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Tremor and Other Hyperkinetic Movements

Articles

Mild Cognitive Impairment, Dementia, and Affective Disorders in Essential Tremor: A Prospective Study

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Abstract

Background: It is now reported that non-motor features, cognitive and affective problems, are becoming a major factor in essential tremor (ET). The aim of this study was to investigate the prevalence of cognitive and affective dysfunction in ET and to prospectively follow-up changes in the subjects.

Methods: Fifty-two persons over the age of 50 years were recruited from the Movement Disorder Clinic. The subjects underwent baseline neurological, cognitive, and mood assessments and repeat assessment 2 years later.

Results: The mean age was 68 years, with an average age of ET onset of 55.8 years and with a mean disease duration of 11.7 years. At initial cognitive assessment using various instruments and the Clinical Dementia Rating Scale, 69.2% had mild cognitive impairment (MCI). There were disturbances in phonemic fluency, verbal memory, concentration, and semantic fluency; 25% suffered from anxiety and 17.6% from depression. During the 2 years there was an annual 8.4% conversion rate to dementia, with all convertors initially suffering from MCI. Another 25% converted from no initial cognitive impairment to MCI within 2 years. At follow-up the same percentage was still suffering from anxiety.

Discussion: The study confirms our hypothesis that ET patients suffer from MCI and anxiety. Though a control group was not used, the conversion rates for patients without ET and with/without MCI are known. The uniqueness of this study is that at follow-up, those with ET and MCI had a similar conversion rate to dementia to those suffering from MCI only. Additionally, persons with ET and no initial cognitive impairment were found to be at greater risk for developing MCI than the normal population. Clinicians must increase their awareness of cognitive impairment and anxiety in persons with ET and begin immediate treatment when indicated.

Keywords: Essential tremor, cognitive impairment, affective disorders

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Introduction

Essential tremor (ET), a progressive, action-based tremor affecting the extremities, produces functional disabilities in basic and instrumental activities of daily living (ADL).[1,2] The Washington Heights–Inwood Genetic Study of Essential Tremor (WHIGET) defines the criteria for clinical diagnosis of ET as the presence of a kinetic tremor in at least one extremity, often occurring during task performance and interfering with at least one ADL.[1,3] It is important to ensure the absence of other conditions or medications that may cause the tremor. ET is the most common cause of movement disorder in humans, with a prevalence rate of about 5% in the general population and rising to over 20% in the elderly, with a more rapid progression in the elderly.[4]

There is increasing evidence that the disease is a multiple-system disorder because of additional motor features (intentional tremor and ataxia) and non-motor features (cognitive deficits and mood disorders). Medical literature has shown that those suffering from ET actually have a higher incidence of dementia.[5,6] Over the last decade reports have been published noting cognitive dysfunction in patients with ET, with

higher prevalence of mild cognitive impairment (MCI), especially in the elderly.[7,8] Studies show that on assessing cognition with a battery of neuropsychological instruments, cognitive deficits were present in phonemic fluency of word generation, in naming, in recent memory, in working memory, and in mental set-shifting (executive function).[9–11]

Another non-motor problem reported is the presence of mood disorders. Lombardi et al.[9] reported higher levels of depression in persons with ET, and Duane and Vermilion[10] described prevalence rates of 49% for depression and 55% for anxiety in those diagnosed with ET.

Cognitive decline is known to develop over an extended period of time,[12] starting from normal through interim stages of cognitive impairment and, finally, to dementia. The stages are often classified by clinical global scales, such as Morris's Clinical Dementia Rating (CDR) Scale.[13] During the interim stages, screening instruments for detection of cognitive decline score in the normal range, yet there is actually some memory impairment.[14] This stage, termed MCI, is defined by a complaint of memory loss as reported by the patient himself, his family, or his physician but with normal performance of ADL and normal global cognitive function. However, there is evidence of objective memory loss greater than 1.5 standard deviation (SD) on neuropsychological testing.

The aim of this study was initially to investigate the prevalence of MCI and mood disorder in persons diagnosed with ET, and, secondly, to follow-up the cohort longitudinally for 2 years and to prospectively investigate possible cognitive and mood changes during this period.

Our working hypotheses were that the subjects with ET would have cognitive dysfunction and affective disorder and also that those with ET and MCI would have a high conversion rate to dementia, higher than that reported in the medical literature for persons with MCI without ET.

