Absence of Rapid Eye Movement Sleep Behavior Disorder in 11 Members of the Pallidopontonigral Degeneration Kindred

Bradley F. Boeve, MD; Siong-Chi Lin, MD; Audrey Strongosky, BA; Dennis W. Dickson, MD; Zbigniew K. Wszolek, MD

Background: Rapid eye movement sleep behavior disorder (RBD) is a parasomnia that is manifested by dream enactment behavior. The electrophysiologic substrate for RBD on polysomnography is rapid eye movement sleep without atonia. Rapid eye movement sleep behavior disorder likely stems from neuronal network dysfunction in the brainstem, although it is not yet clear which specific networks are involved. Rapid eye movement sleep behavior disorder is often associated with the sporadic synucleinopathies but rarely associated with the sporadic tauopathies. There are no reports on the possible association of rapid eye movement sleep without atonia and RBD with any familial tauopathy.

Objective: To characterize the clinical sleep and polysomnography features in a kindred with a familial tauopathy.

Methods: We performed standard polysomnography in 11 members of the pallidopontonigral degeneration kindred irrespective of any sleep-related complaints. Neuropathologic findings were analyzed in those who subsequently underwent autopsy.

Results: Six affected and 5 genealogically at-risk family members were studied. None of the 11 had a history of dream enactment behavior. Nine of the 11 members attained sufficient rapid eye movement sleep on polysomnography, and the electrophysiologic features of rapid eye movement sleep without atonia and behavioral manifestations of RBD were absent in all subjects. Neuropathologic examination of 4 affected individuals revealed marked nigral degeneration in 3 along with mild degenerative changes in the locus coeruleus, pontine nuclei and tegmentum, and medullary tegmentum.

Conclusions: These findings argue against nigral degeneration being the primary cause of RBD. The absence of the historical, electrophysiologic, and behavioral manifestations of RBD in this kindred provides further evidence that RBD is rare in the sporadic and familial tauopathies. The difference in frequencies of RBD associated with the synucleinopathies compared with the tauopathies suggests differences in the selective vulnerability of brainstem circuits between the synucleinopathies and tauopathies.
association of RSWA and RBD with any of the familial tauopathies. If RSWA and RBD were absent in the familial tauopathies, insights into RSWA and RBD pathogenesis and the selective vulnerability of neuronal degeneration between the spectrum of neurodegenerative disorders may be gained.

The family with pallidopontonigral degeneration (PPND) has been longitudinally followed up by one of us (Z.K.W.) since 1987.13 The origin of this family has been traced to mid 18th-century colonial Virginia.14 At present, the kindred contains 317 family members, with 45 affected individuals, of whom 7 are alive. The onset of symptoms occurs at a mean age of 43 years with a range from 32 to 58 years. The average survival time after the symptomatic disease onset is about 8 years. Affected individuals suffer from progressive bradykinesia, rigidity, dystonia unrelated to medications, ocular motility abnormalities, eyelid apraxia, personality changes, memory disturbances, and bladder dysfunction.13,15,16 The pathological studies showed the presence of abundant balloononed neurons in neocortical and subcortical regions as well as tau-rich inclusions in the cytoplasm of neurons and oligodendroglia similar to those seen in sporadic corticobasal degeneration cases, but in a distribution pattern resembling sporadic PSP cases.15 Genetic studies revealed the presence of the N279K mutation in the tau gene.16 Therefore, the PPND family belongs to the class of disorders collectively termed frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).17 At present, there are approximately 80 families known to have or have had individuals affected with FTDP-17,18 of whom the PPND family is one of the largest and the most extensively studied.19 We report herein our clinical sleep and PSG findings on several members of this kindred; these findings address the question of whether RSWA or RBD occurs in a kindred with a familial tauopathy. We also report the neuropathologic findings in members of this kindred who had undergone PSG and consider the findings in the context of the brainstem nuclei implicated in RBD pathophysiology.

METHODS

SUBJECTS

Six affected family members (3 men and 3 women) who were in relatively early stages of the illness (median age 47.5 years at the time of PSG examination), which allowed them to travel to Jacksonville, Fla, were invited to participate in this study. In addition, 5 genealogically at-risk family members (2 men and 3 women) of median age of 32 years were asked to participate. In addition to PSG studies, all 11 family members have undergone clinical examinations with appropriate rating scales, psychological testing, and a variety of laboratory investigations including electrophysiological, neuroimaging, autonomic testing, and others.20-23

POLYSOMNOGRAPHY

All PSG studies involved continuous video monitoring using the following montage: 2 electro-oculogram derivations, 2 electrocorticogram, 2 electrodermal, 2 electroencephalogram derivations (Cz-Oz, C4-A1), electrocardiogram, chin and at least 2 limb surface electromyograms (EMG), oronasal airflow, sonogram, oxyhemoglobin saturation, and chest and abdomen inductance plethysmography. Scoring of sleep stages followed standard guidelines.24 Polysomnograms and videos were reviewed by a registered polysomnography technician and by a sleep medicine clinician who is certified by the American Board of Sleep Medicine and has considerable experience in the diagnosis and management of parasomnias.

