Journal of the Neurological Sciences 371 (2016) 24–31

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Daytime sleepiness and nighttime sleep quality across the full spectrum of cognitive presentations in essential tremor

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ARTICLE INFO

Article history:
Received 17 June 2016
Received in revised form 6 September 2016
Accepted 6 October 2016
Available online 08 October 2016

Keywords:
Essential tremor
Cognition
Sleep
Dementia
Clinical

ABSTRACT

There is increasing evidence that essential tremor (ET) is a complex and heterogeneous disorder with nonmotor features including cognitive deficits and sleep problems. We are unaware of a study that has examined sleep deficits in ET across the full spectrum of cognitive presentations. Cross-sectional (baseline) data on self-reported nighttime sleep dysfunction and excessive daytime sleepiness were collected using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) in 96 ET cases enrolled in a prospective study. Cases underwent a comprehensive neuropsychological assessment, and were classified as ET with normal cognition (ET-NC), ET with mild cognitive impairment (ET-MCI), and ET with dementia (ET-D). PSQI scores did not significantly differ across the three ET cognitive groups ($p = 0.22$). ESS scores were highest (more daytime sleepiness) in the ET-MCI group, followed by the ET-D and ET-NC groups, respectively ($p = 0.016$). We examined sleep dysfunction across the cognitive spectrum in ET. We demonstrate for the first time that excessive daytime sleepiness is greater in ET-MCI than ET-NC. Unpredicted low ESS scores in the dementia group raises two possibilities: a self-report bias related to cognitive impairment and/or the possibility that currently undefined pathological heterogeneity in ET may map onto multiple presentations of non-motor deficits.

1. Introduction

In recent years, traditional views of essential tremor (ET) as a monosymptomatic and 'benign' tremor disorder have given way to awareness of a more complex and heterogeneous disease with nonmotor features [1–6], including mild sleep and cognitive deficits. While it is a distinct disorder, Parkinson's disease (PD) shares both motor and nonmotor features with ET, though these are often milder in ET. Although mixed [1,4,5,7], there is some evidence that both excessive daytime sleepiness and nighttime sleep quality scores in ET fall intermediately between PD and normal controls [1,5], suggesting that a mild form of sleep dysregulation may be present in ET.

Indeed, pathological studies have identified Lewy bodies in the locus coeruleus of some patients with ET [6,8], and this brainstem nucleus has been implicated in the maintenance of normal sleep patterns [9,10].

In general, there is a well-established and widely accepted deleterious effect of poor sleep on cognition; furthermore, it is likely a bidirectional relationship [11]. However, this relationship has not been formally assessed in ET despite the presence of a mild form of sleep dysregulation as well as a reported twofold risk of developing dementia in elderly onset ET patients [12]. In PD, excessive daytime sleepiness in the absence of nighttime sleep dysfunction was associated with deficits in attention and working memory, executive functioning, memory, and visuospatial functioning, across the cognitive spectrum from normal cognition to dementia [13]. That this sleepiness was observed in the absence of nighttime sleep dysfunction suggests a neuropathological basis, rather than a mere secondary symptom of hyposomnia. It is possible that this pattern of excessive daytime sleepiness and cognitive deficits result from a similar underlying pathology. Whether these same findings in PD apply to ET is unknown; there are no similar studies in ET. With regards to ET, the pathology is likely heterogeneous [14–16]. It is possible that pathological heterogeneity in ET could map onto

Abbreviations: ET, essential tremor; PD, Parkinson's disease; ET-NC, ET with normal cognition; ET-MCI, ET with mild cognitive impairment; ET-D, ET with dementia; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; UPDRS, Unified Parkinson's Disease Rating Scale; GDS, Geriatric Depression Scale; CDR, Clinical Dementia Rating Scale; MMSE, Folstein Mini Mental State Examination.

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http://dx.doi.org/10.1016/j.jns.2016.10.006
0022-510X/

multiple presentations of non-motor deficits. For this reason, it is important to study sleep deficits in ET across the full spectrum of cognitive presentations. We are not aware of any studies that have done this to date.

The data used for these analyses were derived from a prospective, clinical-pathological study of cognition in ET that utilized a comprehensive neuropsychological battery and represented patients with a wide range of cognitive presentations, from normal cognition to dementia. In this study, which used baseline data, we cross-sectionally examined the relationships between excessive daytime sleepiness, nighttime sleep quality, and cognition in ET. Based on the similarities between ET and PD, and recently-published findings in PD [13], our *a priori* hypothesis was that excessive daytime sleepiness, but not nighttime sleep dysfunction, would be greatest in ET patients with dementia (ET-D), followed by those with mild cognitive impairment (ET-MCI) and those with normal cognition (ET-NC) (i.e., as there is in PD, there would be a dissociation between daytime sleepiness, nighttime sleep quality and cognition, and that daytime sleepiness would be greatest in the group with dementia).

2. Methods

2.1. Cases

One hundred ET cases were recruited into the Clinical-pathological Study of Cognition in Essential Tremor (COGNET; August 2014–October 2015, NIH R01 NS086736). Cases had been diagnosed by their local neurologist as having ET and diagnoses were confirmed after enrollment based on a detailed history and videotaped neurological examination reviewed by a senior neurologist specializing in movement disorders (EDL) who applied reliable and valid diagnostic criteria, as described below.

