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Tremor and Other Hyperkinetic Movements

Review

The NEDICES Study: Recent Advances in the Understanding of the Epidemiology of Essential Tremor

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Abstract

Background: Essential tremor (ET) is the most common tremor disorder. ET has classically been viewed as a benign monosymptomatic condition. Yet over the past 10 years, a growing body of evidence indicates that this is a progressive condition that is clinically heterogeneous, and may be associated with a variety of different features. Large epidemiological studies such as the Neurological Disorders of Central Spain (NEDICES), a longitudinal, population-based survey, have contributed significantly to the changing view of the disease. Our aim is to review some of the main results of NEDICES within the larger framework of the epidemiology of ET.

Methods: Data for this review were gathered from all our articles published up to October 2011 regarding NEDICES study and "Essential Tremor".

Results: We have published 18 articles up to October 2011. The prevalence, incidence, and mortality of ET were analyzed in this cohort. In addition, ET was found to be associated with increased frailty and low morale, as well as with a series of non-motor manifestations, including cognitive deficits, mild cognitive impairment, dementia, depressive symptoms, and hearing impairment. Finally, the link between ET and Parkinson's disease (PD) was formally quantified in the NEDICES study, which demonstrated that the risk of developing incident PD was 4.3 times higher in prevalent ET cases than in age-matched controls without ET.

Conclusions: This review highlights the contributions of NEDICES towards the advancement of current knowledge of the epidemiology and clinical features of ET, and emphasizes the importance of population-based studies towards the understanding of complex, ageing-related diseases.

Keywords: Epidemiology, essential tremor, NEDICES

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Introduction

Essential tremor (ET) is considered the most prevalent tremor disorder. It has traditionally been viewed as a monosymptomatic disease characterized by kinetic arm tremor.[1,2] Yet over the past decades, a growing body of evidence indicates that ET is a progressive condition that is clinically heterogeneous, and which seems to be associated with a variety of different features. Actually this disease is considered to include several motor features, including tremor and ataxia, and several non-motor features, including possibly cognitive impairment and personality disturbances.[1,2]

Large epidemiological studies, such as the Neurological Disorders of Central Spain (NEDICES), have contributed significantly to the changing view of this disease.[3–5] The aim of this review was to consider some of the main results of NEDICES within the larger framework of ET epidemiology.

Methods

Data for this review were gathered from all our articles published up to October 2011 regarding NEDICES study and "Essential Tremor".

The NEDICES study

The NEDICES study is a longitudinal, population-based survey of major age-associated neurological conditions of elderly people.[3–13] Detailed accounts of the study population and sampling methods have been published.[3,5] The study population was composed of elderly subjects, ⩾65 years of age, living in three communities in central Spain (Las Margaritas, Lista and Arévalo). The registered study population was 6,395, of whom 5,914 were eligible, and 5,278 were enrolled.

As described,[3–5] face-to-face evaluations were performed at baseline (1994–1995) and follow-up (1997–1998). Participants were interviewed using a questionnaire that elicited data on demographics, neurological disorders (ET, Parkinson's disease [PD], stroke, and dementia), current medications (including those with potential central nervous system effects e.g., anxiolytics, stimulants, antihistamines), medical conditions (e.g., diabetes mellitus, hypertension, heart disease), smoking habits, and alcohol use pattern. Depressive symptoms and use of antidepressant medications were also assessed.

The evaluation of tremor and diagnosis of ET has been described in detail,[6,10] and involved a screening question ("have you ever had tremor of the head, hands, or legs that has lasted longer than several days?") with 68.6% sensitivity,[10] followed by a detailed general neurological examination by a senior neurologist, including a focused assessment of postural and kinetic tremors (sustained bilateral arm extension, bilateral finger–nose–finger maneuver, drawing Archimedes spirals),and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS).[6,10] For participants who could not be examined, medical records were obtained from general practitioners, from inpatient hospitalizations, and from neurological specialists (if they had visited one). Diagnostic criteria for ET (used in participants who were examined and in those whose medical records were reviewed) were similar to those used in a study conducted in Sicily.[14] Thus, participants were diagnosed with ET if they had an action tremor of the head, limbs, or voice without any other recognizable cause. Second, the tremor had to be of gradual onset (i.e., slow and progressive) and 1) present for at least 1 year or 2) accompanied by a family history of the same disorder (at least one reportedly affected first-degree relative). In addition, on an Archimedes spiral, tremor severity had to be moderate or greater (rating ⩾2 according to the Washington Heights-Inwood Genetic Study of ET Rating Scale).[15] Participants with tremor related to alcohol withdrawal, hyperthyroidism, anxiety, PD, anti-dopaminergic drug intake, lithium therapy, or other known causes of tremor were not considered to have ET. If ET was diagnosed, data on age of onset of tremor were elicited. ET cases identified by one of the eight NEDICES neurologists (see Acknowledgments) were subsequently examined independently by two additional neurologists who examined the participant together. They were classified as having ET only when the three neurologists agreed.

