



Family History of Dementia in an Essential Tremor Cohort

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Essential tremor (ET) is a neurodegenerative motor disease [1–4] whose defining clinical feature is kinetic tremor [5]. ET patients also have been shown to perform more poorly on cognitive testing than age-matched controls and furthermore, epidemiological studies have demonstrated that a diagnosis of ET significantly increases risk for dementia (relative risks = 1.64–1.89) [6, 7]. In fact, longitudinal data indicate that conversion rate from normal cognition to dementia in older adults with ET is approximately three-times higher than in older adults without ET [8]. Hence, we are witnessing the emerging recognition of a new association – ET with dementia. The pathogenesis of this dementia is not clear, however initial studies suggest that there is a predisposition for ET patients to develop Alzheimer’s disease (AD) [9, 10]. Although scientifically intriguing, given the very high prevalence of ET (2.2% of the entire US population – 7 million people) [11], the increased risk of dementia is troubling from both clinical and public health perspectives.

The association between ET and dementia has been studied using case-control and cohort studies, assessing the relative prevalence and/or incidence of dementia in ET versus control groups. Another pathway to address whether dementia is disease-associated in ET is to conduct a familial aggregation study. Familial aggregation studies ask whether *relatives* of ET cases have cognitive impairment rather than whether *ET cases themselves* have cognitive impairment, and whether this level of cognitive impairment exceeds that seen in relatives of controls. In the absence of a control group, the prevalence of dementia in ET relatives may be compared with the prevalence of dementia in relatives of historical controls.

Here, we report the results of such analyses. ET cases were enrolled in a prospective, longitudinal, nationwide study of older adults with ET (Clinical Pathological Study of Cognitive Impairment in Essential Tremor [COGNET]; National Institutes of Health Award #R01 NS086736), described in detail [8]. To date, cases reside in 43 US states, having responded to an advertisement to enroll in this cohort [8]. The Yale University, Columbia University, and University of Texas Southwestern Medical Center Institutional Review Boards approved the study protocol. All cases provided written, informed consent. During the in-home baseline evaluation, ET cases were asked “Do you have a family history of dementia?”

Data were available on 132 ET cases whose mean age was 76.5 years (range = 65–97 years). Of these, 55 (41.7%, 95% confidence interval = 33.2% to 50.6%) reported that a relative had dementia. Among these 132 were 43 (32.6%) who reported a first-degree relative with dementia and 15 (11.4%) who reported a second-degree relative with dementia. Among the 55 who

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reported relatives with dementia, 37 (67.3%) noted that they knew that dementia had been formally diagnosed by a physician. Among the 132 ET cases were 9 with Mild Cognitive Impairment and 3 with dementia; the proportion of relatives with dementia was reported as 7 (22.2%) and 1 (33.3%), respectively.

Published data on the proportion of controls who report a family history of dementia are as follows. In a worldwide study, 59,571 controls filled out an on-line survey; the proportion of controls reporting a first-degree relative with AD varied by age, but in 70–80 year olds ranged between 20% and 25% [12]. Similarly, in the Rotterdam study, 24.6% of 997 controls with a mean age of 68.4 years reported a family history of dementia [13]. A smaller study of 60 controls with a median age of 76 years reported that 13% had a family history of dementia [14]. All of these values are lower than those we report in our ET cohort.

Relatives of ET cases have rarely been compared with relatives of controls. In a prior study, investigators demonstrated similar mean Montreal Cognitive Assessment (MoCA) scores in 156 relatives of ET cases vs. 73 relatives of controls, but a higher prevalence of MoCA <26 in the former ($p = 0.008$), suggesting that there was some familial aggregation of lower cognitive test scores among relatives of ET cases [15]. These data are in sync with the data we report here on the substantial proportion of ET cases who report relatives with dementia.

Our analyses have a number of notable and important limitations. First, we were unable to compare our cases to controls, therefore relying on historical controls. Differences in study methodologies (e.g., the nature of the questions asked) make comparisons with historical controls susceptible to error. Second, our data focus on reported dementia rather than detailed neuropsychological test batteries in the relatives themselves. Third, the proportion of probands with positive family history can be a function of family size and family age; larger families and older families are more likely to have affected relatives.

These data demonstrate a high prevalence of reported dementia in ET families in our cohort, a value that is considerably higher than those reported in population-based studies of controls. Future familial aggregation studies, enrolling ET cases and controls, are needed to more fully address this issue. Greater understanding of the connections between ET and dementia is needed.

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The authors have no competing interests to declare.

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