Essential tremor is associated with dementia

Prospective population-based study in New York

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ABSTRACT

Background: Mild cognitive deficits, mainly in frontal-executive function and memory, have been reported in patients with essential tremor (ET). Furthermore, an association between ET and dementia has been reported in a single population-based study in Spain. This has not been confirmed elsewhere.

Objective: To determine whether baseline ET is associated with prevalent and incident dementia in an ethnically diverse, community-based sample of elders.

Methods: Community-dwelling elders in northern Manhattan were enrolled in a prospective cohort study. Baseline ET diagnoses were assigned from handwriting samples. Dementia was diagnosed at baseline and follow-up using *DSM-III-R* criteria.

Results: In cross-sectional analyses, 31/124 (25.0%) ET cases had prevalent dementia vs 198/2,161 (9.2%) controls (odds ratio $[OR]_{unadjusted}$ = 3.31, 95% confidence interval [CI] = 2.15–5.09, $p < 0.001$; $OR_{adjusted}$ = 1.84, 95% CI = 1.13–2.98, $p = 0.01$). In prospective analyses, 17/93 (18.3%) ET cases vs 171/1,963 (8.7%) controls developed incident dementia (hazard ratio $[HR]_{unadjusted}$ = 2.78, 95% CI = 1.69–4.57, $p < 0.001$; $HR_{adjusted}$ = 1.64, 95% CI = 0.99–2.72, $p = 0.055$).

Conclusions: In a second population-based study of elders, essential tremor (ET) was associated with both increased odds of prevalent dementia and increased risk of incident dementia. Presence of dementia, therefore, appeared to be greater than that expected for age (i.e., a disease-associated feature). Rather than attributing cognitive complaints in patients with ET to old age, assessment and possible treatment of dementia should be routinely incorporated into the treatment plan. ***Neurology*® 2009;73:621–625**

GLOSSARY

AD = Alzheimer disease; **CES-D** = Center for Epidemiologic Studies–Depression; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **ET** = essential tremor; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **MCI+M** = MCI with memory impairment; **MCI-M** = MCI without memory impairment; **OR** = odds ratio; **UPDRS** = Unified Parkinson's Disease Rating Scale; **WHICAP** = Washington/Hamilton Heights and Inwood Aging Project.

Essential tremor (ET), a progressive neurologic disease, is among the most prevalent movement disorders.[1,2] In addition to action tremor and other motor features, recent studies report nonmotor features.[3-5] In a growing number of studies, mild cognitive problems are being observed in ET cases.[6-8] Furthermore, an association between ET and dementia was reported in a recent population-based study in central Spain.[9,10] This novel association has yet to be verified in other populations. In a large, multiethnic study of elderly persons living in northern Manhattan, NY, we determined whether ET is 1) associated with prevalent dementia and 2) a baseline risk factor for incident dementia. Our overarching goal was to confirm whether dementia occurs in ET above and beyond that expected for age (i.e., to determine whether dementia is a disease-associated feature), which is an issue that has implications for the evaluation and treatment of patients in clinical settings.

Supplemental data at www.neurology.org

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METHODS

Study population. Participants (2,776) were enrolled in the Washington/Hamilton Heights and Inwood Aging Project (WHICAP) II cohort. These participants, who comprise individuals from 3 ethnic categories (white, African American, Hispanic), were identified from a probability sample of Medicare beneficiaries (age ≥65 years) residing in the northern Manhattan communities of Washington Heights and Inwood. The WHICAP II cohort represents a combination of continuing members of a cohort recruited between 1992 and 1994 (WHICAP I; n = 602) and members of a new cohort recruited between 1999 and 2002 (n = 2,174).[11,12]

Participants underwent identical baseline and follow-up assessments every 18 months. Handwriting assessments were at baseline.

Standard protocol approvals, registrations, and patient consents. Study procedures and recruitment were approved by the Columbia University Internal Review Board and written, informed consent was obtained from all participants.

