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Tremor and Other Hyperkinetic Movements

Brief Report

Early Head Tremor in Essential Tremor: A Case Series and Commentary

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Abstract

Background: Classically, the onset of head tremor in essential tremor (ET) patients follows that of hand tremor, such that there is a somatotopic spread of involved areas. Here we present a series of seven self-reportedly "unaffected" relatives of ET cases. These seven were clinically asymptomatic and had normal levels of arm tremor on examination, yet each evidenced a transient head wobble on examination. We estimate the prevalence of this phenotype within the two studies from which cases were ascertained.

Methods: ET cases and their self-reportedly affected and unaffected relatives, enrolled in two family studies, underwent a medical history and videotaped neurological examination.

Results: In seven self-reportedly "unaffected" relatives, a transient and subtle head wobble was seen, always during sustained phonation, speech, or reading aloud. Total tremor score (a measure of arm tremor) ranged from 5 to 12 (i.e., mild tremor within the range of normal). The prevalence of this phenotype of early head tremor was 3.7% in one study and 23.1% in the other.

Discussion: We present a series of seven individuals who had early head tremor in an evolving transition state from normal to ET. These cases raise a number of broad clinical, phenotypic, and pathophysiological issues about ET.

Keywords: Essential tremor, clinical, head tremor, phenotype

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Introduction

Head (i.e., neck) tremor is a common feature in patients with essential tremor (ET), occurring in 10.9–18.0% of ET cases in population-based studies[1–3] and as many as 60.6% of cases in more selected samples such as brain repositories.[4] Indeed, apart from the arms, the head is the region most commonly affected by tremor in patients with ET. Additional interest in head tremor in ET is based on the observation, from neuroimaging studies, that the underlying brain changes may differ from those seen in ET patients who do not have head tremor.[5,6]

Classically, the onset of head tremor in patients with ET is supposed to follow that of hand tremor, such that there is a typical somatotopic spread of involved areas.[7–12] As a corollary, isolated head tremor (i.e., head tremor in the absence of arm tremor) is reported to be rare or non-existent.[13–15]

Recently, in the setting of two family studies, we came across a number of ET cases with 1) no tremor by self-report, 2) no prior diagnosis of ET, 3) tremor in the arms that on examination was mild and within the normal range, and 4) the presence of a transient but unmistakable head wobble on examination.

Our goal here is to present this series of seven cases, highlighting their clinical features and presenting a visual record of the phenomenon. We also wish to determine how common this phenotype is, estimating its prevalence within the two studies from which the cases were ascertained. Finally, we raise a number of broader clinical, phenotypic, and pathophysiological issues about ET in our discussion.

Methods

ET cases and their relatives were enrolled in two family studies, described below. Each enrollee underwent a demographic and medical history and a videotaped neurological examination, as described below. All enrollees signed written informed consent approved by the Yale University institutional ethics board.

Family study of the environmental epidemiology of ET

ET cases and their first-degree relatives were enrolled in a study of the environmental epidemiology of ET (May 2016 to present). ET cases were ascertained from several sources, including study advertisements to the membership of the International Essential Tremor Foundation, membership in current ET research studies at Yale, and the clinical practice of the Yale Movement Disorders Group. The goal of the study was to enroll unaffected first-degree relatives to complete an environmental risk factor assessment, including a measurement of blood harmane concentration. Prior to their in-person assessment, family members were interviewed by telephone, during which a 12-item tremor screening questionnaire[16] was administered, and they were also asked about prior diagnosis of ET. They also submitted four hand-drawn spirals (two right and two left), which were rated by a senior movement disorder neurologist (E.D.L.) using the following scale: 0 (absolutely no oscillations anywhere), 0.5 (subtle, low-amplitude oscillations are present in a few spots; oscillations are not consistently present throughout the spiral), 1 (low-amplitude oscillations are present in multiple places; examining at least one of the spiral's quadrants reveals the presence of these low-amplitude oscillations that occur in each larger and larger line of the spiral within that quadrant), 1.5 (low-amplitude oscillations are present in multiple places and oscillations can at times reach moderate amplitude), 2 (moderate-amplitude oscillations that are present in many areas of the spiral), 3 (oscillations reach large amplitude in one or more places; lines may overlap; pen may lift off the paper) (see examples in Louis et al).[17] Relatives were initially categorized as unaffected if they met each of the following criteria: 1) they did not report tremor during the 12-item telephone-administered tremor screening questionnaire,[16] 2) they had never been assigned an ET diagnosis by a treating physician, and 3) their two right and two left-hand-drawn screening spirals were assigned tremor scores $\leq$1.0. To date, 26 relatives initially categorized as unaffected have been enrolled.

