Sleep Manifestations of Voltage-Gated Potassium Channel Complex Autoimmunity

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Objective: To identify the spectrum of sleep disorders associated with autoantibodies reactive with voltage-gated potassium channel (VGKC) complexes.

Design: Case series of all patients with neurologic disorders of VGKC autoimmunity evaluated in the Mayo Clinic Center for Sleep Medicine (Rochester, Minnesota) between January 1, 1994, and February 1, 2010.

Setting: Academic referral center.

Patients: Fifteen consecutive patients were identified with limbic encephalitis (n=5), Morvan syndrome (n=4), and overlapping features (n=6).

Intervention: Ten patients received immunotherapy (corticosteroids, cyclophosphamide, or mycophenolate mofetil).

Main Outcome Measure: Response to immunotherapy.

Results: The median VGKC autoantibody value at presentation was 1.51 nmol/L (range, 0.09-4.86 nmol/L). Neoplasms were discovered in 5 patients (33%) (thy- moma [n=2], prostate adenocarcinoma, colon adenocarcinoma, and melanoma). In 14 patients (93%), serious sleep disturbances were identified (insomnia, dream enactment behavior, suspected nocturnal epilepsy, and hypersomnia). Severe insomnia occurred in 9 patients (60%), regardless of neurologic presentation. Polysomnography at presentation (7 patients) revealed a mean sleep efficiency of 19% (4 patients had complete absence of sleep). Dream enactment behavior occurred in 8 patients (53%), including 3 of 5 with limbic encephalitis and all 4 with Morvan syndrome. Two of 7 polysomnograms demonstrated loss of rapid eye movement sleep muscle atonia; absent or minimal rapid eye movement sleep precluded interpretation in 4 patients. Sleep disorders resolved completely or almost completely in 8 of 10 patients who received immunotherapy.

Conclusions: Sleep disorders are cardinal manifestations of VGKC complex autoimmunity in association with a spectrum of neurologic presentations. They may respond favorably to immunotherapy.

Arch Neurol. 2011;68(6):733-738
unknown. Insomnia or hypersomnia was identified in 19 of 72 seropositive patients (26%), but details of the sleep disturbances were not delineated. Sleep disturbances may respond favorably to immunotherapy. Severe insomnia is a cardinal feature of Morvan syndrome, with polysomnographic (PSG) studies showing complete absence of recognizable sleep, reduced total sleep time with frequent awakenings, or brief sleep fragments consisting of electroencephalographic (EEG) theta activity interspersed with faster rhythms. The insomnia may be accompanied by periods of sleep with agitation and abnormal motor behavior consistent with rapid eye movement (REM) sleep behavior disorder (RBD). Rapid eye movement sleep behavior disorder is characterized by abnormal behaviors during REM sleep with enactment of typically unpleasant dreams involving physical confrontation. A wide range of vocalizations and motor activities is observed, including potentially injurious behavior to the patient or bed partner. Polysomnography shows loss of normal REM sleep muscle atonia. The pathogenesis is thought to involve dysfunction of brainstem structures that regulate REM sleep muscle tone, such as the pedunculopontine nuclei, and anatomical connections with the limbic system, thalamus, and hypothalamus. Rapid eye movement sleep behavior disorder has been recognized in disorders involving the limbic system without apparent brainstem impairment, including VGKC complex-associated limbic encephalitis.

Given the proposed dysfunction of thalamolimbic structures in VGKC complex autoimmunity and the important role that these circuits play in the physiologic function of normal sleep, we hypothesized that the spectrum of concomitant sleep disorders is likely underrecognized. The goals of this study were to define the spectrum of these sleep disturbances and to relate them to other manifestations of VGKC complex autoimmunity to improve diagnosis and management.

METHODS

This study was approved by the Mayo Clinic Institutional Review Board. The Mayo Clinic (Rochester, Minnesota) medical record system was searched between January 1, 1994, and February 1, 2010, to identify patients fulfilling the criteria for a neurologic disorder within the spectrum of VGKC complex autoimmunity based on consensus agreement among medical providers, seropositivity for a VGKC complex autoantibody, and evaluation at the Mayo Clinic Center for Sleep Medicine.

