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Unaffected first-degree relatives of essential tremor cases have more imbalance than age-matched control subjects

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ABSTRACT

Background: Endophenotypes are measurable clinical characteristics that may be present in individuals with increased risk for disease (e.g., unaffected family members). Endophenotypes are useful; they may clarify diagnosis in genetic studies and foster the development of animal models. In recent years, problems with balance and mild gait ataxia have been associated with essential tremor (ET). We compared gait and balance of first-degree relatives of ET cases (FD-ET) to that of age-matched controls (Co).

Methods: One-hundred-ninety FD-ET and 68 Co, none of whom reported tremor or were diagnosed with ET, underwent a standardized assessment of gait and balance.

Results: FD-ET reported more near-falls in the past year ($p = 0.015$) and lower balance confidence according to the Activities of Balance Confidence (ABC-6) Scale ($p = 0.03$). The specific ABC-6 items for which FD-ET reported lower balance confidence than Co were being bumped into by people while walking ($p = 0.006$) and walking outside on icy sidewalks ($p = 0.007$). On videotaped neurological examination, FD-ET were able to stand in the tandem position for fewer seconds than were Co ($p = 0.048$). The differences between FD-ET and Co, although statistically significant, were clinically mild.

Conclusion: FD-ET reported more near-falls in the past year and a reduction in balance confidence; additionally, ability to maintain tandem stance was impaired compared to Co. These data suggest a more pervasive abnormality of cerebellar dysfunction than previously conceived, extending beyond ET cases themselves and manifesting in mild form in their unaffected family members.

1. Introduction

Essential tremor (ET) is the most prevalent tremor disorder [1]. The disease is often familial [2]; indeed, first-degree relatives of ET cases are five times more likely to develop ET than are members of the population [3].

Endophenotypes are measurable clinical or biological characteristics that are found more often in individuals with the disease than in the general population. They may be present before the onset of disease and in individuals with increased risk for the disease (e.g., unaffected family members). In addition to furthering genetic analysis, endophenotypes can clarify diagnosis and foster the development of animal models [4]. In movement disorders research, endophenotypes have been studied the most in patients and families with dystonia [5] but they have also been studied in patients with Tourette syndrome [6] and more broadly in other neurological [7] and psychiatric [8] illnesses.

Relatives of ET cases are more likely to exhibit mild tremor than are relatives of control subjects [9,10], indicating the burden of ET extends beyond the boundaries of the clinically-defined disease, and partially expressed forms of ET are abundant in ET families. In recent years, ET has been associated with a range of clinical features aside from tremor [11]. For example, problems with balance and a mild gait ataxia have been documented in numerous studies [12]. The basis for these problems is not clear, but is likely to be a result of

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abnormal cerebellar function [13]. Whether these features associated with ET occur in a mild form in unaffected family members is not known.

In this study, we compared gait and balance of first-degree relatives of ET cases (FD-ET) to that of age-matched controls (Co). We hypothesized that FD-ET might exhibit more deficits in gait and balance, albeit mild, than Co. If this were the case, it would serve to strengthen the scientific notion that gait and balance difficulties are associated with ET and, furthermore, it would have implications for the conduct of genetic studies. More broadly, it would strengthen the notion that there may be a pre-tremor phase of illness in ET [14]. Studies of the presymptomatic and early stage of neurodegenerative diseases are pivotal for an advanced understanding of these disorders and for the development of preventive strategies aimed at postponing the clinical onset of these diseases [15]. Therefore, it is important to identify the earliest and most sensitive clinical signs and biological markers that herald the onset of the illness [15].

2. Methods

2.1. Introduction

FD-ET and their spouses (i.e., Co) were screened for enrollment in an environmental epidemiological study of ET (May 2016 – present) [16].

ET cases had been ascertained from study advertisements to the membership of the International Essential Tremor Foundation, membership in current ET research studies at Yale University, and the clinical practice of the Yale Movement Disorders Group [16].

