Progressive Dementia and Hypersomnolence With Dream-Enacting Behavior

Oneiric Dementia

Jean E. Cibula, MD; Stephan Eisenschenk, MD; Michael Gold, MD; Thomas A. Eskin, MD; Robin L. Gilmore, MD; Kenneth M. Heilman, MD

Background: Sleep disorders are associated with several types of degenerative dementias, including Alzheimer and prion diseases. Animal models have demonstrated abolition of rapid eye movement atonia, resulting in dream-enacting complex movements termed oneiric behavior, and patients with fatal familial insomnia may have vivid dreams that intrude on wakefulness.

Objective: To describe a new form of progressive dementia with hypersomnia and oneiric behavior.

Methods: Neuropsychological and polysomnographic studies of a middle-aged woman with a progressive dementia, excessive daytime sleepiness, and a vertical gaze palsy.

Results: Neuropsychological testing revealed decreased verbal fluency, impaired attention and working memory, amnesia, poor recall, and bradyphrenia with hypersomnia. Polysomnography revealed a rapid eye movement behavioral disorder with complete absence of slow wave sleep. Prion protein analysis did not reveal the mutation associated with fatal familial insomnia, and other diagnostic test findings were unrevealing.

Conclusion: Our patient had a previously unreported syndrome of progressive dementia associated with rapid eye movement behavioral disorder and the absence of slow wave sleep.

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The co-occurrence of sleep disorders with dementing illnesses has led to recognition of several syndromes. Lugaresi et al described a “fatal familial insomnia” (FFI) characterized by progressive loss of slow wave sleep (SWS) with autonomic dysfunction, motor dysfunction, and dementia. Animal models have demonstrated abolition of rapid eye movement (REM) atonia, resulting in dream-enacting complex movements termed oneiric behavior. In patients with FFI, Tinuper et al described episodes of “sleep” with vivid dreams that intruded spontaneously on wakefulness, described as an “oneiric stuporous state.” In addition, sleep disorders may also be associated with diseases that induce dementia, such as Lewy body disease or Alzheimer disease. We examined and studied a patient with loss of SWS and REM atonia and progressive dementia without the genetic deficit or postmortem findings associated with FFI. Therefore, we suspect that this patient had a form of dementia with a sleep disorder that has not been previously reported.

The patient was a right-handed, 50-year-old woman who presented initially to the University of Florida, Gainesville, in September 1995 with memory decline and sleep difficulties. Her symptoms began in spring 1991 with horizontal and vertical diplopia and severe depression. She underwent a psychiatric evaluation and was believed to have an obsessive-compulsive disorder with severe depression. She had daytime hypersomnia and fell asleep while driving. She also complained of episodes of bilateral hand shaking and the inability to speak without loss of awareness. She “talked and thrashed” during sleep and had fallen out of bed, fractured her toes, and injured her husband. In January 1993, she underwent polysomnography with a multiple sleep latency test. She demonstrated sleep onset–REM periods in 4 of 5 naps. She was prescribed imipramine hydrochloride for treatment of her neurologic and psychiatric disorders, but she discontinued the medication because of weight gain. By summer 1993, she could not manage her finances and was severely amnestic.
At the time of her evaluation at the University of Florida, she was taking 100 mg of sertraline hydrochloride daily, as well as calcium and magnesium supplements. Her history was significant only for colitis during her 20s. She was adopted and her family history was unknown. She had achieved her bachelor’s degree in graphic arts, was married, but had no children. She had a 68 pack-year history of smoking and acknowledged prior ethanol abuse, quitting 4 years before her presentation to the hospital. She noted thinning and coarsening of her hair and tinnitus. She was sleeping from 9 PM to 7 AM consistently but was frequently falling asleep throughout the day. There was no snoring, but intermittent movements were present during all periods of sleep.

On examination, she was initially asleep. While sleeping, she exhibited diffuse asynchronous myoclonic twitches. Bell sign was present. She could follow some commands during this episode but had no recall after awakening. Her husband reported this as a typical sleep episode, lasting 5 to 10 minutes. Her hair was coarse and thin. Otherwise, the general examination was normal. Cranial nerve examination revealed a right exophoria with normal pupillary responses. She could not make vertical eye (pursuit and saccadic) movements except with an oculocephalic maneuver. Her horizontal movements were not restricted. Other cranial nerves, muscle bulk, strength, tone, fine motor movements, gait, sensation to all modalities, and deep tendon reflexes were normal.