TERMINOLOGY AND DIAGNOSES

The diagnosis of probable RBD was made if the patient had exhibited dream enactment behavior (ie, fulfilled criterion B.i. of the International Classification of Sleep Disorders classification25). The PSG feature of RSWA was considered present if muscle tone during REM sleep had abnormally increased, according to the PSG reviewers. The diagnosis of definite RBD was made if (1) the patient had a history of dream enactment behavior. (2) RSWA was present with or without prominent motor activity during REM sleep on PSG, and (3) no epileptiform discharges were noted on the PSG; these criteria are essentially the same as the International Classification of Sleep Disorders criteria.25

NEUROPATHOLOGY

For those who died and underwent autopsy, the left hemi-brain was fixed in 10% neutral formalin and examined for hemorrhage and cerebral cortical atrophy. Sections were obtained from superior/medial frontal gyrus, superior/medial temporal gyrus, inferior parietal lobule, parahippocampal gyrus/entorhinal cortex, thalamus, putamen, pallidum, midbrain, pons, medulla, and cerebellum. Sections were then stained with hematoxylin-eosin and modified Bielschowsky silver stain. Using the peroxidase-antiperoxidase or the avidin-biotin complex method, representative sections were immunostained using antisera directed toward tau, amyloid, ubiquitin, α-synuclein, and phosphorylated neurofilament.

The severity of neuronal loss and gliosis in brainstem structures was assessed using slides stained with hematoxylin-eosin. A semiquantitative approach was used in which grade 0 was used for regions without inclusions, grade 1 for mild, grade 2 for moderate, and grade 3 for severe inclusions. The frequency of RSWA was assessed using slides stained with hematoxylin-eosin. A similar semiquantitative approach was used, in which grade 0 was used for regions without inclusions, + for a low frequency, ++ for moderate, and +++ for severe frequency of inclusions.

RESULTS

Six affected and 5 at-risk members of the kindred underwent PSG. The clinical features and PSG findings are shown in Table 1. None of the 11 members had a history of dream enactment behavior. Ten of the 11 members attained sufficient REM sleep on PSG, and the electrophysiologic features of RSWA and behavioral manifestations of RBD were absent in all subjects.

Since the PSG studies were conducted, 3 previously affected members have died and undergone autopsy (cases 1, 3, and 5 in Table 1, marked with an asterisk), and 1 previously asymptomatic member developed parkinsonism within 1 year after PSG, died at age 48 years, and un-
derwent autopsy (case 7). All 4 had widespread tau-positive inclusions in cortical, subcortical, and brainstem structures typical of what has been reported in other members of this kindred.15 The severity and distribution of neuronal loss and gliosis, and frequency and distribution of tau-positive inclusions in brainstem structures are shown in Table 2. There was tau-positive pathology in all brainstem structures that were assessed. Severe neuronal loss and gliosis were present in the substantia nigra in 3 cases and in the locus coeruleus in 2. More minimal degenerative changes were present in the raphe nucleus, pontine nucleus and tegmentum, medullary tegmentum, dorsal motor nucleus, and inferior olive.

The literature suggests that RBD is rarely associated with sporadic tauopathies. Rapid eye movement sleep behavior disorder has been reported in 2 cases of clinically suspected sporadic PSP2-28 and in 13% of a group of PSP subjects.27 Rapid eye movement sleep without atonia has been reported in a single case of sporadic corticobasal degeneration,28 but this patient did not have clinical RBD features. There are no published reports of RBD associated with the syndromes of FTDP-17, sporadic frontotemporal dementia, primary progressive aphasia, and posterior cortical atrophy.29 This is the first report regarding possible RSWA and RBD in a kindred with a familial tauopathy, and the absence of the historical, electrophysiologic, and behavioral manifestations of RBD in this kindred provides further evidence that RBD is rare in the tauopathies, whether sporadic or familial.