In-person evaluation. A trained research assistant administered an in-person structured health interview (demographics, medical history, medications). The 10-item Center for Epidemiologic Studies–Depression (CES-D) scale assessed depressive symptoms; as done previously, scores ≥4 were coded as depressed.[13,14]

General medical doctors administered a neurologic examination, including a 10-item version of the motor Unified Parkinson's Disease Rating Scale (UPDRS).[15] These doctors were trained using a structured protocol.[15] Interrater reliability was substantial to excellent and percent concordance with a movement disorder neurologist's ratings was high.[15]

A neuropsychological battery, conducted by a trained tester, included measures of abstract reasoning, learning and memory, language, visuospatial ability, and orientation.[15-17]

Participants also generated several handwriting samples. The first sample, collected during neuropsychological testing, was a series of 5 shapes (e.g., triangle, diamond) that were copied.[18] The second sample was a trail making test.[19] As documented,[20] a medical student (S.T.) was trained by a senior movement disorder neurologist (E.D.L.) to rate the severity of tremor in these 6 items; interrater agreement was high (intraclass correlation coefficient = 0.80). These ratings (examples in figure 1 in reference 20) were blinded to demographic, clinical, and neuropsychological data and dementia diagnoses. Ratings were 0 (no tremor), 0.5 (possible tremor), 1.0 (clear tremor that was mild, equivalent to a rating of 2 on an Archimedes spiral in the rating scale of Bain and Findley[21]), 1.5 (mild to moderate tremor, equivalent to a rating[21] of 3–4), or 2 (moderate or greater tremor, equivalent to a rating[21] ≥5). Based on the 6 rated items, a total tremor score was generated (range = 0–12).

Diagnoses. The method of diagnosing ET, documented in detail,[20] was based on published data on observed differences in severity of tremor in ET cases vs normal controls.[21] Bain and Findley[21] indicated that their tremor rating ≥2 may be used to distinguish ET from enhanced physiologic tremor because this rating corresponded with twice that of the 95th percentile seen in healthy controls. Their rating of 2 is equal to our rating of 1.0. A tremor rating of 1.0 on each of our 6 rated items would result in a total tremor score of 6.0. To be more inclusive (accounting for the possibility that 1 of 6 items could have received a rating of 0.5), we considered those with total tremor scores ≥5.5 as having preliminary diagnoses of ET. The senior neurologist reviewed the records of all participants with preliminary ET diagnoses, and independently re-rated tremor, assigning a total tremor score. Also, as an additional test, a handwritten sentence, which was completed by participants, was rated (E.D.L.) A final ET diagnosis was conservatively assigned to participants when the senior neurologist confirmed a total tremor score ≥5.5 or rated the handwritten sentence ≥2 (moderate or greater tremor, equivalent to a rating ≥5 in Bain and Findley[21]) (example in figure 2 in reference 20). These final ET diagnoses were blinded to all clinical data. Patients with PD by history or neurologic examination or with tremor related to medications, hyperthyroidism, or another neurologic disorder were not assigned final ET diagnoses. Subsequently, 9 ET cases were randomly selected for enrollment in an epidemiologic study[22]; each had a complete videotaped tremor examination (arm extension, pouring, drinking, using spoon, finger-nose-finger, writing); the ET diagnosis was confirmed using published research criteria[22] in 100% of these.

The general medical doctors assigned a preliminary diagnosis of PD if a participant 1) had ≥2 cardinal signs of parkinsonism on neurologic examination, 2) was told previously that he or she had a diagnosis of PD, or 3) had ever used levodopa.[15] PD diagnoses were confirmed by a WHICAP study neurologist based on a second, more detailed neurologic examination.

Dementia diagnoses, assigned by consensus conference of neurologists and neuropsychologists, were based on a neuropsychological battery and the physician-administered neurologic examination, blinded to tremor ratings.[23] Participants were considered demented if, based on neuropsychological testing, they demonstrated impairment in memory and at least 2 other cognitive domains, in the absence of delirium.[15,23] Criteria for dementia from the *DSM-III-R* were applied in addition to ancillary information from medical charts and laboratory studies in the final evaluation.[24] Evidence of deficits in social or occupational functioning was also required for the consensus diagnosis. This information was also used to determine the type and etiology of dementia. Diagnosis of probable or possible Alzheimer disease (AD) was based on National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[25]

Based on the neuropsychological test battery, participants were assigned diagnoses of mild cognitive impairment (MCI) according to published criteria.[16,17,26,27] MCI was stratified into MCI with memory impairment (MCI+M) and MCI without memory impairment (MCI-M).[15]

