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Short communication

Prevalence and features of unreported dystonia in a family study of "pure" essential tremor

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ABSTRACT

Background: Essential tremor (ET) is considered to be a highly heritable disorder, yet no susceptibility genes have been identified. The search for ET genes is severely hampered by clinical and genetic heterogeneity; the existence of this heterogeneity complicates the genetic analyses. We sought to determine the prevalence and clinical features of unreported dystonia in a family study of "pure" ET.
Methods: ET probands and their reportedly affected first-and second-degree relatives were enrolled in a genetics study, the Family Study of Essential Tremor (FASET) at Columbia University Medical Center. The goal was to enroll cases with "pure" ET (i.e., ET without dystonia or other neurological problems). Each enrollee underwent a detailed neurological evaluation.
Results: There were 100 enrollees (28 probands, 72 relatives). Dystonia (primarily torticollis) occurred in 9 (32.1%) of 28 families, with 5 cases in one family, 2 cases in two families, and 1 case in six families. Those affected with dystonia included 3 (10.7%) probands and 12 (16.7%) relatives. There was a gender predilection: 14/15 (93.3%) with dystonia vs. 41/85 (48.2%) without dystonia were women ($p = 0.001$). Dystonia was previously undiagnosed in 14/15 (93.3%) cases.
Conclusions: Dystonia (esp. torticollis in women) was present in nearly one-third of the ET families in a genetics study, including 10.7% of ET probands. Dystonia was unreported and previously undiagnosed in nearly all of these individuals. The overarching biological issue is whether ET and dystonia should be regarded as one disease or two; this has obvious implications for the structuring of analyses in genetic studies.

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1. Introduction

Essential tremor (ET) is considered to be a highly heritable disorder [1,2]. The search for underlying susceptibility genes has intensified in recent years [2]. The aim of these genetic studies is to identify etiological factors that will lead to an understanding of disease pathogenesis and will form a basis for the development of more effective pharmacotherapeutics. Despite this promising scenario, no susceptibility genes for ET have been identified to date, and a number of important methodological issues have been raised [3]. A central issue is that families with "pure ET" are less common than anticipated; for example, probands and family members may have features of dystonia. These "mixed-motor" families, in which affected members have ET, dystonia, or both, likely represent a subcategory of ET [4], and the existence of this heterogeneity complicates the genetic analyses, and reduces power for gene identification.

One strategy to reduce such heterogeneity is to exclude from genetic analyses individuals with dystonia or entire families in which one member has dystonia. However, this approach would be difficult to implement. First, as many as 50% of people with dystonia ascertained during family studies of DYT1 dystonia did not seek medical attention or were not diagnosed [5]. Individuals with mild,

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intermittent movements were most likely to be missed by screening [6]. Second, screening questions for dystonia may have reduced sensitivity in members of ET families because dystonic movements might be falsely attributed to ET.

ET cases (probands) and their relatives were enrolled in a genetics study of ET at Columbia University Medical Center (CUMC); the goal was to enroll cases with "pure" ET (i.e., ET without dystonia or other neurological problems). Here, we sought to determine the prevalence and clinical features of unreported dystonia in the first 100 enrollees (probands and relatives). In addition to estimating the magnitude of the problem, the goal was to increase awareness among investigators of this issue. The larger biological issue is whether ET and dystonia should be regarded as one disease or two; this has obvious implications for the structuring of analyses in genetic studies.

2. Methods

2.1. Ascertainment of probands

ET cases (probands) and their reportedly affected first-and second-degree relatives were enrolled in a genetics study of ET, the Family Study of Essential Tremor (FASET) at CUMC. The three initial inclusion criteria for probands were: (1) a diagnosis of ET had been assigned by a doctor, (2) age of tremor onset $\leq$40 years, (3) $\geq$2 living relatives in the United States have ET that was diagnosed by a doctor, and these relatives were not reported to have dystonia or Parkinson's disease (PD). The two exclusion criteria for probands were a prior diagnosis of dystonia or PD. Potential ET probands contacted the FASET study coordinator in response to advertisements on two ET society websites. Prior to final selection for enrollment, a set four Archimedes spirals (two right, two left) were submitted by probands, and rated by a senior movement disorder neurologist (E.D.L.) Probands were included if one or more of the spirals had a Washington Heights Inwood Genetic Study of Essential Tremor rating of 2 (moderate tremor) or higher [7].

2.2. Ascertainment of relatives

Based upon a telephone interview with the proband, relatives with ET were identified. With the proband's permission, these relatives were then contacted by telephone, and were pre-enrolled if they reported the presence of tremor in the absence of a prior diagnosis of dystonia or PD. Prior to final selection for enrollment, four Archimedes spirals were submitted by relatives and rated (E.D.L.) Relatives were included if one or more of the spirals had a rating $\geq$2 [7].