Before June 2008, the Mayo Clinic Neuroimmunology Laboratory performed the radioimmunoprecipitation screening assay for VGKC complex autoantibody and, when necessary, the Mayo Clinic Center for Sleep Medicine performed the assay for VGKC complex autoantibody. Since June 2008, VGKC complex autoantibody testing has been an integral component of this laboratory’s comprehensive paraneoplastic serologic evaluation. Results are reported as nanomoles of [125I]-α-dendrotoxin–ligated VGKC bound per liter of serum. A positive level is greater than 0.02 nmol/L. Other components of the comprehensive paraneoplastic serologic evaluation include immunofluorescence screening for IgG autoantibodies that bind to neuronal or glial nuclei or cytoplasm, radioimmunoprecipitation assays for neuronal voltage-gated calcium channels (P/Q type and N type), neuronal (gangliionic α3) and muscle nicotinic acetylcholine receptors and glutamic acid decarboxylase-65, enzyme-linked immunosorbent assay for striational antibodies, and latex agglutination assays for thyroglobulin and thyroperoxidase autoantibodies.

A comprehensive review of the medical record system was performed for all the patients, including demographic information, neurologic and sleep evaluations, autoantibody test results, oncologic history, and response to immunotherapy. All reported PSGs were performed at the Mayo Clinic Center for Sleep Medicine using standard scoring practices. Dream enactment behavior was defined as descriptions by bed partners of vocalizations and semi-purposeful movements of the arms, trunk, or legs in bed congruent with dream ideation when reported.

RESULTS

We identified 15 patients (9 men and 6 women), 2 of whom were previously reported to have diagnoses of Morvan syndrome. The mean patient age was 56 years (age range, 17-80 years). Race/ethnicity was known for 14 patients; 13 were white.

NEUROLOGIC PRESENTATION AND EVALUATION

The mean time from symptom onset to diagnosis of VGKC complex autoimmunity was 15.4 months (range, 1-91 months). Clinical presentation included cognitive impairment in 14 patients (93%), seizures in 7 (47%), dysautonomia in 9 (60%), and peripheral nerve hyperexcitability in 8 (53%). Results of EEG, performed in 13 patients, were normal in 8. In 5 patients, all with clinical seizures, epileptogenic activity localizing to the temporal (n=3) and extratemporal (n=2) regions was recorded. Electromyography showed peripheral nerve hyperexcitability in 4 of 14 patients tested (29%). Brain imaging (discussed in the next paragraph) revealed abnormalities in 5 patients (33%). Cerebrospinal fluid abnormalities were found in 7 patients (47%); 6 had mild elevation of protein levels (range, 39-81 mg/dL; reference range, 0-35 mg/dL) and 1 had a mild elevation of protein level combined with mild leukocytosis (white blood cell count: 6/µL; reference range, 0-5/µL [to convert to ×109/L, multiply by 0.001]). Results of neurophysiologic testing were abnormal in all 7 patients examined, ranging from subtle cognitive deficits across multiple domains to a severe amnestic disorder.

The constellation of findings was categorized as limbic encephalitis in 5 patients (33%) based on subacute onset of memory impairment, seizures, confusion, and behavioral change, with corresponding hyperintensity in the mesial temporal lobes observed on fluid-attenuated inversion (Table 1). The other 10 patients had normal head magnetic resonance imaging findings. Fludeoxyglucose positron emission tomography/computed tomography in 6 patients without limbic encephalitis did not reveal any significant brain abnormalities. Cerebral spinal fluid was abnormal in 3 of 5 patients with limbic encephalitis.

Four patients were diagnosed as having Morvan syndrome based on subacute onset of fluctuating encephalopathy, insomnia, prominent dysautonomia, and clinical neuromyotonia, with electromyographic evidence of peripheral nerve hyperexcitability. None of these pa...
patients had clinical or electrographic seizures. Milder symptoms suggestive of dysautonomia or peripheral nerve hyperexcitability were recognized in 5 patients without Morvan syndrome. Cerebrospinal fluid was abnormal in 2 of 4 patients with Morvan syndrome. Six patients had overlapping features that could not be definitively categorized as either limbic encephalitis or Morvan syndrome.