Family study of essential tremor

ET cases and their affected and unaffected first- and second-degree relatives were enrolled in the Family Study of Essential Tremor (FASET), a genetics study of ET (Phase 1, 2011–2014 and Phase 2, 2015 to present).[18] The study was advertised on ET society websites and e-mail outreach to their membership. Based upon a telephone interview with the proband, relatives were identified. Prior to their in-person assessment, relatives were categorized as unaffected if they met each of the following criteria: 1) they did not report tremor during a three-item telephone screening questionnaire, 2) they had never been assigned an ET diagnosis by a treating physician, and 3) their two right- and two left-hand-drawn screening spirals were assigned tremor scores $\leq$1.0. To date, 27 relatives initially categorized as unaffected have been enrolled.

In-person assessment

In both studies, all enrollees were evaluated in person by a trained tester who administered structured clinical questionnaires that elicited demographic and clinical information. As in our previous studies,[19] each enrollee underwent a 20–30-minute standardized videotaped neurological examination, which included a detailed assessment of postural tremor, five tests for kinetic tremor, the motor portion of the Unified Parkinson's Disease Rating Scale[20] excluding an assessment of rigidity, and a comprehensive assessment of dystonia. The examination also included a detailed assessment of head, jaw, and voice tremors. For head tremor, enrollees first were assessed while seated quietly and facing the camera, during brief conversational speech, during sustained phonation ("ahh" and "eee" for 10–15 seconds each) and while reading a standard passage from a sheet of paper. Head tremor was also potentially detectable during much of the remainder of the 20–30-minute videotaped assessment (e.g., while drinking water from a cup, while using a spoon, while touching finger-to-nose). A senior movement disorders neurologist reviewed all videotaped examinations. The severity of postural and kinetic tremors were rated (0–3), resulting in a total tremor score (range 0–36 (maximum)), a measure of the severity of the action tremor. Based on the videotaped examination, the senior movement disorders neurologist assigned ET diagnoses to relatives using published diagnostic criteria (moderate or greater amplitude kinetic tremor on $\geq$3 tests, or head tremor, in the absence of Parkinson's disease or dystonia).

Statistical analyses

We calculated 95% confidence intervals (CI) on prevalence estimates.

Results

There were seven cases in whom a subtle horizontal head wobble was seen fleetingly. In each case, the movement was seen in the setting of sustained phonation, speech or reading aloud during the videotaped neurological examination (Video 1). Six cases were ascertained from the Family Study of the Environmental Epidemiology of ET (cases 1–6, Table 1) and one from FASET (case 7, Table 1). All were from separate families. The age range was 41–73 years (mean 57.9 years, median 60.5 years) and all were women (Table 1).

One (case 6) had voice tremor on videotaped neurological examination, but none had jaw tremor and none had tremor ratings of 2 (moderate tremor) or higher in the arms on that examination. The total tremor scores ranged from 5 to 12 (mean 8.1, median 8).

Video 1. Early head tremor. Patient 1, after the patient states what she had for breakfast, a brief horizontal head wobble is evident. Patient 2, as the patient states the date ("2016"), a brief horizontal head tremor is evident. Patient 3, as the patient states the date ("May 10th"), a brief horizontal head tremor is evident. Patient 4, as the patient states the date ("September 22nd"), a brief horizontal head tremor is evident. Patient 5, just after sustained phonation (eee sound), a brief horizontal head wobble is evident. The head tilt towards the right at the end is voluntary rather than dystonic. Patient 6, after sustained phonation, a horizontal head tremor is seen. She also has mild voice tremor. Patient 7, just after the patient finishes reading the rainbow passage and looks up, a brief horizontal head tremor is evident.

In six cases, the proband's age of tremor onset was known; in five of these, the case had progressed beyond that age (e.g., case 1 was 52 years of age and the proband's age of tremor onset was 11 years). All cases had familial ET, with 1–4 (mean 2.0, median 2) reportedly affected first-degree relatives.

The prevalence of early head tremor in the Family Study of the Environmental Epidemiology of ET was six out of 26 (23.1%) (95% CI 11.0–42.1%). The prevalence of early head tremor in FASET was one out of 27 (3.7%) (95% CI 0.7–18.3%).

Discussion

We present a series of seven individuals at risk for ET, each of whom has what seems to be early head tremor as a marker of a transition state evolving from normal to ET. These cases raise a number of discussion points. First, the cases emphasize the need to look carefully for head tremor when phenotyping subjects of clinical research and genetic studies; tremor was fleeting in each case, seen only as a transient head wobble during a 20–30-minute videotape segment.

Second, they remind us that although arm tremor must cross a certain severity threshold to be classified as ET rather than normal or enhanced physiological tremor, the presence of any head tremor is consistent with ET rather than normal tremor. That is, head tremor is not normal nor is it a feature of drug-induced tremor. The particular nature of this study, with the enrollment of at-risk individuals, made it more likely that we would be able to capture head tremor early, while it was in a fleeting, transient, evanescent state.