2.3. In-person evaluation

After enrollment, an in-person evaluation was then conducted in the enrollees' homes; this included a series of questionnaires and a videotaped neurological examination, which included a detailed assessment of postural, kinetic, intention and rest tremors, as well as dystonia and other movement disorders [8]. The use of videotaped neurological examinations is a standard and valid method to diagnose a wide range of movement disorders including ET, PD and dystonia [2,5,6,9]. A senior movement disorders neurologist (E.D.L.) reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors were rated (0–3), resulting in a total tremor score (range = 0–36 [maximum]) [8]. In addition to dystonic postures or tremor during sustained arm extension, the videotape was assessed for the presence of spasmodic torticollis, voice tremor and blepharospasm. The study was approved by the CUMC Institutional Review Board and all participants signed written informed consent.

2.4. Diagnoses

All ET diagnoses were reconfirmed based on review of questionnaires and videotaped neurological examination data. Diagnoses of ET were assigned by E.D.L. based on published diagnostic criteria (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor in the absence of PD or another known cause) [7,10]. In addition to the presence or absence of dystonic postures during sustained arm extension, the videotape was assessed for the presence of spasmodic torticollis (while seated, while walking and while lying down), voice tremor and voice breaks (during spontaneous speech, reading, sustained vowel sounds) and blepharospasm. Diagnoses of dystonia were initially assigned (E.D.L.). A second neurologist specializing in movement disorders (R.N.A.) independently re-reviewed the videotaped neurological examinations of all 15 enrollees who had been diagnosed with dystonia. Criteria for dystonia followed those recommended by Fahn [11], and consisted of sustained muscle contractions, often causing abnormal postures, or twisting and repetitive movements [11]. Spasmodic torticollis was defined as the presence of twisting or tilting movements of the neck, jerk-like or sustained neck deviation, often with mild hypertrophy of neck muscles. Dystonic head tremor was distinguished from ET-related head tremor by the presence of directional or irregular tremor and the tendency for the tremor to continue while the patient was supine [12]. If present, voice tremor was attributed to ET or dystonia (tremor with voice breaks, strangled speech). The two neurologists agreed on all 15 diagnoses of dystonia.

2.5. Statistical analyses

Analyses were performed in SPSS (Version 19.0).

3. Results

There were 100 enrollees, including 28 probands and 72 relatives (58 first-degree, 11 second-degree, and 3 third-degree) (Table 1). Up to 6 relatives (excluding probands) were examined per family.

Despite our attempt to pre-screen for dystonia, we found that dystonia was present in 3 (10.7%) probands and 12 (16.7%) relatives; in 1 proband and 8 relatives dystonia occurred in the presence of ET, and in 2 probands and 4 relatives it occurred in the absence of ET (Tables 1 and 2). Dystonia occurred in 9 (32.1%) of 28 families; with 5 cases in one family, 2 cases in two families, and 1 case in six families. After initial telephone contact (i.e., after enrollment), one of the probands (diagnosed in our study with ET + dystonia) reported having been diagnosed with both ET and writer's cramp. None of the other probands or family members had been diagnosed with dystonia. Hence, dystonia had been previously undiagnosed in 14 (93.3%) of 15 individuals.

The dystonia was mild and the location of the dystonia was torticollis (n = 8), torticollis and spasmodic dysphonia (n = 2), torticollis and blepharospasm (n = 1), torticollis and arm (n = 3), and blepharospasm (n = 1). The large majority with dystonia (14, 93.3%) were women (Table 2).

Table 1
Demographic and clinical characteristics of 100 enrollees.

	Proband (N = 28)	Relative (N = 72)
Age (years)	64.6 ± 11.5, 37–83	56.9 ± 18.8, 19–95
Female gender	16 (57.1)	39 (54.2)
White race	25 (89.3)	63 (87.5)
Ashkenazi Jewish ancestry	2 (7.1)	10 (13.9)
Relationship to proband		
Self	28 (100)	0 (0)
Child	0 (0)	27 (37.5)
Sibling	0 (0)	24 (33.3)
Parent	0 (0)	7 (9.7)
Grandchild	0 (0)	1 (1.4)
Aunt/Uncle	0 (0)	3 (4.2)
Nephew/Niece	0 (0)	7 (9.7)
Other (Third-degree)	0 (0)	3 (4.2)
Diagnosis		
ET	25 (89.3)	54 (75.0)
Dystonia	2 (7.1)	4 (5.6)
ET + Dystonia	1 (3.6)	8 (11.1)
Not enough tremor to qualify for ET	0 (0)	6 (8.3)
Total tremor score on neurological examination	22.1 ± 4.8	15.9 ± 6.3
Voice tremor on neurological examination	9 (32.1)	7 (9.7)
Head (neck) tremor on neurological examination	14 (50.0)	10 (13.9)
Currently takes medication to treat ET	19 (67.9)	20 (27.8)
Age of tremor onset (years)	24.0 ± 16.3	29.6 ± 19.2
Duration of tremor (years)	40.6 ± 14.6	26.4 ± 19.8

All values are mean ± standard deviation, range or number (%), unless otherwise specified.

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