2.2. Screening process for unaffected FD-ET

The screening process for unaffected FD-ET was as follows. First, ET cases informed the investigator of all reportedly unaffected living first-degree relatives age ≥40. With permission, these family members were contacted by telephone. During this telephone call, they were consented (using a protocol approved by the Yale University Institutional Review Board) and interviewed. During the interview, a 12-item tremor screening questionnaire [17] was administered and they were asked about a prior diagnosis of ET. They also completed and mailed four hand-drawn spirals (two right, two left), which were rated by a senior movement disorder neurologist (E.D.L.) using the following scale: 0, 0.5, 1, 1.5, 2, 3 (see definitions and examples in Louis et al.) [18].

These FD-ET 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 [17], (2) they had never been assigned an ET diagnosis by a treating physician, and (3) each of their four screening spirals were assigned scores <2.0.

2.3. In-person clinical evaluation of FD-ET

FD-ET were invited for an in-person clinical evaluation if initially categorized as unaffected. The evaluation was conducted by trained interviewers in enrollees' homes and included questionnaires (e.g., demographics, tremor features, medical history, medications). The number of reportedly affected first-degree relatives was defined as the genetic load. The Cumulative Illness Rating Scale (CIRS) (range = 0–42 [maximum co-morbidity]) [19], a measure of medical co-morbidity, was administered; this assessed the presence and severity (none = 0, mild = 1, moderate = 2, severe = 3) of illnesses in 14 body systems. Depressive symptoms were assessed using the Beck Depression Inventory, for which 21 items were rated from 0 to 3 (total score = 0–63 [maximal symptoms]) [20].

The interviewer administered the six-item Activities of Balance Confidence (ABC-6) Scale [21]. The scale asked enrollees to self-rate their confidence in performing functional activities without losing balance or becoming unsteady during a range of situation-specific activities (e.g., walking outside on icy sidewalks). The ABC has been shown to have excellent utility in evaluating balance-related confidence, and scores for each item range from 0 to 100 (completely confident). The interviewer also asked FD-ET to indicate how many falls they had had during the past year. Falls were defined as “an event which results in a person coming to rest inadvertently on the ground or supporting surface, and other than as a consequence of a violent blow, loss of consciousness or sudden onset of paralysis.” [22] The interviewer also asked about the number of near-falls (i.e., when subjects felt they were going to fall but did not actually fall) they had had in the past year [22].

The in-person evaluation also included a videotaped neurological examination [23], which included a detailed assessment of postural, kinetic, intention and rest tremors, as well as dystonia and other movement disorders [24]. E.D.L. reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors was rated on 12 examination items using a reliable rating scale [25]. As reviewed [18,26], ratings were 0, 0.5, 1.0, 1.5, 2, 3 and 4; these resulted in a total tremor score (range = 0–46 [maximum]) [24].

An assessment of tandem gait was performed during the study visit and was videotaped so that the number of mis-steps could be counted later by E.D.L. Tandem gait was explained and demonstrated to enrollees; they were carefully instructed to walk placing one foot directly in front of the other, being careful to touch toe to heel with each step. They could choose their own line (i.e., a line was not drawn or placed on the floor). The number of mis-steps (i.e., steps to the side) during a single 10-step trial was counted. Enrollees were also asked to stand in the tandem position, with the dominant foot in front, and the number of seconds (range = 0–10) without falling to the side was counted (E.D.L.).

FD-ET were re-evaluated for a potential ET diagnosis based on review of questionnaires and videotaped neurological examination data. Diagnoses of ET were assigned 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 [e.g., medication-induced tremor, tremor from hyperthyroidism]) [23,25,27].

2.4. Final inclusion of FD-ET

FD-ET were included in these analyses if they were initially categorized as unaffected (see above) and if they were NOT diagnosed with ET based on the in-person evaluation.

2.5. Parallel procedure for screening and evaluating Co

Co were also screened, if available. Each then underwent the same screening process, in person questionnaire, and videotaped examination. They were included in these analyses if (1) they were initially categorized as unaffected, (2) reported no family history of ET, and (3) they were NOT diagnosed with ET during the in-person evaluation.

2.6. Final sample

We screened 451 individuals of whom 336 were initially categorized as unaffected. We further excluded 44 who were diagnosed with ET based on published diagnostic criteria and another 34 who were considered to have borderline ET – that is, they did not fully

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