The second (i.e., follow-up) evaluation (1997–1998) also included a neuropsychological test battery, which was implemented by psychologists, social workers, student nurses, and general physicians, all of whom had been trained by a senior clinical investigator with expertise in health sciences research (see Acknowledgements, J.R.-N.).

Results

Currently, we have published 18 NEDICES articles regarding ET. These articles assessed a variety of epidemiological issues, including the prevalence, incidence, and mortality of ET. In addition, NEDICES studies demonstrated that ET was associated with increased frailty, low morale, and PD. Studies also demonstrated that ET was associated with a series of non-motor manifestations, including cognitive deficits, mild cognitive impairment, dementia, depressive symptoms, and hearing impairment. These studies are summarized in Table 1 and their data will now be reviewed.

Prevalence and incidence

The NEDICES researchers identified 256 persons (152 females, 104 males) with ET out of 5,278 screened. Thus, the prevalence of ET (age 65 and older) on May 1 1994 was 4.8% (95% confidence interval [CI]=4.2–5.4); for males, the prevalence was 4.6% (95% CI=3.7–5.4) and for females it was 5.0% (95% CI=4.2–5.8).[6] The prevalence increased with advancing age for both males and females.[6] Of 256 prevalent ET cases, 87 (34.0%) reported having an affected relative, and 204 (79.7%) were detected through the NEDICES screening and had not been diagnosed prior to the NEDICES study.

To estimate the incidence of ET, the ET-free cohort was evaluated at follow-up (a median of 3.3 years after the initial assessment in 1997 to 1998). Eighty-three incident ET cases were identified among 3,942 individuals assessed at follow-up. The adjusted annual incidence (per 100,000 person-years) in the population aged 65 years and older was 616 (95% CI=447–784).[10] Sixty-four (77.1%) of 83 incident cases were detected through the NEDICES study and had not been diagnosed by a physician prior to the NEDICES study assessment. The point estimates for incidence increased with age, until the oldest age stratum, and no gender differences in incidence were found.[10] These incidence data represent the only population-based incidence data on ET.

Mortality

Outside of the NEDICES study, there have been no population-based and no prospectively collected data on mortality in ET. Also, there have been other studies comparing mortality in ET cases to that of a simultaneously enrolled control group. In the NEDICES study, the risk of mortality was assessed and was found to be slightly yet significantly increased in ET. Specifically, there were 33 (16.4%) deaths among 201 ET cases and 465 (13.9%) among 3,337 controls at follow-up 3 years after baseline assessment.[16] In an unadjusted Cox model, the risk of mortality was increased in ET (RR=1.59, 95% CI=1.11–2.27, p=0.01).[16] In a Cox model that adjusted for baseline age, gender, educational category, current alcohol drinking, use of antidepressant medication, and community, RR=1.45, 95% CI=1.01–2.08, p=0.04.[16] In an adjusted Cox model restricted to persons with longer (>3 years) follow-up, RR=4.69 (95% CI=2.18–10.07,