Numerous cases of RBD have been reported in association with clinically diagnosed PD, dementia with Lewy bodies, and multiple-system atrophy (reviewed in detail elsewhere).30-34 Until 2003, all autopsied cases of RBD have had synucleinopathy pathology.10,30-34 Rapid eye movement sleep behavior disorder was identified in several members of a kindred with a parkin mutation,15 and Lewy body disease pathology has been reported in a different

Table 1. Clinical Features and Polysomnographic Findings in 11 Members of the PPND Kindred With the N279K Mutation in the Tau Gene

<table>
<thead>
<tr>
<th>Case No./Sex</th>
<th>Age at Onset/Age at PSG, y</th>
<th>Clinical Features</th>
<th>Probable RBD</th>
<th>TST, min</th>
<th>TST in REM Sleep on PSG, %</th>
<th>RSWA on PSG</th>
<th>Dream Enactment Behavior on PSG</th>
<th>Other PSG Findings</th>
</tr>
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<tbody>
<tr>
<td>1/F 53/F</td>
<td>46/49</td>
<td>D + P</td>
<td>No</td>
<td>159</td>
<td>10</td>
<td>No</td>
<td>No</td>
<td>PLMI 125</td>
</tr>
<tr>
<td>2/F 48/F</td>
<td>44/45</td>
<td>P</td>
<td>No</td>
<td>218</td>
<td>10</td>
<td>No</td>
<td>No</td>
<td>PLMI 34</td>
</tr>
<tr>
<td>3/M 52/M</td>
<td>57/59</td>
<td>D + P</td>
<td>No</td>
<td>43</td>
<td>11</td>
<td>No</td>
<td>No</td>
<td>PLMI 64</td>
</tr>
<tr>
<td>4/M 63/F</td>
<td>41/43</td>
<td>P</td>
<td>No</td>
<td>234</td>
<td>18</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>5/M 52/M</td>
<td>41/48</td>
<td>D + P</td>
<td>No</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>6/F 48/F</td>
<td>40/41</td>
<td>P</td>
<td>No</td>
<td>314</td>
<td>7</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>7/F 52/F</td>
<td>45/45</td>
<td>P</td>
<td>No</td>
<td>314</td>
<td>7</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>8/M 48/F</td>
<td>NA/24</td>
<td>Normal</td>
<td>No</td>
<td>488</td>
<td>24</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>9/F 52/F</td>
<td>NA/33</td>
<td>Normal</td>
<td>No</td>
<td>350</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>AHI 8, PLMI 16</td>
</tr>
<tr>
<td>10/F 48/F</td>
<td>NA/47</td>
<td>Normal</td>
<td>No</td>
<td>421</td>
<td>26</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>11/M 48/F</td>
<td>NA/23</td>
<td>Normal</td>
<td>No</td>
<td>445</td>
<td>25</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 2. Severity and Distribution of Neuronal Loss and Gliosis and Frequency and Distribution of Tau-Positive Neuronal Inclusions in 4 Deceased Members of the PPND Kindred Who Underwent PSG

<table>
<thead>
<tr>
<th>Case 1 (53 y/F)</th>
<th>Case 3 (63 y/M)</th>
<th>Case 5 (52 y/M)</th>
<th>Case 7 (48 y/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substantia nigra</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
<tr>
<td>Raphe nucleus</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pontine tegmentum</td>
<td>+</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
<tr>
<td>Pontine base</td>
<td>0</td>
<td>+ + +</td>
<td>0</td>
</tr>
<tr>
<td>Medullary tegmentum</td>
<td>+</td>
<td>+ + +</td>
<td>0</td>
</tr>
<tr>
<td>Dorsal motor nucleus</td>
<td>+</td>
<td>+ + +</td>
<td>0</td>
</tr>
<tr>
<td>Inferior olive</td>
<td>+</td>
<td>+ + +</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: PPND, pallidopontonigral degeneration; PSG, polysomnography.
*For neuronal loss and gliosis, 0 indicates absent; +, minimal; + +, moderate; + + +, severe neuronal loss and gliosis; NA, not applicable.
†For tau-positive inclusions, 0 indicates absent; +, low frequency; + +, moderate; + + +, high frequency of inclusions; NA, not applicable.
large kindred with parkin mutations. 35 Therefore, the clinical and pathologic literature suggests that when associated with a neurodegenerative disorder, RBD often (but not always) reflects an underlying synucleinopathy. 9,11,20 Further support for this hypothesis would be gained by demonstrating that RSWA and RBD are often present in kindreds with familial synuclein mutations and duplications, and rare or absent in kindreds with other familial neurodegenerative disorders such as familial tauopathies.

Gagnon et al 16 recently demonstrated that some patients with PD have PSG evidence of RSWA, but have no history of dream enactment behavior. Such patients are believed to represent subclinical or preclinical RBD, and their findings underscore the necessity and utility of performing PSGs to assess for abnormal REM sleep electrophysiology and behavior. We suggest sleep interviews and PSGs be performed in sporadic cases and members of kindreds with familial synucleinopathies and familial non-synucleinopathies to further analyze the relative specificity of RSWA and RBD for the synucleinopathies.