2.2. Collection of demographic and clinical data

Upon enrollment, all cases provided informed written consent approved by the Institutional Review Boards of both Columbia University and Yale University. Cases were evaluated in person by a trained tester who administered structured clinical questionnaires that elicited demographic and clinical information.

During the evaluation, all current medications were recorded. It is important to consider the effects of medication on sleep as well as cognition. First, as in a previous sleep study [7], a "graded medications with sleep effects" score was carefully assigned to each case with regards to medications and their potential effects on sleep quality (1 = case takes one or more medications that increases drowsiness; 0 = case either takes no medications with sleep effects or case simultaneously takes a combination of medications that stimulate wakefulness and increase drowsiness; −1 = case takes one or more medications that stimulate wakefulness). Second, the number of cases taking sleep medication (medication whose sole purpose is to facilitate sleep) in each group was determined. In addition, the number of cases taking cognition enhancing medication (medication whose sole purpose is to enhance cognition or prevent cognitive decline, e.g., memantine) was determined.

Height and weight of each case were collected via self-report. Body mass index (BMI) was calculated by dividing weight (kilograms) by the square of height (meters).

2.3. Sleep evaluation

Sleep quality was evaluated using two self-administered, validated and widely-used measures: the Epworth Sleep Scale (ESS) [17] and the Pittsburgh Sleep Quality Index (PSQI) [22]. The ESS is a self-report measure that assesses the likelihood that an individual might doze off in eight common situations. Each situation is graded on a scale from 0 to 3 (maximum score, 24 = greatest daytime sleepiness). As in prior studies [1,13,17], an ESS score ≥ 10 was used as an indicator of greater than normal levels of daytime sleepiness. The PSQI assesses a variety of nighttime sleep issues, which are then converted into seven sleep components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, medication use for sleep, and daytime dysfunction) and translated into a global PSQI score (maximum score, 21 = worst sleep quality). As in prior studies [18], a PSQI score > 5 was used as an indicator of poor nighttime sleep quality.

To address the possibility that the cases may under-perceive their sleep symptoms, we used the Bed Partner/Roommate section of the PSQI to determine whether informants reported nighttime sleep dysfunction that cases did not. These sleep dysfunctions included the following items: loud snoring, long pauses or breaths between sleep, legs twitching or jerking during sleep, episodes of disorientation or confusion during sleep, and an "other restlessness" category. The total number of these disturbances was used for analyses.

2.4. Videotaped neurological examination and confirmation of ET diagnoses

As in our previous studies [7], each case underwent a videotaped neurological examination, which included a detailed assessment of postural tremor, five tests for kinetic tremor, and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) [19], excluding an assessment of rigidity. A senior movement disorders neurologist reviewed all videotaped examinations. Severity of postural and kinetic tremors were rated (0–3), resulting in a total tremor score (range 0–36 [maximum]), a measure of the severity of the action tremor. Based on the videotaped examination, the senior movement disorders neurologist confirmed ET diagnoses using published diagnostic criteria (moderate or greater amplitude kinetic tremor on ≥3 tests, or head tremor, in the absence of PD or dystonia).

2.5. Neuropsychological evaluation

The neuropsychological evaluation included a comprehensive cognitive battery, a semi-structured interview with a close family member or friend informant, and clinical impressions of the case's general cognitive function and functional abilities as reported by a trained tester. The cognitive battery included individual tests that were not dependent on efficient motor functioning, and which were grouped into the following cognitive domains: Attention and working memory (Digit Span subtest from the Wechsler Adult Intelligence Scale-III (WAIS; [20]), Symbol-Digit Modalities test [21]), executive function (Delis-Kaplan Executive Function System [22] subtests Verbal Fluency, Color Word Interference, Sorting, and Twenty Questions), language (The Boston Naming Test [23] and the Multilingual Aphasia Examination Token subtest [24]), memory (California Verbal Learning Test–II [25], Verbal Paired Associates subtest from the Wechsler Memory Scale (WMS; [26]), and the Logical Memory subtest A from the WMS-Revised Edition [27]), visuospatial abilities (Judgment of Line Orientation [28], Benton Facial Recognition [29], and the Visual Puzzles subtest of the WAIS-IV [30]), global cognition (Mini Mental State Examination (MMSE; [31]), Montreal Cognitive Assessment (MoCA; [32])), and premorbid intellectual functioning (Wechsler Scale of Adult Reading (W-TAR; [33–34])).

The Geriatric Depression Scale (GDS) [35] was chosen to assess depression; this scale minimizes the influence of somatic symptoms on the total depression score. Informants (when available) provided reports of the cases' everyday functioning.

2.6. Cognitive classification

ET cases were classified into cognitive groups (ET-NC, ET-MCI, ET-D) through a consensus conference (neuropsychologist SC; neuropsychiatrist EH; neurologist EDL) using data from the semi-structured interviews with the patient and informant, and clinical and