Methods

Subjects

Fifty-two persons of both genders over the age of 50 with diagnosis of ET by neurological clinical assessment and who had attended the Movement Disorder Clinic in Carmel Medical Center were recruited into the cohort. The inclusion criteria required that the subjects fulfill the WHIGET criteria for definite ET, score 24 or more on Folstein's Mini-Mental Status Examination (MMSE) cognitive screening instrument, and be medically stable at the time of recruitment. Exclusion criteria were those with another neurological disorder such as stroke or parkinsonism.

The study was approved by the local hospital ethics review board. Prior to partaking in the study, the subjects signed an informed consent form.

Study protocol

At the initial consultation, demographic and health characteristics were recorded, and thereafter the subjects underwent a full neurological, cognitive, and affective assessment. Each subject underwent cognitive and affective assessments twice, at baseline and after 2 years, for the purpose of detecting the presence of dementia and/or MCI, and the presence of anxiety and/or depression

Demographic and health characteristics

All subjects had their demographic characteristics recorded, including age, gender, marital status, education, and profession. Health characteristics relating to neurological history of ET were also collected, including duration of the disease and the age of onset.

Cognitive assessment

Screening instruments. Initially, the subjects were screened using Folstein's MMSE and Pfeiffer's Short Portable Mental Status Questionnaire (SPMSQ), both validated screening instruments for global cognitive function. Further cognitive assessment was evaluated by means of the Saint Louis University Mental Status Examination (SLUMS),[15] which has a maximum score of 30 and a cut-off point of 20 for dementia and 21–23 for MCI. The global instrument, the CDR Scale,[13] was used by the physician for clinical impression of the subjects' cognitive status with a score of 0 as normal, 0.5 defining MCI, and 1.0 or more defining dementia.

Neuropsychological instruments. Neuropsychological instruments were used to determine the specific areas of cognitive impairment. Generating a list of animals assessed category fluency and F–A–S word generation for phonemic fluency. For category fluency, an elderly person should be able to list at least 10 animals within a time limit of 1 minute. For phonemic fluency, the participant must generate within the time limit of 1 minute as many words as possible beginning with one of the letters, F, A, or S, as chosen by the physician. A total of 10 words or less generated within this time limit indicates a disturbance in phonemic fluency. To test logical memory, after being read a story, the participant should be able to remember up to 12 points. A score between 8 and 12 is suggestive of MCI. To assess verbal memory, the participant was given a modified version of Rey's Auditory Verbal Learning Test (RAVLT). Here the participant was repeatedly read a list of 15 words. After each reading, the participant was requested to repeat as many words as possible. The subject was then tested in other areas, and after 10 minutes was requested to recall the list of words. For testing the final area of recognition, the participant was read a list of 30 words, which contained the original 15 words. The results were graded as normal if the participant remembered eight out of 15 or more words in immediate acquisition, seven out of 15 or more on delayed free-recall, and 12 out of 15 or more on recognition. The cognitive abilities of speed and fluid intelligence were examined using the timed Trail Making Test Part A. The participant was given a piece of paper with numbers from 1 to 25 and was requested to join the numbers sequentially, with the completion rate timed. The number 10,000 is divided by time (in seconds). A score of over 25 is regarded as normal, and a score below 12 is regarded as abnormal. A score in the "grey" area is probable MCI. Finally, for concentration, the number of items recalled was documented. The elderly should be able to remember a sequence of up to five items.

Diagnosis of dementia and MCI

The diagnosis of MCI in this study was made by ensuring that the MMSE score was greater than 24 out of 30 with a CDR grade of 0.5

Table 1. Demographic and Health Characteristics of the Study Population

Variable	Number (n=52)	%
Male	29	55.8
Mean age (SD) (years)	68.2 (7.46)	50–88
Mean education (SD) (years)	11.7 (4.19)	0–20
Mean age of onset (SD) (years)	55.8 (15.1)	
Mean duration of illness (SD) (years)	11.7 (13.59)	
WHIGET rating		
Mild kinetic tremor	12	23.1%
Obvious kinetic tremor	31	59.6%
Large-amplitude kinetic tremor	9	17.3%

Abbreviations: SD, Standard Deviation; WHIGET, Washington Heights–Inwood Genetic Study of Essential Tremor.

and a score between 21 and 23 on the SLUMS instrument.[15] The scores from multiple neuropsychological instruments were used to indicate the areas of cognitive impairment in MCI. Dementia was defined by a score below 24 out of 30 on MMSE with a CDR grade of 1 or more and a score of 20 or less on the SLUMS instrument.