The brainstem regions that have been implicated in RBD pathophysiology include the gigantocellular reticular formation (GCRF), peri–locus coeruleus region, pedunculopontine nucleus, and the laterodorsal tegmental nucleus. 10,11,20 Lesions in the GCRF and peri–locus coeruleus region cause REM sleep without atonia in animal models. 37–39 It is not yet known if lesions in these nuclei or the pedunculopontine nucleus and laterodorsal tegmental nucleus are sufficient to cause human RBD. 40–42 Increased phasic loco-motor drive and/or loss of REM sleep atonia has been suggested as the likely mechanism for the clinical expression of human RBD. 43 Since there is ample evidence of neuronal degeneration in many brainstem nuclei in the tauopathies of Alzheimer disease, corticobasal degeneration, PSP, as well as the synucleinopathies of PD, dementia with Lewy bodies, and multiple system atrophy, it is curious that RBD occurs frequently in the synucleinopathies and rarely in the tauopathies. This discrepancy likely reflects differences in the selective vulnerability of REM sleep-related brainstem circuits between the synucleinopathies and tauopathies.

Dopaminergic dysfunction is certainly common to all of the synucleinopathies and many of the tauopathies, and dopaminergic dysfunction has been implicated in RBD pathophysiology based on anatomic 40 and functional neuroimaging studies. 4,7 Yet there is no convincing evidence that dopaminergic dysfunction is the primary cause of RBD. The severe neuronal loss and gliosis in the substantia nigra, yet absence of RBD, in 3 of our autopsied cases provides further evidence that nigral degeneration and dopamine deficiency are not sufficient to cause RBD. Two of our cases also had severe locus coeruleus degeneration, suggesting that severe locus coeruleus degeneration may also not be sufficient to cause RBD.

The most caudal brainstem nucleus involved in REM sleep-associated motor functioning is the GCRF, and this nucleus was relatively preserved in all of our cases. The GCRF is affected early in PD, with marked degeneration developing as the disorder progresses. According to the Braak staging scheme of PD, 44,45 the dorsal motor nucleus and olfactory bulb are affected in stage 1, the GCRF is affected in stage 2, followed by the substantia nigra in stage 3, and more rostral limbic and neocortical structures in stages 4 through 6. This sequence of degeneration would explain the tendency of RBD to precede parkinsonism and/or dementia. 1,10,11,20 The presence of smell abnormalities in patients with idiopathic RBD, along with evidence of nigrostriatal dysfunction on functional neuroimaging studies, 8 provides further support for caudal brainstem dysfunction being critically involved in RBD pathophysiology. The relative preservation of the GCRF in our cases is also consistent with this hypothesis. Although the onset of RBD was not specifically stated in the recent report of 2 PSP subjects, 47 the onset of RBD occurring concurrently or after the onset of parkinsonism in most of the nonsynucleinopathy cases suggests that significant degeneration of the caudal brainstem occurs later in the course of the nonsynucleinopathy disorders.

We acknowledge the limitations in this study. We only evaluated 6 of the 45 affected members and 5 at-risk members of the PPND kindred, and the clinical sleep features, PSG findings, and neuropathological findings may not be generalizable to the entire family. We did not employ any methods for quantifying the degree of RSWA, 46,47 but in our view this was not necessary because the atonia during REM sleep in our subjects was unequivocally normal. Although semi-quantitative assessments of neuronal loss and gliosis in several brainstem nuclei were possible, techniques that have been used by other investigators 48,49 were not used to determine the number of neurons in the substantia nigra, pedunculopontine nucleus, locus coeruleus, and GCRF more precisely. Yet our findings do suggest additional clinical, PSG, and neuroanatomic studies are warranted in patients with idiopathic RBD as well as in patients with neurodegenerative diseases with and without coexisting RBD to further elucidate the RBD–neurodegenerative disease association.

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Correspondence: Bradley F. Boeve, MD, Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905 (bboeve@mayo.edu).

Author Contributions: Study concept and design: Lin and Wszolek. Acquisition of data: Lin, Strongosky, Dickson, and Wszolek. Analysis and interpretation of data: Boeve, Lin, and Wszolek. Drafting of the manuscript: Boeve, Lin, and Strongosky. Critical revision of the manuscript for important intellectual content: Boeve, Lin, Dickson, and Wszolek. Obtained funding: Dickson and Wszolek. Administrative, technical, and material support: Boeve, Lin, Strongosky, Dickson, and Wszolek. Study supervision: Boeve and Wszolek.

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