Table 1. Main Results Regarding Essential Tremor in NEDICES Study

	Results	Comments
Prevalence	Overall: 4.8% (95% CI=4.2–5.4). Men: 4.6% (95% CI=3.7–5.4). Women: 5.0% (95% CI=4.2–5.8).	34% of the ET cases had an affected relative and 79.7% were detected through the NEDICES study and had not been diagnosed by a physician prior to the NEDICES study assessment.
Incidence	616 per 100,000 person-years (95% CI=447–784)	77% of incident cases were detected through the NEDICES study and had not been diagnosed by a physician prior to the NEDICES study assessment.
Mortality	Unadjusted RR=1.59, 95% CI=1.11–2.27, p=0.01). Adjusted RR=1.45, (95% CI=1.01–2.08, p=0.04).	ET may be a disease not only of increased morbidity but of increased mortality as well.
Frailty	A 20-item frailty score, which assessed comorbid conditions, number of medications, and functional activity was higher in ET cases than in controls (8.6 ± 5.2 vs. 6.8 ± 4.6, $p<0.001$)	This study suggests that there may be an additional frailty syndrome in ET that is above and beyond what has been described previously.
Subjective well-being	The Philadelphia Geriatric Center Morale Scale score was lower in ET cases than controls (9.41 ± 3.21 vs. 10.39 ± 2.92, $p<0.001$)	Morale may be lower in ET cases than in matched controls.
Self-reported depressive symptoms	Prevalent ET cases were twice more likely than controls to report depression and three times more likely to be taking antidepressant medications. In prospective analyses, baseline self-reported depression and, perhaps, baseline use of antidepressant medication were associated with incident ET.	ET seems to be associated with depressive symptoms.
Cognitive functioning	ET cases performed less well than controls especially on tests of global cognitive performance and frontal executive function. Lower cognitive test scores were associated with more reported functional difficulty. During the 3-year follow-up period, baseline cognitive test scores declined at a rate that was seven-times faster in ET cases than controls	A frontosubcortical-type dysfunction occurs in some ET patients. Lower cognitive test scores in ET, rather than being clinically inconsequential, seem to have a clinical-functional correlate.
MCI	ET cases with tremor onset after age 65 years were 57% more likely to have mild cognitive impairment than controls (OR=1.57, 95% CI=1.03–2.38, p=0.03).	Elderly-onset ET may be associated with MCI
Prevalent dementia	ET cases with tremor onset after age 65 were 70% more likely to be demented than were controls (OR=1.70, 95% CI=1.04–2.76, p=0.03).	Elderly-onset ET may be associated with dementia
Incident dementia	ET cases with tremor onset after age 65 years were twice as likely to develop incident dementia than were controls (RR=1.98, 95% CI=1.14 -3.45, p=0.01).	Elderly-onset ET may be associated with incident dementia
incident Parkinson's disease	ET cases were four times more likely than controls to develop incident PD during prospective follow-up.	The link between ET and incident PD has for the first time been formally quantified

Table 1. Continued

	Results	Comments
Hearing impairment	In an adjusted logistic regression analysis participants who reported hearing impairment were 30% more likely to suffer from ET than were controls (OR=1.3; 95% CI=1.01–1.7, p=0.04).	ET may be associated with hearing impairment.
Smoking	Smokers were nearly half as likely to have ET as were never smokers (adjusted OR=0.58, p=0.004). In addition, baseline heavy cigarette smoking was also associated with a lower risk of incident ET (adjusted RR=0.29, p=0.03)	Smoking may be associated with decreased the risk of developing ET
Ethanol	In an adjusted Cox model, the highest baseline drink-year quartile doubled the risk of incident ET (RR=2.29, p=0.018)	Higher levels of chronic ethanol consumption may be associated with increased the risk of developing ET

Abbreviations: CI, confidence interval; ET, essential tremor; MCI, mild cognitive impairment; NEDICES, Neurological Disorders of Central Spain; OR, odds ratio; PD, Parkinson's disease; RR, relative risk.

p=0.001).[16] These data suggest that ET is a disease not only of increased morbidity but of increased mortality as well. Additional studies are needed to confirm these results.

Frailty

Although ET has been associated with a variety of comorbidities (hearing impairment, cancer, and depressive symptoms), frailty had not been studied in ET prior to NEDICES. Data collected during the NEDICES evaluations were compiled, and a 20-item frailty score was constructed, which assessed comorbid conditions, number of medications, and functional activity.[17] The frailty score was compared in 237 non-demented elderly ET cases and 3,903 non-demented age-matched controls from the NEDICES.[17] The frailty score was higher in ET cases than in controls (8.6 ± 5.2 vs. 6.8 ± 4.6, $p<0.001$).[17] Stratifying the frailty score into quartiles and tertiles similarly revealed case–control differences (both $p<0.001$).[17] The frailty score also increased with age ($r=0.25$, $p<0.001$), was higher in females than males ($p=0.02$), was correlated with subjective rating of health status ($r=0.42$, $p<0.001$), and was inversely correlated with body weight ($r=-0.06$, $p<0.001$) and hours/day that participants performed moderate or intensive physical activities ($r=-0.16$, $p<0.001$).[17] Although ET has previously been associated with several comorbidities, this study demonstrated the presence of case–control differences in additional comorbidities, medication usage, self-reported limitations, and functional activities, suggesting that there may be an additional frailty syndrome in ET that is above and beyond what has been described previously. Whether this increased frailty is a contributor to the increased risk of mortality that has been observed in some studies is a question that deserves further scrutiny.