Baseline study sample. The baseline sample included 2,776 participants (mean age 78.2 ± 7.1 years, mean education 9.9 ± 4.9 years). We excluded 491 participants who had 1) refused the writing tasks due to poor eyesight or difficulty following the instructions (n = 381) (none refused these tasks due to tremor); 2) incomplete neuropsychological tests (n = 62); or 3) preliminary or confirmed diagnoses of PD (n = 48 of 2,776 = 1.7%). The remaining 2,285 (82.3% of 2,776) participants were similar to the initial 2,776 in gender (1,553 [68.0%] vs 1,889 [68.0%] women, $p = 0.93$), ethnicity (874 [38.2%] vs 1,099 [39.6%] Hispanic, $p = 0.34$), and education (10.1 ± 4.8 vs 9.9 ± 4.9 years, $p = 0.15$). The remaining 2,285 were 0.6 years younger than the initial 2,776 (77.6 ± 6.9 vs 78.2 ± 7.1 years, $p = 0.002$).

Analyses. Analyses, performed in SPSS version 11.0, included χ^2 and t tests and analysis of variance.

In cross-sectional analyses, logistic regression analyses tested the association of the outcome variable with the independent variable (ET vs control). In different models, outcome variables were 1) demented vs nondemented (nondemented included MCI categories and no cognitive impairment), 2) MCI+M vs no cognitive impairment (excluding demented and MCI-M),

and MCI-M vs no cognitive impairment (excluding demented and MCI+M).

In prospective analyses, Cox proportional hazards regression, which yielded hazard ratios (HRs), compared the risk of developing incident dementia (or incident MCI) in participants with vs without baseline ET. The time-to-event variable was time from baseline examination to diagnosis of dementia or MCI.

In adjusted models, we included variables that were associated with both ET and dementia (or MCI) ($p < 0.05$) or for which a priori evidence was considerable that the variable may be a confounder. Variables considered included age (years), gender, ethnicity, education (years), depression, *APOE* σ4 status, and self-reported medical illnesses (hypertension, congestive heart failure, stroke, diabetes, arthritis, peripheral vascular disease). We also considered a cohort variable (1992–1994 vs 1999–2002). A complete inventory of all current medications (including tremor-exacerbating medications) was available, and medication variables were added as covariates (taking each medication vs not) in an adjusted model.

RESULTS

Cross-sectional analyses (baseline data). There were 124 (5.4% of 2,285) prevalent ET cases and 2,161 controls. ET cases were older than controls (80.9 ± 7.5 vs 77.4 ± 6.8 years, $p < 0.001$), had fewer years of education (8.2 ± 4.8 vs 10.2 ± 4.7 years, $p < 0.001$), and fewer were white (21/124 [16.9%] vs 625/2,161 [28.9%], $p = 0.01$). *APOE* σ4 gene status did not differ (table e-1 on the *Neurology*® Web site at www.neurology.org).

There were 229 (10.0% of 2,285) participants with prevalent dementia and 452 (19.8% of 2,285) with prevalent MCI (235 MCI+M, 217 MCI-M) (table e-2). Participants with prevalent dementia were older than participants with no cognitive impairment, had fewer years of education, and fewer were white. Also, a larger proportion had depression (CES-D ≥4), hypertension, congestive heart failure, stroke, and positive *APOE* σ4 gene status (table e-2).

Thirty-one (25.0%) of 124 ET cases had prevalent dementia vs 198 (9.2%) of 2,161 controls. ET was associated with prevalent dementia in unadjusted models (odds ratio [OR] = 3.31, 95% confidence interval [CI] = 2.15–5.09, $p < 0.01$) and adjusted models (OR adjusted for age [years], education [years], and ethnicity = 1.84, 95% CI = 1.13–2.98, $p = 0.01$). Participants with dementia were stratified by etiology; 29 of 31 [93.5%] ET cases with dementia had AD and 179 of 198 [90.4%] controls with dementia had AD ($\chi^2 = 0.32$, $p = 0.57$).