**AUTOANTIBODIES**

The median VGKC complex autoantibody value at initial presentation was 1.51 nmol/L (range, 0.09-4.86 nmol/L) based on data from 14 patients; the 15th patient (with Morvan syndrome) was reported to be seropositive by an assay performed elsewhere. The median peak VGKC complex autoantibody value for all patients during follow-up was 1.97 nmol/L (range, 0.17-7.63 nmol/L). Comprehensive autoantibody testing was available in 14 patients. Eight patients had coexisting autoantibodies (53%), including striational (4 patients), glutamic acid decarboxylase-65 (3 patients), ganglionic nicotinic acetylcholine receptor (α3) (2 patients), thyroid peroxidase (2 patients), muscle acetylcholine receptor (1 patient), and amphiphysin (1 patient) antibodies.

**ONCOLOGIC HISTORY**

Neoplasms were detected and confirmed by histopathologic analysis during follow-up in 5 patients (33%) (Table 1). The mean duration from neurologic symptom onset to cancer diagnosis was 28 months (median, 8 months; range, 6 months to 9 years). Melanoma, colon adenocarcinoma, and prostate adenocarcinoma were found in 3 patients with limbic encephalitis. Thymoma was identified in 2 patients with Morvan syndrome.

**SLEEP PRESENTATION AND EVALUATION**

Although 14 patients (93%) experienced significant sleep disturbance within 3 months of neurologic symptom onset (Table 1), the mean time from sleep symptom onset to sleep evaluation was 17 months (range, 2-93 months). Sleep concerns consisted of insomnia, dream enactment behavior, nocturnal spells, and hypersomnia. Ten patients underwent PSG at the time of initial presentation in the Mayo Clinic Center for Sleep Medicine (Table 2). Two of us (J.R.C. and M.H.S.) reviewed 5 available PSG recordings and concurred with the originally reported findings.
Insomnia was the primary concern in 10 patients. The diagnosis of chronic psychophysologic insomnia was made in 1 of these patients several years earlier and may be unrelated to the autoimmune disorder. Severe insomnia in the other 9 patients coincided with the onset of neurologic symptoms, including all 4 patients with Morvan syndrome and 3 of 5 with limbic encephalitis. Two patients with limbic encephalitis and 2 with Morvan syndrome reported almost complete absence of sleep. In 1 patient with Morvan syndrome, wrist actigraphy showed no evidence of sleep for 72 consecutive hours. Three patients with insomnia were observed by family to have brief periods of apparent sleep throughout the day and night interrupted by prominent motor activity or vocalizations. The PSGs performed at initial presentation in 7 of the 9 patients with insomnia revealed a mean sleep efficiency of 19%. The mean percentage of slow-wave (stage N3) sleep was 5%, and the mean percentage of stage REM sleep was 4%. In 4 patients (2 with Morvan syndrome and 2 with limbic encephalitis), PSG revealed complete absence of recognizable sleep, with disorganized EEG activity consisting primarily of theta frequency intermixed with 2- to 4-Hz transients. One of the 2 patients with insomnia without PSG data was suspected of having sleep apnea that may have contributed to difficulty maintaining sleep.

Dream enactment behavior was suspected via history in 8 patients (53%), including the 4 patients with Morvan syndrome and 3 of 5 with limbic encephalitis. Medication history was available for 6 of these 8 patients; only 1 was taking a long-term psychotropic medication (escitalopram) at the time. Polysomnography was performed at initial presentation in 7 patients. REM sleep muscle atonia was assessed in 1 patient but was lost in 2 in the absence of sleep-disordered breathing or periodic limb movements. Assessment of REM sleep atonia was not possible in 4 other patients due to insufficient stage REM sleep. A later repeated PSG in 1 of these patients (with Morvan syndrome) showed excessive muscle tone with the return of REM sleep. No REM sleep–related abnormal behaviors were observed by video PSG, but in 1 patient, there was loss of REM sleep muscle atonia and confusional arousals from stages N2 and N3 sleep. Sixteen-channel EEG, monitored during PSG in all patients with dream enactment behavior, did not show any evidence of epileptiform activity. Loss of REM sleep muscle atonia was not identified in any patient lacking a history of dream enactment behavior. One patient, who did not undergo PSG at initial presentation, developed dream enactment behavior 3 years later. Polysomnography at that time showed marginally increased REM sleep muscle tone. Six years after initial presentation, this patient was diagnosed as having mild parkinsonism, an alternative possible explanation for the RBD. No patient with dream enactment behavior at initial presentation was diagnosed as having a neurodegenerative condition during follow-up.