Subjective well-being

Subjective well-being (morale) was assessed in 187 ET cases and 561 matched controls from NEDICES using the Philadelphia Geriatric Center Morale Scale (PGCMS) (range =0 low morale to 17), which included three-dimensions of psychological well-being: agitation, lonely dissatisfaction, and attitude toward own aging. The PGCMS score was lower in ET cases than controls (9.41 ± 3.21 vs. 10.39 ± 2.92, $p<0.001$), as were the Agitation subscore (3.17 ± 1.71 vs. 3.78 ± 1.67, $p<0.001$) and the Lonely Dissatisfaction subscore (3.75 ± 1.34 vs. 4.02 ± 1.24, $p<0.05$). Nearly one-half of the ET cases were classified as having low morale compared with only one-third of controls ($p=0.006$). In a linear regression analysis adjusting for demographic factors and multiple comorbid conditions, ET cases had a lower PGCMS score than controls ($p<0.001$), and exclusion of participants on antidepressant medication did not change the results. The results of the study indicated that morale was significantly lower in community-dwelling ET cases than in matched controls. Detection and possible treatment of this problem might improve the psychological well-being of patients with ET.

Depressive symptoms

In NEDICES, self-reported depression and use of antidepressant medications were evaluated at baseline (1994–1995) and 3 years later.[18] In cross-sectional analyses, prevalent ET cases were twice more likely than controls to report depression (103 [43.8%] of 235 ET cases vs. 1,137 [26.0%] of 4,379 controls; adjusted odds ratio OR=2.20, 95% CI=1.66–2.93, $p<0.001$) and three times more likely to be taking antidepressant medications (16 6.8% cases vs. 113 2.6% controls; adjusted OR=3.33, 95% CI=1.91–5.82, $p=0.001$).[18] In prospective analyses, baseline self-reported depression (adjusted RR =1.78, 95% CI=1.11–2.89, $p=0.018$) and, perhaps, baseline use of antidepressant medication (adjusted RR =1.90, 95% CI=0.59–6.05, $p=0.28$) were associated with incident ET.[18] This study indicated that, rather than being totally benign, ET seems to be associated with a mood disorder. Furthermore, aside from being a secondary response to disease

manifestations (i.e., the tremor), the mood disorder could be a primary feature of the underlying disease, preceding the motor manifestations.

Cognitive function, mild cognitive impairment, and dementia

Two-hundred and thirty-two ET cases and 696 matched controls (median 75 years) from the NEDICES underwent a neuropsychological assessment, including tests of global cognitive performance, frontal executive function, verbal fluency, and memory.[19] Fifty-six ET cases were first diagnosed with ET during the NEDICES evaluation and only 14 (6%) were taking medication for tremor.[19] Even after adjusting for age, gender, education, premorbid intelligence, medications, and depressive symptoms, ET cases performed less well than controls on most neuropsychological tests, and especially tests of global cognitive performance (37-item Mini-Mental State Examination score $=27.0\pm6.7$ in cases vs. 28.9 ± 5.9 in controls, $p<0.001$) and frontal executive function (Trail Making Test number of errors $=8.7\pm11.0$ in cases vs. 3.8 ± 7.6 in controls, $p<0.001$).[19] Forgetfulness was reported in 117 (50.4%) ET cases vs. 300 (43.1%) controls ($p=0.05$).[19]