We conducted several secondary analyses. First, we excluded 452 participants with MCI; adjusted (age, education, ethnicity) OR = 1.84, 95% CI = 1.11–3.06, $p = 0.02$. Second, we excluded 462 participants with depression (CES-D score ≥4); adjusted OR = 2.10, 95% CI = 1.20–3.68, $p = 0.01$. Third, each medication variable (including tremor-exacerbating medications) was added as a covariate; adjusted (age, education, ethnicity, each medication) OR = 1.97, 95% CI = 1.08–3.58, $p = 0.03$. Fourth, we considered cohort as a covariate; adjusted (age, education, ethnicity, cohort) OR = 1.82, 95% CI = 1.12–2.95, $p = 0.02$. Finally, participants were stratified by *APOE* σ4 gene status: adjusted (age, education, and ethnicity) $OR_{APOE\ \text{å}4\ \text{gene positive}} = 1.82$, 95% CI = 0.72–4.59, $p = 0.20$, and adjusted $OR_{APOE\ \text{å}4\ \text{gene negative}} = 1.48$, 95% CI = 0.72–3.04, $p = 0.29$.

Eleven (8.9%) ET cases had MCI+M and 15 (12.1%) had MCI-M vs 224 (10.4%) and 202 (9.3%) in controls. ET was not associated with MCI+M (unadjusted OR = 1.13, 95% CI = 0.59–2.16, $p = 0.72$; adjusted OR = 1.08, 95% CI = 0.56–2.10, $p = 0.81$) or MCI-M (unadjusted OR = 1.70, 95% CI = 0.96–3.04, $p = 0.07$; adjusted OR = 1.47, 95% CI = 0.81–2.66, $p = 0.20$).

Prospective analyses. We excluded 229 participants with baseline dementia, leaving 2,056 participants (93 ET cases, 1,963 controls). Mean follow-up was 3.8 ± 2.2 years. Seventeen (18.3%) of 93 ET cases developed dementia vs 171 (8.7%) of 1,963 controls. ET was associated with risk of incident dementia in unadjusted (HR = 2.78, 95% CI = 1.69–4.57, $p < 0.001$) and adjusted models (HR adjusted for age, education, ethnicity = 1.64, 95% CI = 0.99–2.72, $p = 0.055$). All participants with incident dementia had AD.

In secondary analyses, we excluded 316 participants with incident MCI; adjusted (age, education, ethnicity) HR = 2.07, 95% CI = 1.18–3.66, $p = 0.01$. Second, we excluded 388 participants with depression; adjusted HR = 1.76, 95% CI = 1.01–3.07, $p = 0.048$. Third, each medication variable was added as a covariate; adjusted (age, education, ethnicity, each medication) HR = 1.71, 95% CI = 0.97–3.01, $p = 0.06$. Fourth, adjusting for cohort, adjusted (age, education, ethnicity, cohort) HR = 1.61, 95% CI = 0.97–2.67, $p = 0.07$. Finally, we attempted to stratify by *APOE* σ4 gene status, but there were only 2 *APOE* σ4 positive ET cases with dementia. In these analyses, adjusted (age, education, and ethnicity) $HR_{APOE\ \text{å}4\ \text{gene positive}} = 0.40$, 95% CI = 0.09–1.71, $p = 0.22$ and adjusted $HR_{APOE\ \text{å}4\ \text{gene negative}} = 1.89$, 95% CI = 0.97–3.65, $p = 0.06$. Finally, 4 cases and no controls developed incident PD during follow-up (ET + PD); after excluding these 4, adjusted HR = 1.64, 95% CI = 0.00–2.71, $p = 0.056$.

We excluded 452 participants with baseline MCI. In these prospective analyses, 1 (1.5%) ET case developed incident MCI+M and 7 (10.4%) developed incident MCI-M; 156 (10.1%) controls developed MCI-M and 152 (9.9%) controls developed MCI-M. ET was not associated with increased risk of incident

MCI+M (unadjusted HR = 0.18, 95% CI = 0.03–1.31, $p = 0.09$; HR adjusted for age, education, ethnicity = 0.14, 95% CI = 0.02–1.00, $p = 0.05$) or MCI-M (unadjusted HR = 1.33, CI = 0.62–2.84, $p = 0.46$; HR adjusted for age, education, ethnicity = 0.97, 95% CI = 0.45–2.09, $p = 0.94$).

DISCUSSION In a population-based sample of elderly, ET was associated in adjusted analyses with a near-doubling of the odds of prevalent dementia and an approximately 60% increased risk of incident dementia.

