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Topography of essential tremor

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ABSTRACT

Introduction: Topography of tremor manifestations is poorly investigated in essential tremor. The present study explores the prevalence and clinical correlates of head and/or voice tremor in essential tremor.
Methods: Out of a prospectively designed registry of 972 patients, 884 patients with definite and probable essential tremor had complete information on tremor localization. Demographic and clinical characteristics were compared among four subgroups: group A (without head or voice tremor, $n = 619$), B (with head but without voice tremor, $n = 155$), C (with voice but without head tremor, $n = 47$), and D (with both head and voice tremor, $n = 63$).
Results: In our patients, total prevalence of tremor was 24.7% for head, 12.4% for voice and 7.1% for the combination of head and voice. Logistic regression analyses showed that female gender is strongly associated with head tremor, which was confirmed by an additional meta-analysis. Severe hand tremor was the only factor associated with voice tremor. Both female gender and severe hand tremor increase the odds for having the combination of head and voice tremor. For males, hand tremor severity is significantly increased among those with head and voice tremor alone and in combination, but for females only for the combination. Patients with both head and voice tremor have more frequent involvement of legs and other localizations and are less responsive to β-blockers.
Conclusions: Female gender and severe hand tremor may increase the odds of head and/or voice tremor in essential tremor. The association of hand tremor severity with midline tremor is stronger for males than females.

1. Introduction

Essential tremor (ET) is a common tremor disorder affecting about 1–5% of the population above the age of 60 years [1]. Emerging evidence indicates that ET is not a single entity but a group of diseases with clinical and etiological heterogeneity [2]. It has not yet been clarified whether ET is caused by neurodegeneration or abnormal neuronal oscillation in the cerebello-thalamo-cortical circuit [3,4]. There is no biomarker reflecting disease severity or progression. Research on disease subtypes may yield better insights into the underlying disease mechanism and therapeutic strategy of ET [5,6].

The clinical hallmark of ET is an involuntary postural and kinetic tremor affecting mainly the hands and arms [7–9]. Often, head and voice are also affected in ET, as described in several previous reports (Supplementary Table 1) [10–19]. Neuroimaging studies found that ET cases with head tremor presented with more cerebellar atrophy [20,21], especially in the vermis of the anterior lobe. A recent pathological study found that patients with head and voice tremors had more Purkinje cell axonal swellings with torpedo formation in the cerebellar vermis [22]. These findings suggest that head and voice tremor may represent distinct subtypes in ET.

The objective of this study was to explore the prevalence and clinical correlates of head and/or voice tremor in ET by comparing demographic and clinical characteristics among subgroups of patients with head and/or voice tremor in a large prospective patient registry.

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2. Methods

2.1. Patients

Patients with ET were recruited prospectively within a regional cross-sectional study of the Department of Neurology at the University Hospital Schleswig Holstein, Germany between 2001 and 2013. Detailed information can be found in our previous report [6]. The flow diagram of the study population is shown in Supplementary Fig. 1. Briefly, we examined 1137 tremor patients, and diagnosed 972 with definite or probable ET according to the consensus criteria proposed by the Tremor Investigation Group (TRIG) [7]. All tremor patients were examined according to a standard protocol and tremor localizations were determined by one of five movement disorder specialists. Isolated head tremor without clinically visible hand tremor ($n = 6$) and cases with missing data on tremor localizations ($n = 88$) were excluded in this study. We included ET patients with bilateral hand tremor and known status of head and voice tremor conditions ($n = 884$) in the final analysis. Based on head and voice tremor conditions, we defined four subgroups: group A (without head or voice tremor, $n = 619$), B (with head tremor but without voice tremor, $n = 155$), C (with voice tremor but without head tremor, $n = 47$), and D (with both head and voice tremor, $n = 63$). The study was approved by the local ethical committee, and written informed consent was obtained from each participant.

