. Another explanation is they may have had affected relatives about which they were unaware. Alternatively, they may have had a genetic form of ET, but had no affected relatives due to reduced penetrance or variable expressivity. A final possibility is that their disease was triggered by an early, unidentified environmental exposure or that the basis for the tremor, if genetic, was due to a *de novo* mutation.

Despite a younger age at onset distribution of $ET_{F,}$ cases continued to arise even after age 60 years; indeed, these cases accounted for nearly 1 in 4 ET_F cases. These data suggest that the presence of variable expressivity.

Overall, the data paint a picture of a disease for which, even in its familial form, there is a broad range of disease onset, with cases arising from the first decade of life all the way to the ninth decade. Hence, there seem to be an array of forces ranging from those that push onset at a very early age (i.e., even during early childhood) (e.g. rare highly penetrant mutations) to those whose influence on disease expression seems muted until advanced age (“uncommon” risk factors).

The current study had a number of limitations. First, our study utilized patients from a single cohort and it would be of value to extend these studies to additional cohorts. Second, in some cases, age of onset can be mis-remembered, so it is possible that some of our data on

age of onset lack precision. Third, we asked our cases to self-report the presence of a family history but did not examine their immediate or extended families. This, too, could have resulted in some misclassification of ET_F as ET_S and vice versa.

The study also had several strengths. First, the large sample of nearly 400 ET cases provided sufficient clinical observations to be able to detect a range of clinical patterns. Second, all cases were diagnosed with ET using stringent research criteria. Third, we also considered in our analyses alternative definitions of ET_F.

In summary, the age of onset of ET differs between ET_F and ET_S and furthermore, is variable within each of these groups. Understanding the sources of this heterogeneity will provide some insight into the nature of underlying etiological and patho-biological processes, about which so little is presently known.

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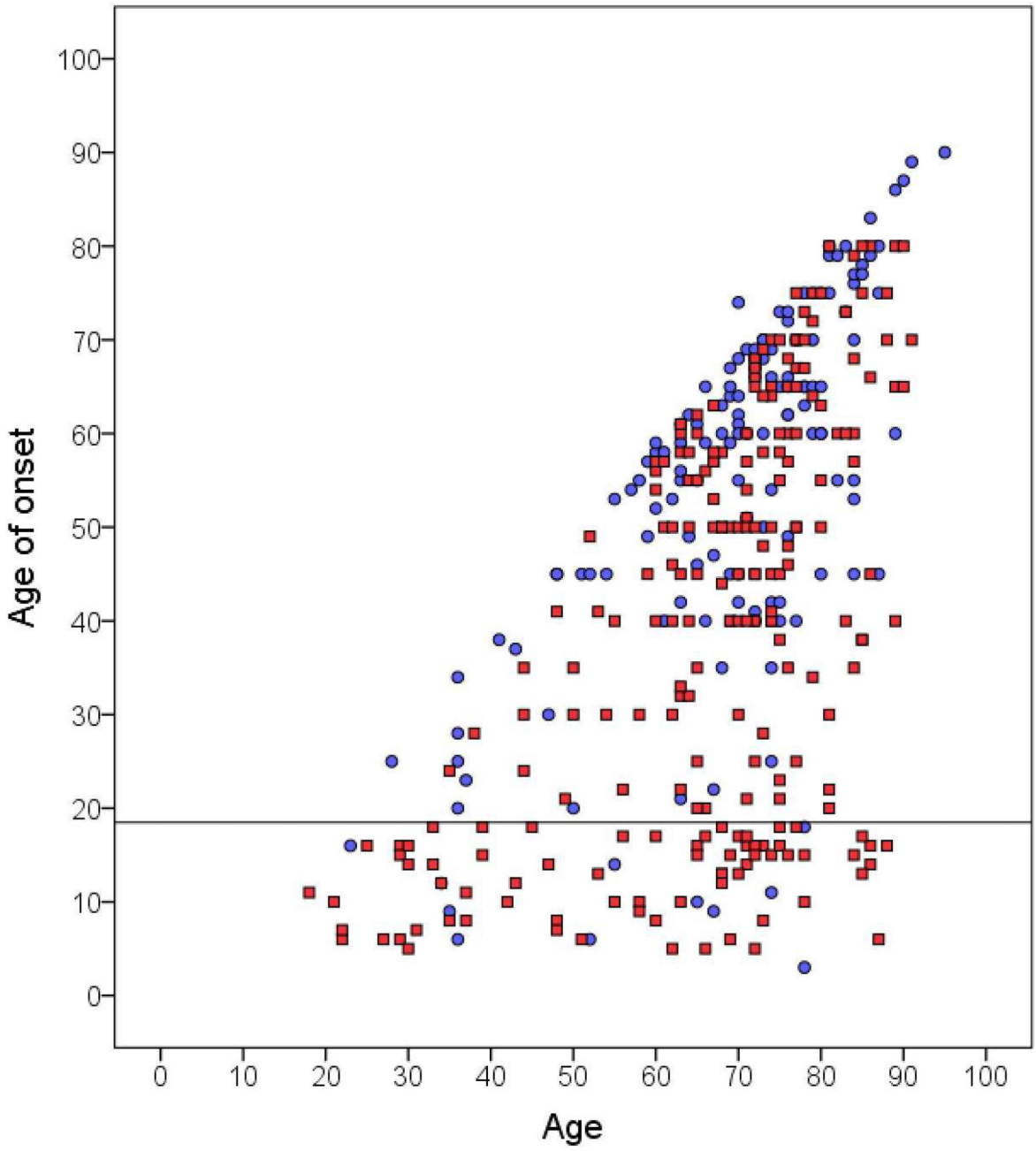