Table 2. Polysomnographic Findings Available for 10 Patients at Initial Presentationa

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Primary Sleep Disturbance</th>
<th>TST, min</th>
<th>SE, %</th>
<th>N3, %</th>
<th>REM, %</th>
<th>PLMI, per Hour</th>
<th>AHI</th>
<th>Stage REM Sleep Muscle Tone</th>
<th>16-Channel EEG Monitoring Results</th>
<th>Other Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Dream enactment behavior</td>
<td>160</td>
<td>86</td>
<td>0</td>
<td>9</td>
<td>100</td>
<td>7</td>
<td>Normal</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Insomnia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Insomnia, dream enactment behavior</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Insomnia, dream enactment behavior</td>
<td>146</td>
<td>33</td>
<td>15</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>NA</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Insomnia, dream enactment behavior</td>
<td>146</td>
<td>32</td>
<td>16</td>
<td>19</td>
<td>0</td>
<td>1</td>
<td>High</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>Insomnia, dream enactment behavior</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Insomnia, dream enactment behavior</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>Hypersomnia</td>
<td>422</td>
<td>76</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>None</td>
<td>Multiple confusional arousals with vocalizations from stages N2 and N3 sleep</td>
</tr>
<tr>
<td>12</td>
<td>Insomnia, dream enactment behavior</td>
<td>324</td>
<td>67</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>High</td>
<td>NEG</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>Chronic insomnia predating neurologic symptoms</td>
<td>64</td>
<td>63</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>Not performed</td>
<td>Split-night study with CPAP titration for mild OSA</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; EEG, electroencephalographic; NA, not applicable; NEG, no evidence of epileptiform or potentially epileptogenic activity; N3, stage N3 sleep; OSA, obstructive sleep apnea; PLMI, periodic limb movement index; REM, stage rapid eye movement sleep; SE, sleep efficiency; TST, total sleep time.
aAll studies represent full-night diagnostic recordings unless otherwise noted.
RESPONSE TO IMMUNOTHERAPY

Eleven of 15 patients received immunotherapy. The mean available follow-up was 31 months (range, 1-106 months). Neurologic improvement was noted to be significant and sustained in 9 of 11 patients (82%), including all 5 patients with limbic encephalitis and 2 of 3 with Morvan syndrome. Levels of VGKC became undetectable in 5 of 11 patients. Sleep disturbance improved dramatically in 8 of 10 patients with available sleep follow-up information. Two patients responded to 5 to 7 days of treatment with intravenous methylprednisolone alone, whereas the other 6 required longer-term therapy in the form of interval dosing of oral or intravenous corticosteroids with or without the addition of cyclophosphamide or mycophenolate mofetil. Dream enactment behavior resolved completely or almost completely in 3 of 4 treated patients, and insomnia resolved in 4 of 5 treated patients. The patient with suspected nocturnal extratemporal seizures had no further spells. The 4 patients with insomnia who responded favorably to immunotherapy had not benefitted from trials of various sedative-hypnotic agents (melatonin, ramelteon, gabapentin, and zolpidem). The benefits of immunotherapy were incomplete for insomnia in 1 patient with Morvan syndrome who required long-term use of oxycodone for sleep maintenance. Follow-up PSG data were not available for any patient treated with immunotherapy.

COMMENT

To our knowledge, this is the first study to systematically analyze sleep dysfunction in a series of patients with varied neurologic manifestations of VGKC complex autoimmunity. The abnormalities documented support a pathophysiologic role for VGKC complex autoantibodies in disrupting thalamolimbic circuits that mediate normal sleep.

The long interval between symptom onset and sleep evaluation (mean, 17 months) suggests that the treating physician initially overlooked the sleep disturbances, perhaps owing to more overt neurologic symptoms during wakeness. Consistent with our continuing experience, diverse cancer types were detected in 33% of patients. Note that both patients with thymoma presented with Morvan syndrome. It is possible that cancers remained occult in other patients given the median follow-up of just 8 months.