2.2. Clinical characteristics

We collected general clinical information including age at examination, gender, age at disease onset, disease duration, tremor localizations, alcohol response and family history. Tremor severity was measured by Archimedes spiral rating (ASR) and Fahn-Tolosa-Marin (FTM) scale, which are widely used for measuring tremor in ET [23]. ASR was evaluated with Bain criteria on a 10-point scale [24]. FTM scale consists of 3 parts: FTM A assesses examiner-reported tremor localization/severity, FTM B evaluates examiner-reported ability to perform specific motor tasks, and FTM C assesses patient-reported functional disability resulting from tremor [25]. A higher score in ASR, FTM A, FTM B and FTM C, corresponds to a more severe tremor. As previously reported, tremor progression was calculated by dividing tremor severity (ASR and FTM B) by disease duration [6]. Hand tremor severity was expressed as ASR and as the sum score of hand items of the FTM A subscale. Self-reported treatment response to tremor medication was collected and analyzed with regard to the different tremor conditions. In our clinic, primidone is usually prescribed up to doses of 500 mg, and propranolol up to doses of 180 mg depending on side effects, with gradual increment from a low initial dosage.

We also performed a meta-analysis on the relationship between female gender and the occurrence of head and voice tremor in ET. We searched PUBMED for relevant papers in English language published between 1992 and 2016. The keywords were: "essential tremor", "head tremor" and "voice tremor". We included studies which met the following criteria: i) Clinical diagnosis of ET made by a movement disorder specialist; ii) ET patients with and without head or voice tremor were identified in the same study; iii) The sample size was $\geq$100 individuals.

2.3. Statistical analysis

Statistical analyses were performed utilizing SPSS (version 23.0 for Windows). GraphPad Prism (version 5.0 for Windows) was used for plotting graphics, and Review Manager (version 5.3) was used for the meta-analysis [26]. We used mean and standard deviation (SD) for numerical variables (age at examination, etc.) with normal distribution; median and interquartile range (IQR, 25th-75th percentile) for those with skewed distributions. To compare categorical data among groups, we applied the chi-square test or Fisher's exact test. We analyzed the continuous variables by one-way analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test, depending on whether the data were normally distributed or not. For clinical characteristics with a significant p-value for the global test, each of the three subgroups B, C and D was separately compared to group A. P-values for these three group comparisons were adjusted using the Bonferroni method.

We fitted binary logistic regressions for each of the three subgroups B, C and D separately and together (B + C + D) versus group A to identify associated variables (eg. age, gender, disease duration, onset age, hand tremor severity) with head and/or voice tremor in ET. To prevent potential collinearity, the Forward Stepwise (conditional) method was used. We defined late-onset ET as disease onset beyond the age of 45 years [6] and severe hand tremor as having an ASR > 5 score based on the mean value in our data. Age at examination (median value = 67 years) and disease duration (median value = 20 years) were dichotomized by their median values for binary logistic regression analyses. To validate our results, additional regression models were examined, in which age at exam, age at onset, and disease duration were treated as continuous variables.

For the fixed effect meta-analysis, we calculated pooled odds ratios (OR) and 95% confidence intervals (CI) of all identified studies and included our samples as well.

In all analyses, a two-tailed p-value < 0.05 was considered statistically significant.

3. Results

3.1. Prevalence of tremor localizations

The tremor localizations in our patients were hands ($n = 884$, 100% by definition of ET), head ($n = 218$, 24.7%), voice ($n = 110$, 12.4%), legs ($n = 71$, 8.0%) and others ($n = 52$, 5.9%). 7.1% ($n = 63$) of patients suffered from both head and voice tremor. Tremor in other body parts included tongue ($n = 38$), face ($n = 19$) and trunk ($n = 4$). In line with earlier reports, head and voice tremor were the second and third most frequently involved body parts in ET in the present study (Supplementary Table 1).

3.2. Clinical correlates

We compared several clinical characteristics separately between the four groups (Table 1). They showed that female gender was significantly more frequently represented in ET patients with head tremors (group B and D), compared to patients with neither head nor voice tremor (group A). Patients with voice tremor (group C and D) were older at examination. There is a trend that patients with both head and voice tremor (group D) had a longer disease duration at the time of examination ($p = 0.091$). No differences in age at onset, alcohol responsiveness or positive family history for ET could be identified across the four groups. Tremor progression did not significantly differ among the four subgroups. Patients with both head and voice tremor (group D) had more frequently additional leg tremor (30% vs. 6%) and tremor of other localizations (32% vs. 2%). Their response to β-blockers was significantly lower compared to group A.

Patients with voice tremor (group C) and those with head and voice tremor (group D) had more severe hand tremor (ASR and FTM A hand items) and tremor related disability (FTM B and FTM C), compared with those without head or voice tremor (group A)