Figure 1.

Current age in years (X axis) by age of onset in years (Y axis) in ET_F (red squares) and ET_S (blue circles). Childhood onset cases (age at onset ≤18 years) appear below the horizontal line.

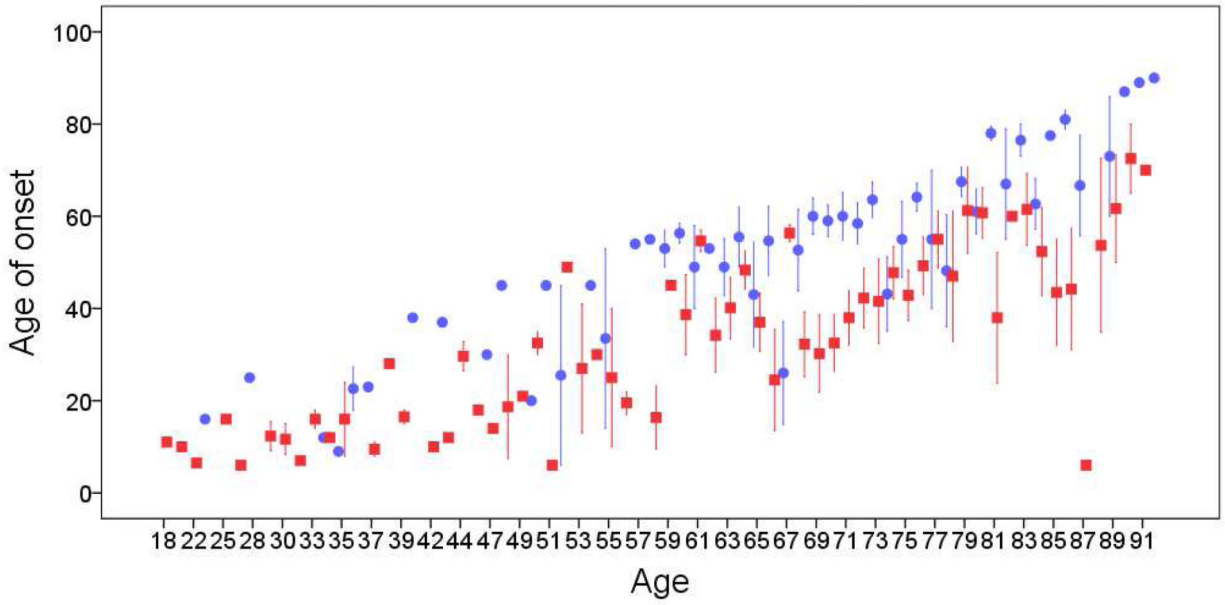

Figure 2.