Diagnosis of anxiety and depression

Finally, the subjects completed two instruments for screening for a mood disorder: the short interviewer-assisted depression screening instrument (short Zung) for depression[16] and the Short Anxiety Screening Test (SAST) for anxiety.[17] The short Zung Scale is a 10-question validated screening instrument for the presence of depression. An index score of 70 or more out of 100 is suggestive of suffering from depression. SAST is also a 10-question scale screening for anxiety, where a score of 24 or more out of 40 is regarded as positive.

Statistical analysis

The data were analyzed using SPSS software version 21.0. The means, SD, and ranges were calculated for the interval variables, and the mode for nominal variables. A variable of time from initial assessment (T1) until follow-up after 2 years (T2) was generated, as well as an interval variable for change in cognitive and mood state defined by a worsening score on instruments from initial assessment to follow-up. The two groups, those with and those without MCI, were compared for differences at initial entry to the study and at follow-up. A p-value of <0.05 was considered statistically significant for all analyses.

Results

The study population consisted of 52 subjects, 55.8% of whom were males. The mean age was 68.2 years (range 50–88 years) and the mean education level was 12 years. On examination of the characteristics of the sample, the mean age of onset of ET was 55.8 years with an average disease duration of 11.7 years at the time of the study (Table 1).

At initial assessment (T1), no subjects were demented as defined by the instruments; however, 69.2% were diagnosed as suffering from MCI (Table 2). On more detailed neuropsychological testing to define the areas of cognitive disturbance, 63.6% had disturbances in phonemic fluency, 44% had difficulty in concentration, and 30% had disturbance in verbal memory by RAVLT. Minor disturbances were also found in semantic fluency, in logical memory, and in spatial orientation. With regard to mood disorders, 25% were found to be suffering from anxiety and 17.9% from depression.

By the above cognitive assessment, the study population was divided into two sub-groups, those with MCI and those without any evidence of cognitive dysfunction. Comparing the two groups, differences only in mean scores on some of the cognitive instruments were found. The group with MCI scored lower on MMSE, on SLUMS, and on verbal memory and showed a trend for worsening scores on SPMSQ and listing on semantic memory (Table 3).

On follow-up at time T2, after a mean of 27.5 months, 28 of the initial 52 subjects (53.8%) failed to complete the study (Table 4). Of the 28 failure-to-complete subjects, 25 refused to continue, two were institutionalized, and one died. On analysis of the 24 patients who did complete the follow-up, four had converted to dementia over the 2-year period (giving a conversion rate of 8.35% per annum). All of the four converters had been diagnosed as suffering from MCI at initial assessment. Of the 20 subjects who were non-convertors to dementia, 16/20 (80%) were diagnosed as suffering from MCI at time T2 and the rest had normal cognition. Seventy-five percent (12/16) of those with MCI at follow-up were suffering from MCI at initial assessment; however, 25% (4/16) had no cognitive impairment at initial assessment. Within the MCI group, those with a further decline in their cognitive state had a mean MMSE loss of around 2 points and a mean loss of 3 points on the SLUMS instrument over the 2 years. On neuropsychological testing, 70% showed disturbances in phonemic fluency, 63.6% had difficulty in concentration, and 37.5% had disturbance in verbal memory by RAVLT. We still

Table 2. Cognitive and Affective Assessment at T1

Screening Instruments	T1 (n=52)	
MMSE mean scores (SD)	27.3 (1.9)	
SLUMS mean scores (SD)	21.9 (3.9)	
MCI by MMSE >24/30; CDR scale score=0.5 and SLUMS=21–23/30	36 (69.2%)	
Neuropsychological instruments		Abnormal
Semantic fluency mean scores (SD)	12.9 (3.1)	25%
Phonemic fluency mean scores (SD)	8.9 (4.2)	63.6%
Trail Making Test A mean scores (SD)	15.8 (5.2)	19%
RAVLT verbal memory mean scores (SD)		
Immediate	8.8 (2.3)	33%
Delayed	7.0 (3.2)	39%
Recognition	11.3 (3.1)	37%
Logical memory—mean scores (SD)	10.4 (3.0)	25%
Items mean score (SD) (concentration)	5.6 (1.2)	44%
Percentage with anxiety by SAST	25%	
Percentage with depression by short Zung instrument	17.9%	