The association between mild cognitive impairment and ET had only been examined in one prior study.[20] In NEDICES, all dementia-free persons with mild cognitive impairment and ET were identified. Forty-two (20.3%) of 207 ET cases had mild cognitive impairment vs. 399 (16.1%) of 2,472 controls (OR=1.32, 95% CI=0.93–1.89, $p=0.12$).[21] In a model that adjusted for age, gender, educational level, smoking, hearing impairment, depressive symptoms or anti-depressant use, and use of a medication that could potentially affect cognitive function, ET was associated with mild cognitive impairment (OR=1.28, 95% CI=0.88–1.84, $p=0.19$).[21] Yet in an adjusted model, ET cases with tremor onset after age 65 years were 57% more likely to have mild cognitive impairment than controls (OR=1.57, 95% CI=1.03–2.38, $p=0.03$), whereas ET cases with tremor onset prior to age 65 and controls were equally likely to have mild cognitive impairment (OR=0.73, 95% CI=0.34–1.57, $p=0.43$).[21]

NEDICES provided evidence that the cognitive deficits in ET are not static, and they appear to be progressing at a faster rate than in elders without this disease.[22] A 37-item version of the Mini-Mental State Examination (37-MMSE) was administered to 2,319 non-demented participants (72.4 ± 5.8 years of age), including 135 prevalent ET cases and 2,184 controls.[22] At baseline, the mean 37-MMSE in cases was 28.8 ± 5.8 vs. 30.2 ± 4.8 in controls ($p=0.02$).[22] During the 3-year follow-up period, the 37-MMSE declined by 0.70 ± 3.2 points in cases vs. only 0.11 ± 3.8 points in controls ($p=0.03$).[22] In analyses that adjusted for age, education, and other potential confounders, the case–control difference remained robust.[22]

NEDICES also demonstrated that lower cognitive test scores in ET, rather than being inconsequential, have a clear clinical–functional correlate.[23] In NEDICES, the 37-MMSE and an 11-item version of the Pfeffer Functional Activities Questionnaire (FAQ) were administered to non-demented ET cases and controls.[23] The FAQ was 55.5% higher (i.e., lower function) in 208 ET cases than 3,616 controls (2.8 ± 4.8 vs. 1.8 ± 4.2, $p<0.001$).[23] Patients reported more difficulty (i.e., higher FAQ scores) with FAQ items that were cognitive measures as well as FAQ items that were cognitive-motor in nature.[23] In cases, a lower 37-MMSE was associated with more difficulty on both cognitively based and cognitive–motor-based FAQ items ($p<0.001$).[23]

The association between ET and prevalent dementia had not previously assessed prior to NEDICES. In NEDICES, 31 (11.4%) of 273 ET cases had prevalent dementia vs. 204 (6.0%) of 3,382 controls (OR=2.00, 95% CI=1.34–2.98, $p=0.001$).[24] In a model that adjusted for age, stroke, and educational level, OR=1.35, 95% CI=0.87–2.18, and $p=0.17$.[24] In an adjusted model, ET cases with tremor onset after age 65 were 70% more likely to be demented than were controls (OR=1.70, 95% CI=1.04–2.76, $p=0.03$), whereas ET cases with early tremor onset ($\leq$ age 65) and controls were equally likely to be demented (OR=0.38, 95% CI=0.09–1.73, $p=0.21$).[24]

In longitudinal analyses, non-demented ET cases and controls were followed prospectively, and the risk of incident dementia was estimated in ET cases vs. controls using Cox proportional hazards models.[25] The 3,891 participants had a mean duration of follow-up of 3.2 years.[25] Sixteen (7.8%) of 206 ET cases developed incident dementia vs. 145 (3.9%) of 3,685 controls (unadjusted RR=2.08, 95% CI=1.24–3.50, $p=0.006$ and adjusted RR=1.66, 95% CI=0.99–2.80, $p=0.054$).[25] In an adjusted model, ET cases with tremor onset after age 65 years were twice as likely to develop incident dementia than were controls (RR=1.98, 95% CI=1.14–3.45, $p=0.01$), whereas ET cases with earlier tremor onset ($\leq$age 65) and controls were equally likely to develop incident dementia (RR=0.74, 95% CI=0.19–3.20, $p=0.79$).[25]

PD

In NEDICES, ET cases were four times more likely than controls to develop incident PD during prospective follow-up.[26] After a median of 3.3 years, 12 (5.8%) of 207 ET cases developed parkinsonism compared with 56 (1.6%) of 3,606 controls (adjusted RR=3.47, 95% CI=1.82–6.59, $p=0.001$).[26] Six (3.0%) of 201 ET cases developed incident PD vs. 24 (0.7%) of 3,574 controls (adjusted RR=4.27, 95% CI=1.72–10.61; $p=0.002$).[26]