Severe insomnia and dream enactment behavior were the most common sleep presentations, regardless of the category of neurologic syndrome. In contrast to Morvan syndrome, in which insomnia is a cardinal feature, insomnia has not generally been appreciated in patients with VGKC-associated limbic encephalitis. The severity of the insomnia in 3 of the present patients with limbic encephalitis was comparable with that seen in the 4 patients with Morvan syndrome. Rapid eye movement sleep behavior disorder is present in most patients with Morvan syndrome, but it has been recognized in only 1 previous series of patients with VGKC-associated limbic encephalitis. We confirm these findings, reporting histories of dream enactment behavior in all 4 patients with Morvan syndrome and in 3 of 5 patients with limbic encephalitis. Largely because minimal REM sleep was recorded in patients with profound insomnia, we could definitively diagnose RBD in only 3 patients. This study also identifies the novel finding of a patient with increased muscle tone in REM sleep and confusional arousals from slow-wave sleep (sometimes referred to as parasomnia overlap disorder) in association with VGKC complex autoimmunity. Hypersomnia, sleep apnea, and suspected nocturnal frontal lobe epilepsy (1 patient) occurred infrequently. The significant sleep improvement with immunotherapy in 80% of the present patients is consistent with previous studies of favorable response. This supports an autoimmune basis for the sleep disturbance and suggests that the sleep manifestations are not due to irreversible structural changes but rather to functional disruption of neural circuitry. It would be helpful for future studies to include follow-up PSG or actigraphy to confirm these observations objectively. The present findings emphasize the importance of establishing the diagnosis of VGKC autoimmunity because appropriate therapeutic intervention is often successful.

The association of RBD with VGKC complex autoimmunity, and its favorable response to immunotherapy, provides insight into its pathogenesis. In particular, the possibility of a primary autoimmune pathogenesis for some cases of RBD should be considered. The limbic system may be more involved with promoting RBD than previously considered. Strong reciprocal anatomical connections between the limbic system and brainstem regions are thought to regulate REM sleep muscle atonia. Rapid eye movement sleep behavior disorder frequently occurs in the context of neurodegenerative disorders, particularly the synucleinopathies of Parkinson disease, dementia with Lewy bodies, and multiple system atrophy in which pathologic changes are commonly observed in the brainstem and limbic system. Rapid eye movement sleep behavior disorder has been identified in 2 other disorders involving the limbic system without apparent brainstem impairment: autoimmune paraneoplastic Ma2 encephalitis and acute (likely...
autoimmune) aseptic limbic encephalitis.14,26,27 Fatal familial insomnia, an autosomal dominant prion disease that shares many PSG and clinical features with Morvan syndrome, is characterized by selective atrophy of the anteromedial and mediodorsal "limbic" nuclei of the thalamus in the absence of brainstem involvement.12,13 Imaging studies have demonstrated increased cerebral blood flow in limbic areas during REM sleep, and the intense metabolic activation in these regions has been related to the affective content of dreams.32 The frightening dream recall in RBD may be mediated by the amygdala, which has anatomical connections to brainstem nuclei thought to regulate REM sleep muscle tone.23,32 This suggestion is supported by animal experiments in which unilateral damage to the central nucleus of the amygdala after bilateral pontine lesions can produce attack behaviors associated with increased electromyographic activity during REM sleep.33

The retrospective design of this study precludes determination of the frequency of sleep disorders in an unselected population of patients with neurologic autoimmunity targeting VGKC complex or the frequency of VGKC complex autoantibodies in patients with similar sleep disorders without overt evidence of neurologic disease. We conclude from this study, however, that sleep disorders are an important manifestation of VGKC complex autoimmunity, occur in association with a spectrum of neurologic presentations, and are amenable to immunotherapy.

Accepted for Publication: January 28, 2011.
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Author Contributions: Drs Cornelius and Silber had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cornelius, Pittock, Tippmann-Peikert, and Silber. Acquisition of data: Cornelius, Pittock, McKeon, Lennon, Aston, and Josephs. Analysis and interpretation of data: Cornelius, Pittock, Lennon, Tippmann-Peikert, and Silber. Drafting of the manuscript: Cornelius, Pittock, and Silber. Critical revision of the manuscript for important intellectual content: Cornelius, Pittock, McKeon, Lennon, Aston, Josephs, Tippmann-Peikert, and Silber. Statistical analysis: Cornelius. Administrative, technical, and material support: Cornelius and Pittock. Study supervision: Pittock, Tippmann-Peikert, and Silber.

Financial Disclosure: Dr Silber has received honoraria for attendance at board of directors meetings for the American Academy of Sleep Medicine and for lectures delivered at meetings of the American Academy of Sleep Medicine and the American Academy of Neurology. He has also received reimbursement for travel and accommodations from the American Board of Psychiatry and Neurology.

REFERENCES


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