Abbreviations: CDR, Clinical Dementia Rating Scale; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental Status Examination; RAVLT, Rey's Auditory Verbal Learning Task; SAST, Short Anxiety Screening Test; SD, Standard Deviation; SLUMS, Saint Louis University Mental Status Examination.

found minor disturbances in semantic fluency, in logical memory, and in spatial orientation (Table 4). On examination of mood disorder at follow-up, five out of 24 were suffering from anxiety as defined by the SAST instrument and by short Zung instrument, and two out of 24 were diagnosed as suffering from depression.

Discussion

In our longitudinal prospective study of 2 years on patients suffering from ET we showed that at initial assessment a high percentage of the patients were found to have MCI (69.2%) and that some also had a mood disorder (25% anxiety and 17.9% depression), confirming our first hypothesis. Even though ET is the most common movement disorder seen in neurology[1] and the majority of the patients actually show only limited decrease in their function and continue to be active in the community, many seek help for the concomitant non-motor aspects of the disease.[18]

This is in line with previous studies in medical literature, which show that patients with ET have a high rate of non-motor manifestations.[2,3,11,18]

Table 3. Comparison of Subgroups with and without MCI

	Without MCI (n=16)	With MCI (n=36)	p-Value
Mean MMSE score (SD)	28.4 (1.6)	27.2 (1.8)	<0.01
Mean SPMSQ score (SD)	9.6 (0.6)	8.9 (0.8)	NS
Mean SLUMS score (SD)	25.1 (3.7)	20.1 (4.2)	<0.01
Mean Phonemic Fluency (SD)	10.1 (1.6)	8.7 (3.3)	<0.05
Listing on Semantic Memory (SD)	14.3 (2.7)	12.5 (2.8)	NS

Abbreviations: MCI, Mild Cognitive Impairment; MMSE, Mini-Mental Status Examination; NS, Not Significant; SD, Standard Deviation; SLUMS, Saint Louis University Mental Status Examination; SPMSQ, Short Portable Mental Status Questionnaire.

Table 4. Cognitive Assessment at Follow-up (T2) (n=24)

Screening Instruments		Abnormal
Mean time to follow-up (months) (SD)	27.5 (7.5)	
MMSE mean scores (SD)	27.0 (1.9)	4%
SPMSQ mean scores (SD)	9.2 (1.0)	
SLUMS mean scores (SD)	21.2 (4.0)	13%
CDR Scale score		
Convertors to dementia (n=4)		
1 (dementia), MMSE<24/30 and SLUMS≤20/30	4/24 (16.8%)	
Non-convertors to dementia (n=20)		
0.5 (MCI), MMSE≥24/30 and SLUMS=21–23/30	16/20 (80%)	
0 (normal), MMSE≥24/30 and SLUMS≥24/30	4/20 (20%)	
MCI at T1 and MCI at T2	12/16 (75%)	
Normal at T1 and MCI at T2	4/16 (25%)	
Neuropsychological instruments		
Semantic fluency mean scores (SD)	11.8 (3.6)	25%
Phonemic fluency mean scores (SD)	8.7 (3.3)	70%
Trail Making Test A mean scores (SD)	15.5 (6.0)	21%
RAVLT verbal memory mean scores (SD)		
Immediate	9.5 (2.5)	18.2%
Delayed	7.3 (3.3)	38.1%
Recognition	12.3 (2.6)	38.1%
Logical memory mean scores (SD)	10.3 (2.5)	21%
Item mean score (SD) (concentration)	5.6 (0.9)	63.6%
Percentage with anxiety by SAST instrument	26.1%	
Percentage with depression by short Zung instrument	8.6%	

Abbreviations: CDR, Clinical Dementia Rating; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental Status Examination; RAVLT, Rey's Auditory Verbal Learning Task; SAST, Short Anxiety Screening Test; SD, Standard Deviation; SLUMS, Saint Louis University Mental Status Examination; SPMSQ, Short Portable Mental Status Questionnaire.

In fact, in our study almost 70% of the subjects showed the presence of MCI using the criteria of the International Working Group on MCI.[19] Around 20% of our subjects had either depression, anxiety, or both.