Hearing impairment

In NEDICES, ET seemed to be associated with reported hearing impairment.[27] Ninety-six (38.7%) of 248 ET cases vs. 1,371 (29.4%) of 4,669 controls ($p=0.002$) reported hearing impairment.[27] In a logistic regression analysis that adjusted for age, gender, educational level, depressive symptoms, and dementia, participants who reported hearing impairment were 30% more likely to suffer from ET than were controls (OR=1.3; 95% CI=1.01–1.7, $p=0.04$).[27]

Smoking and ET

In NEDICES, cigarette smoking habits were assessed in 221 prevalent ET cases (75.5 ± 7.1 years old) and 663 matched controls (74.6 ± 7.0 years old),[28] and the results suggested that cigarette smoking might be a protective factor for ET. Those who smoked were marginally less likely to have ET than those who had never

smoked (22.0% vs. 27.0%, OR=0.76, 95% CI=0.55–1.04, p=0.09).[28] In an analysis that adjusted for confounding factors (drink-years and depressive symptoms), those who smoked were nearly half less likely to have ET than those who had never smoked (OR=0.58, 95% CI=0.40–0.84, p=0.004).[28] There was a strong inverse association between pack-years and odds of ET (adjusted OR=0.991, 95% CI=0.984–0.997, p=0.005, i.e., with every 10 pack-year increase, odds of ET were lowered 10%).[28]

Smokers in the highest pack-year tertile were one-third as likely to have ET than those who had never smoked (adjusted OR=0.39, 95% CI=0.22–0.69, p=0.001).[28]

In prospective analyses, the NEDICES study also demonstrated an association between baseline heavy cigarette smoking and lower risk of incident ET.[29] Participants were stratified into baseline pack-year tertiles, and few incident ET cases were in the highest baseline tertile (4 [5.2%] cases vs. 431 [13.2%] controls, p=0.039).[29] In Cox proportional hazards models, the highest baseline pack-year tertile was associated with lowest risk of incident ET; those in the highest pack-year tertile were one-third as likely to develop ET as non-smokers (RR=0.37, 95% CI=0.14–1.03, p =0.057 unadjusted model and RR=0.29, 95% CI=0.09–0.90, p=0.03 adjusted model).[29]

Drinking alcohol and risk of ET

In NEDICES, higher levels of chronic alcohol consumption seemed to increase the risk of developing ET.[30] In a Cox proportional hazards model adjusting for cigarette pack-years, depressive symptoms and community, the baseline number of drink-years was marginally associated with a higher risk of incident ET (RR=1.003, p=0.059). In an adjusted Cox model, the highest baseline drink-year quartile doubled the risk of incident ET (RR=2.29, p=0.018), while other quartiles were associated with more modest elevations in risk (RR in 3rd quartile =1.82, p=0.10, RR in 2nd quartile =1.75, p=0.10, RR in lowest quartile =1.43, p=0.34 vs. non-drinkers, RR=1.00).[30] With each higher drink-year quartile, the risk of incident ET increased an average of 23% (p=0.01, test for trend).[30]

Antihypertensive drugs and risk of ET

Recent interest in antihypertensive agents, especially calcium channel blockers, has been sparked by the notion that these medications may be neuroprotective.[31] However, in NEDICES, baseline use of antihypertensive agents was not associated with reduced risk of incident ET.[32]

Discussion

NEDICES and other neuroepidemiological, clinical, and pathological studies[1,33,34] have substantially contributed to the changing of view of ET in recent years. The traditional view of ET as a monosymptomatic condition is being replaced by an appreciation of the spectrum of clinical features and clinical associations, with both motor and non-motor elements.[1,35] It is even possible that ET might be a family of diseases, unified by the presence of kinetic tremor, but further characterized by etiological, clinical, and pathological heterogeneity.[34]

The prevalence of ET in NEDICES among persons age 65 and older was 4.8%.[6] This figure is similar to that which has been reported in other population-based studies.[36] The finding that approximately 80% of the ET cases had not been diagnosed previously points to the fact that this is an underdiagnosed disease.[6] Estimates of disease incidence are difficult to obtain as they require longitudinal data. Prior to NEDICES, the incidence of ET had been estimated in only one study.[37] That study was based on a retrospective review of medical records in Rochester, MN, and probably underestimated the true incidence of ET because entry into the medical record system as an ET case would have required that the illness was severe enough to be recognized by the treating physician.[37] The incidence estimates from NEDICES (616 per 100,000 person-years in persons ⩾65 years)[10] were substantially higher than those reported using data from the study in Rochester (incidence 58.6 per 100,000 among those aged 60–69; 76.6 among those aged 70–79; and 84.3 among those ⩾80 years).[37]