One may ask how common this phenomenon is in a group of "unaffected" relatives. In one study, the prevalence was only 3.7%, yet in the other it was 23.1%, indicating that the prevalence may depend on the study design, and that it can be considerable.

In a prior study of 583 established and diagnosed ET cases, we reported that 2.7% of cases had clear head tremor in the presence of only mild arm tremor, a value that is similar to the 3.7% noted above in the current study.[13] Although this suggests that the prevalence of head tremor in ET in the presence of minimal/mild limb tremor is less than 5%, as noted above, selection biases could increase the number of such cases and, in some study samples, the value may be as high as 23.1% as also reported above in the current study.

These data are relevant to the debate about whether head tremor represents a state of ET or an ET trait. That is, does the presence of head tremor represent a stage in the development of ET or does it represent a distinct clinical phenotype?[21,22] Substantial data indicate that tremor severity increases over time in ET and that ET cases accumulate other clinical features with the passage of time; among these features is head tremor.[21,22] Yet at the same time, there are data to indicate that ET cases with head tremor differ from those without head tremor in substantive ways.[21,22] The presence of an "early head tremor" group suggests that in some cases this could be a trait and not merely a manifestation of advanced disease. In other words, the data raise the question whether there is an early head tremor "subtype" of ET.

It is worthwhile noting that in all of these cases, the tremor was very subtle and was seen fleetingly in the setting of sustained phonation or speech or reading aloud. In a prior paper, we noted that head tremor may be triggered or exacerbated during or immediately following sustained phonation. That is, sustained voice activation is a useful examination maneuver that may elicit or amplify head tremor in ET and that the maneuver, by triggering head tremor, may be a useful diagnostic tool, particularly in research/clinical settings where arm tremor is mild and the diagnosis (mild ET vs. enhanced physiological tremor) would otherwise be ambiguous.[23]

All of the cases we report were women. This could reflect the higher prevalence of head tremor among women than men with ET; previous studies have shown that women with ET are far more likely to manifest head tremor than men with ET.[24,25]

None of the cases was aware of the presence of head tremor. The fleeting presence of the head tremor and its mild nature, and the observation that ET cases are often unaware of their head tremor, may account for this lack of awareness.[26]

The total tremor scores in these subjects ranged from 5 to 12 (mean 8.1). Although none of the cases had a tremor rating of 2 on any examination maneuver and none met diagnostic criteria for ET, the average amount of tremor was approximately 70% higher than that seen in a similarly aged group of population-dwelling controls (mean age 54.4 years, mean total tremor score 4.8, range 0 to 12.5).[27] Previous work has shown that the burden of tremor among relatives with ET, and even among those who don't qualify for a diagnosis of ET, is higher than that of individuals selected from the population.[28,29]

We present a series of seven individuals who are at risk for ET, each of whom had what seems to be early head tremor in an evolving transition state from normal to ET. These cases raise a number of broad clinical, phenotypic, and pathophysiological issues about ET.

Table 1. **Demographic and Clinical Features of ET Cases**

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)	52	54	67	41	73	67	51
Gender	F	F	F	F	F	F	F
Hand dominance	L	R	R	R	R	R	L
Proband's age of tremor onset	11	Unknown	16	15	53	7	7
Number of affected first-degree relatives	2	1	4	1	2	2	2
Voice tremor[1]	No	No	No	No	No	Yes	No
Jaw tremor[1]	No	No	No	No	No	No	No
Tremor rating on R extension[1]	0	0	0	0.5	0	0.5	0
Tremor rating on L Extension[1]	0	0	0	0.5	0	0.5	0
Tremor rating on R pouring[1]	0.5	0	0	1	0.5	0.5	1
Tremor rating on L pouring[1]	0.5	0	0	0	0.5	0	1
Tremor rating on R using spoon[1]	0.5	0.5	1	1	0	1	0.5
Tremor rating on L using spoon[1]	1	1.5	1	1.5	1.5	0.5	0.5
Tremor rating on R drinking[1]	0.5	1	0	1	1.5	0.5	0.5
Tremor rating on L drinking[1]	0.5	0	0.5	1	1.5	0.5	1
Tremor rating on R FNF[1]	1	1.5	0.5	1	0.5	1	1
Tremor rating on L FNF[1]	0.5	1.5	1	1.5	0.5	1.5	1
Tremor rating on R drawing[1]	0.5	1	0	1.5	1	1	1.5
Tremor rating on L drawing[1]	1	1	1	1.5	0.5	1	1
Total tremor score	6.5	8	5	12	8	8.5	9

Abbreviations: F, Female; FNF, Finger–Nose–Finger Maneuver; L, Left; R, Right.
[1]On videotaped neurological examination.

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