It is known that MCI is a common cognitive dysfunction found in the general population from middle age onwards, with a prevalence rate of around 20%.[20] Most clinicians rely on clinical and neuropsychological markers to help them in their diagnosis of MCI and dementia.[19] Since screening instruments of general cognitive dysfunction, such as MMSE, are usually normal, the diagnosis of MCI relies on the results of other tests done by means of pen and paper. The instruments used for clinical assessment need to examine episodic memory (the ability to learn and retain new information) for both immediate and delayed recall. The neuropsychological tests for testing

episodic memory may comprise a number of different individual tests, such as RAVLT or delayed recall of a paragraph from the Wechsler Logical Memory Scale. However, there is also a need to examine areas such as executive function (by the Trail Making Test), language (using phonemic and category fluency), visuospatial skills (using figure copying), and attention control (by digit span forward and backward). Some clinicians may use integrated and validated tests such as the SLUMS examination, as was used in this study. Additional neuropsychological testing pinpointed the domain of cognitive dysfunction.

It was not surprising that those with ET also suffer from MCI, but the higher percentage (around 70% in our study) indicates that MCI is a more common and widespread non-motor manifestation of ET than originally thought. It is reported in the medical literature that between 10% and 15% of those suffering from early MCI will convert to dementia each year.[14] In our study we found an annual conversion rate of 8.4%. In addition, all of the convertors to dementia suffered from MCI at initial recruitment. At follow-up, the non-convertors to dementia still had a high prevalence rate for MCI (80.0%). Of note, 25% of MCI sufferers at follow-up were convertors from a normal cognitive state at the start of the study. The above findings emphasize that the cognitive decline in ET is progressive over time, with the non-motor cognitive decline often occurring prior to the onset of motor signs.[21,22]

MCI is now regarded by many as a state preceding dementia of any type.[23] It is recommended that on a regular basis, these persons continue follow-up for general cognitive assessment, especially to diagnose the convertors. The findings in our study support this as there were 16.7% who converted to dementia over the 2-year period. Our second hypothesis was incorrect since there was not a higher conversion rate to dementia in persons with ET and MCI than in the general population with MCI only. This finding may be due to the significant dropout rate. Similar to reports in the medical literature, our study subjects with ET showed a particular problem with verbal memory in their impaired ability to remember words.[9,18,24] The impairment was evident in all areas of verbal memory, immediate, delayed, and recognition, but especially problematic in delayed verbal memory. In such a small sample it is difficult to predict whether this finding is a significant factor for further cognitive decline and the development of dementia. Further longitudinal studies using a larger population sample are needed.

Interestingly, this study showed that the one-quarter of persons diagnosed with ET but having no evidence of cognitive impairment would develop MCI within 2 years. This is a higher incidence rate (12.5% per year) than the literature documents for the general population (5% per year).[25]

Another finding in our study was the relatively high rate of anxiety and/or depression at initial recruitment, a rate similar to that found at follow-up. This supports our initial statement that mood disorders are common in patients with ET and MCI, similar to reports in the literature that persons with MCI alone suffer from anxiety.[26]

There are limitations to this study in that the study population was small and there was a high dropout rate. Our study showed that the dropout rate was mainly related to the refusal of the subjects to return for a follow-up visit, despite repeated requests, due to a lack of incentive and time. This may be related to the fact that most individuals with MCI are highly functioning persons in the community, and are often still working. In any longitudinal study for cognitive assessment one expects a high dropout rate since many MCI sufferers often have impaired self-awareness of their cognitive decline and the necessity to continue with follow-up examinations is a major logistical problem.[27] The absence of a control group in our study limited its efficacy; however, the conversion rates of persons without MCI and with MCI to dementia are well known. Taking into account the above limitations, we want to emphasize that the importance of this longitudinal study is its descriptive value.

In summary, the uniqueness of our study is the long follow-up period of up to 2 years, allowing sufficient time to lapse for any conversion to occur. It was seen that the conversion rate to dementia (8.35% per year) was similar to that reported in the medical literature for the general population with MCI but without ET, but, as mentioned above, the conversion from normal to MCI was higher than expected (12.5% compared to 5%). It is of importance, therefore, to emphasize this fact in order to encourage those diagnosed as suffering from ET to undergo an early cognitive assessment and to understand the need for follow-up visits. If treatment, either pharmacological or non-pharmacological, is started early, the rate of decline may be slowed, which is a saving for the individual and society.[28]

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