Mortality in ET had not been studied systematically prior to NEDICES. However, with the presence in some patients of functional impairments,[38] gait difficulty,[39] mild cognitive impairment,[21] dementia,[20,24,25] and increased frailty,[40] it was conceivable that ET could influence the risk of mortality. In one retrospective study, survival of patients with ET was similar to that of a historical control group.[37] In that study, the mean age at diagnosis was 58 years, and the mean length of follow-up was 9.7 years; therefore, cases were not all followed into advanced age, when the risk of mortality in ET is likely to rise.[37] By contrast, in the NEDICES study, which enrolled a contemporary rather than historical control group, the risk of mortality was slightly but significantly increased in ET cases (adjusted RR=1.45, 95% CI=1.01–2.08, p=0.04) at 3 years.[16] Additional prospective, population-based studies are needed.

The NEDICES study demonstrated that ET cases were twice more likely than controls to report depression and three times more likely to be taking antidepressant medications.[18] In prospective analyses, baseline self-reported depression was associated with an increased risk of incident ET.[18] These prospective data suggest that the mood disorder in ET may be more than a secondary response to disease manifestations; this mood disorder may be a primary feature of the underlying disease as it is in PD.[18]

Mild cognitive deficits, mainly in frontal-executive function and memory, have been reported to occur in ET patients in many independent studies,[41] including NEDICES.[19] In line with this, in the NEDICES study, lower cognitive test scores were associated with more reported functional difficulty, indicating that lower cognitive test scores in ET, rather than being clinically inconsequential, seem to have a clinical–functional correlate.[23] In the NEDICES study, baseline cognitive test scores were lower in non-demented ET cases than non-demented controls; moreover, during the 3-year follow-up period, these scores declined at a rate that was seven-times faster in the ET cases.[22] In a second population-based study of elders in New York, ET was also associated with both increased odds of prevalent dementia

and increased risk of incident dementia,[20] with ORs and RRs similar to those reported in the NEDICES study.

The relationship between ET and PD has been the subject of scrutiny and debate for a long time, but there is now growing evidence that the two tremor disorders are related, at least in some patient populations.[42] The link between ET and incident PD has for the first time been formally quantified in the NEDICES study, which demonstrated that the risk of developing incident PD was 4.3 times higher in prevalent ET cases than in age-matched controls without ET.[26] The NEDICES researchers found another link between both diseases, the effect of smoking on ET. It has long been known that PD is inversely associated with smoking cigarettes.[43] Using a population-based, nested case–control design in the NEDICES study, smokers were nearly half as likely to have ET as those who had never smoked (adjusted OR=0.58, p=0.004).[28] Furthermore, in the NEDICES cohort, baseline heavy cigarette smoking was also associated with a lower risk of incident ET (adjusted RR=0.29, p=0.03).[29]

The NEDICES study also examined the effect of alcohol, a well-known Purkinje cell toxin,[44] on the risk of ET. Thus, higher levels of chronic alcohol consumption were associated with increased the risk of developing ET.[30] Further studies are required to explore whether higher consumption levels are a continued source of underlying cerebellar neurotoxicity in patients who already manifest this disease.

Finally, hearing impairment in ET has been examined in the NEDICES study.[27] ET cases reported more hearing impairment than did matched controls.[27] This finding had been found in ET in a previous clinical series.[45] Although the basis for this possible hearing impairment is unknown, both central and peripheral nervous system mechanisms have been suggested.[27,45]

In conclusion, we can say that NEDICES study has been very important not only for the epidemiology of ET but for the epidemiology of other aging-related diseases, such as PD, dementia, and stroke. Its longitudinal design makes it ideal for analyzing risk factors and mortality. As different diseases have been assessed, different associations that were not even suspected at the time of the onset of the study, such as dementia and ET, have been found. This fact supports its value as a study that has been able to find important clues about the risk factors for and mechanisms behind neurodegeneration and aging.

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