ET is a progressive neurologic disease whose prevalence is particularly high among elders, and which continues to rise with advancing age; in the oldest old, the prevalence has been reported to be as high as 21.7%.[20] A variety of non-motor features, including cognitive and psychiatric, are now appreciated and undergoing further scientific scrutiny in case-control studies. While mild problems in cognition in excess of aging have been reported in many case-control studies,[6-8] there have been few attempts to examine whether these cognitive problems are more considerable.

One prior population-based study in central Spain reported an association between ET and prevalent dementia; their adjusted OR, 1.70, is similar to that which we report in New York.[10] In that study, the association was limited to older onset ET and dementia. We did not collect data on age at onset of ET so we were not able to determine whether the association was more robust in older onset cases. When taken together, these 2 studies, in different populations, suggest that ET, like PD, is a neurologic disorder associated with increased odds of dementia. In PD, however, the reported ORs are higher (e.g., 3.75)[28] than those reported in ET. An incidence study from the same cohort in central Spain reported an association between ET and incident dementia (adjusted HR of 1.66).[9] These results are strikingly similar to the HRs reported here (1.64) in a second population.

Both this and the Spanish study were population-based. Patients in clinical settings (especially movement disorder practices) are probably self-selected not to have dementia, thereby minimizing any apparent association between ET and dementia in those samples. This is because patients with dementia are more likely to attend memory disorders clinics. Also, onset of dementia may make attendance at a movement disorders clinic more difficult, especially if the motivation for attending that clinic is marginal (e.g., longstanding tremor that responds poorly to medication).

We excluded 1.7% of participants who either were diagnosed with PD (in the present study or in the past) or had ever used levodopa. Indeed, this prevalence of PD or possible PD (1.7%) is slightly in excess of that in other elderly population-based samples (approximately 1%).[29] Therefore, it is unlikely that our participants with ET actually had PD (i.e., diagnostic misclassification by underdiagnosis of PD).

As in our published prevalence study,[20] ET was diagnosed based on handwriting. This approach to distinguishing ET tremor from normal tremor has been advocated by other researchers as well.[21] Yet it is conceivable that there was some diagnostic misclassification. However, this would have biased our results toward the null hypothesis, making it more difficult to detect an association between ET and dementia. We further evaluated the validity our ET diagnoses in a small random subsample of cases, demonstrating complete (100%) agreement. Further indicating that the diagnostic method was valid is that our prevalence estimate, 5.5%,[20] based on this method, falls well within the range of other population-based studies that used different diagnostic methods.

The mechanistic basis for this association is unclear. Recent postmortem studies have demonstrated an increased prevalence of brainstem Lewy bodies in ET,[30,31] raising the question as to whether ET cases with dementia have Lewy body pathology. Alternatively, other pathologic mechanisms (e.g., cerebrovascular, Alzheimer-type changes) could better explain this association. Imaging and postmortem studies have yet to compare the prevalence of subcortical vascular pathology in ET cases and controls. In the Spanish study, the majority of ET cases with dementia had clinical diagnoses of AD[9]; we report similar findings here. Interestingly, a recent postmortem study found slightly more Alzheimer-type plaque and tangle pathology in ET cases than age-matched controls.[32,33] Clearly, the mechanistic basis for the dementia in ET merits additional study. Furthermore, a longer follow-up of our cohort would provide additional information about the possible subsequent development of other neurodegenerative disorders.

It is unclear why neither we nor the Spanish study found an association between ET and MCI. Participants with MCI represent a mixed group, some of whom eventually convert to dementia yet others do not.

Our analyses were limited to the elderly. ET may occur in younger patients; it would be advantageous to examine if this association is also found in a younger sample.

This and the Spanish study have clinical implications. Prevalence of dementia in ET appears to be greater than expected for age, indicating that dementia is likely to be a disease-associated feature of ET rather than a mere consequence of aging. This suggests that cognitive issues and dementia should more formally enter the clinical dialogue in ET rather than being regarded as normal features of aging. The implication of these findings, in terms of the routine clinical assess-

ment of cognitive impairment in patients with ET, requires further consideration. Furthermore, possible treatment of dementia should be considered.

AUTHOR CONTRIBUTIONS

The statistical analyses were conducted by S.P. Thawani and E.D. Louis.

DISCLOSURE

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