Current age in years (x axis) by age of onset in years (y axis) of ET_F cases (red squares) vs. ET_S cases (blue circles). Circles and squares represent mean age of onset at each current age and bars represent 1 standard error.

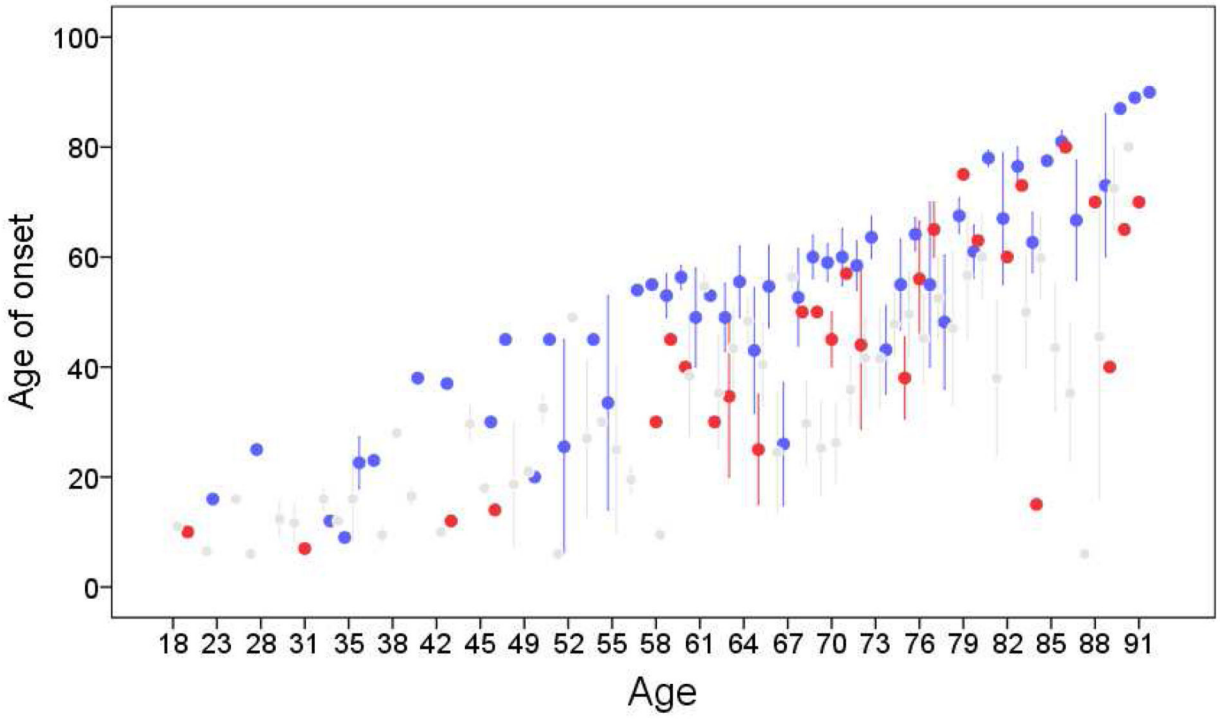

Figure 3.

Current age in years (x axis) by age of onset in years (y axis). Red circles are ET_F cases whose affected relatives are in the same generation or in a younger generation than the proband. Gray circles are ET_F cases whose affected relatives are in preceding generations. Blue circles are ET_S cases (blue circles). Circles represent means and each bar represents 1 standard error.

Table 1

Demographic and clinical features of 376 ET cases

Demographic and clinical features	Familial ET (n = 232)	Sporadic ET (n = 144)	All Cases (n = 376)
Current age in years	66.6 ± 15.8 Median = 71	68.9 ± 14.0 Median = 71	67.5 ± 15.1 Median = 71
Female gender	124 (53.4)	72 (50.0)	196 (52.1)
Education in years	15.4 ± 3.6	14.7 ± 4.1	15.1 ± 3.8
Total tremor score *	19.5 ± 7.2	17.6 ± 7.2	18.8 ± 7.2
Tremor duration in years *	27.5 ± 19.2	15.0 ± 14.9	22.8 ± 18.7
Age of tremor onset in years *	39.1 ± 22.2	53.9 ± 19.8	44.7 ± 22.5
Currently taking medication for tremor *	139 (59.9)	65 (45.1)	204 (54.3)

All values are means ± standard deviations or proportions (percentages).

* $p < 0.05$ (familial ET vs. sporadic ET).

Table 2

Age of onset by current age stratum in ET_F vs. ET_S

Current age stratum (years)	n	Age of onset (years, ET_F) [1]	n	Age of onset (years, ET_S) [1]	Significance [2]
<25	4	8.5 ± 2.4 [8.5]	1	16 (n = 1)	NA
25 – 29	5	11.8 ± 5.3 [15.0]	1	25 (n = 1)	NA
30 – 34	7	12.3 ± 4.7 [14.0]	1	12 (n = 1)	NA
35 – 39	7	16.0 ± 7.8 [15.0]	7	20.7 ± 10.1 [23.0]	p = 0.38
40 – 44	5	22.2 ± 11.1 [24.0]	2	37.5 ± 0.7 [37.5]	p = 0.095
45 – 49	6	18.2 ± 12.5 [16.0]	3	40.0 ± 8.7 [45.0]	p = 0.048
50 – 54	7	29.1 ± 15.1 [30.0]	5	32.2 ± 18.2 [45.0]	p = 0.64
55 – 59	8	22.9 ± 14.1 [19.5]	6	47.0 ± 16.4 [53.5]	p = 0.01
60 – 64	28	42.1 ± 17.0 [48.0]	14	51.8 ± 11.1 [55.5]	p = 0.04
65 – 69	32	36.8 ± 19.6 [42.0]	18	48.4 ± 18.6 [57.0]	p = 0.025
70 – 74	44	41.0 ± 19.7 [45.0]	33	56.3 ± 15.0 [61.0]	P < 0.001
75 – 79	39	49.7 ± 20.5 [55.0]	23	58.2 ± 18.4 [65.0]	p = 0.081
80 – 84	19	53.4 ± 20.7 [60.0]	18	66.8 ± 12.2 [71.5]	p = 0.049
≥85	21	50.0 ± 21.2 [65.0]	12	77.4 ± 13.0 [79.5]	p = 0.001

NA = not applicable

[1] All values are means ± standard deviations [medians].

[2] Mann-Whitney test comparing age of onset in ET_F vs. ET_S.

Table 3

Number (proportion) of ET_F vs. ET_S cases in each age of onset stratum

Age of onset stratum (years)	ET_F (n = 232)	ET_S (n = 144)
By 5-year age of onset stratum		
<5	0 (0.0)	1 (0.7)
5 - 9	19 (8.2)	4 (2.8)
10 – 14	21 (9.1)	4 (2.8)
15 – 18 [1]	31 (13.4)	2 (1.4)
19 – 24 [1]	12 (5.2)	5 (3.5)
25 – 29	5 (2.2)	4 (2.8)
30 – 34	11 (4.7)	2 (1.4)
35 – 39	8 (3.4)	4 (2.8)
40 – 44	17 (7.3)	11 (7.6)
45 – 49	14 (6.0)	15 (10.4)
50 – 54	18 (7.8)	8 (5.6)
55 – 59	23 (9.9)	14 (9.7)
60 – 64	16 (6.9)	19 (13.2)
65 – 69	15 (6.5)	21 (14.6)
70 – 74	11 (4.7)	10 (6.9)
75 – 79	6 (2.6)	12 (8.3)
80 – 84	5 (2.2)	4 (2.8)
≥85	0 (0.0)	4 (2.8)
By larger age of onset stratum		
≤18	71 (30.6)	11 (7.6)
19 - 39	36 (15.5)	15 (10.4)
40 - 59	72 (31.0)	48 (33.3)
≥ 60	53 (22.8)	70 (48.6)

Percentages are column percentages.

[1] These two age strata were modified slightly in order to better present data for childhood onset ET (i.e., onset ≤ 18 years).