On neurobehavioral testing, the patient was alert and oriented but was mildly bradykinetic and bradyphrenic. She answered questions with monosyllabic answers. Although no semantic or phonemic paraphasic errors were noted, her husband had noted such errors at home. She scored 49 out of 60 on the Boston Naming Test.6 Speech repetition was intact, and she followed simple and sequential commands. In an abbreviated Controlled Oral Word Repetition was intact, and she followed simple and sequential commands during this episode but had no recall after awakening. Her husband reported this as a typical sleep episode, lasting 5 to 10 minutes. Her hair was coarse and thin. Otherwise, the general examination was normal. Cranial nerve examination revealed a right exophoria with normal pupillary responses. She could not make vertical eye (pursuit and saccadic) movements except with an oculocephalic maneuver. Her horizontal movements were not restricted. Other cranial nerves, muscle bulk, strength, tone, fine motor movements, gait, sensation to all modalities, and deep tendon reflexes were normal.

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A neuro-ophthalmologic evaluation demonstrated 20/20 visual acuity bilaterally. Horizontal movements were full; however, vertical movements were present only with the oculocephalic maneuver. There was a variable 6- to 8-diopter exotropia. There were no Kayser-Fleischer rings. Her eye movements were believed to be suggestive of Whipple disease, with ocular convergence movements synchronized with facial contractions, primarily involving the jaw (oculomotoratory myorhythmia).9

**DIAGNOSTIC EVALUATION**

Magnetic resonance imaging revealed diffuse atrophy, most pronounced in the mesial temporal region. Hexamethylpropylene amineoxine single-photon emission computed tomography revealed no areas of abnormal blood flow.

Polysomnography revealed a total absence of SWS and loss of REM atonia, with demonstration of dream-enacting behavior, including simulating conduction of an orchestra. No other sleep-related disorder was noted. She was admitted to the Epilepsy Monitoring Unit. Over several days, medications were administered in an attempt to induce SWS and sleep spindles on electroencephalographic testing. These medications included diazepam, methohexital sodium, trihexyphenidyl hydrochloride, methylphenidate hydrochloride, carbamazepine, valproic acid, and dextroamphetamine sulfate. Electroencephalographic testing was performed with the patient under light diprivan sedation with nitrous oxide. Serial intravenous administration of 1 mg of pyrrolide and 5 mg of neostigmine bromide resulted in the observation of sleep spindles and abbreviated K complexes on the electroencephalogram. Intravenous administration of 25 mg of methohexital and 10 mg of diazepam resulted in the generation of frontal beta activity and drug spindles following the recovery from methohexital administration.

Serum chemistries, complete blood cell count, liver functions, hemogram, B12, free thyroxine, thyrotropin, serum treponemal antibody, and folic acid levels showed no abnormalities. Additional study findings are summarized in **Table 1**, with elevated serial serum and urine gold levels for the patient and her husband shown in **Table 2**.

An analysis of blood for FFI in the laboratory of Pierluigi Gambetti, MD, at Case Western Reserve University, Cleveland, Ohio, revealed that she was homozygous for methionine at codon 129, normally a polymorphic site in the prion protein gene associated with sporadic Creutzfeldt-Jakob disease (CJD). This was believed to be a normal variant. The aspartic acid to asparagine mutation at codon 178 associated with FFI was not present.

Cerebrospinal fluid (CSF) revealed 20 red blood cells; 9 white blood cells (all monocytes); protein, 0.05 g/dL; glucose, 3.8 mmol/L; IgG, 10.4 mg/dL; albumin, 0.04 g/dL; positive oligoclonal bands; and myelin basic protein that was below detectable limits. Cerebrospinal fluid periodic acid–Schiff stain was negative for particles associated with Whipple disease. Flow cytometry for CSF cytology was negative.

Nerve conduction studies revealed no evidence of a peripheral neuropathy, which has been reported with Morvan fibrillary chorea and with heavy metal toxicity. A small bowel biopsy revealed no evidence of Whipple disease. A bone marrow biopsy demonstrated a few sea-blue histiocytes but no foamy macrophages.

**CLINICAL COURSE**

By May 1996, she had difficulty with ocular convergence. Mild rigidity was also present. She was treated with 50/200 mg of carbidopa-levodopa extended release 4 times a day, without improvement. By January 1997, vertical and horizontal movements in response to optokinetic nystagmus were lost. In an attempt to treat her sleep disorder, she was prescribed pemoline, 37.5 mg twice daily, but this induced no improvement in her somnolence.

The patient’s dementia continued to progress, and she developed incontinence of urine and bowel. She was treated...
with tacrine hydrochloride, 10 mg/d, but no improvement was seen. She had poor insight into her difficulties. She received sertraline, 150 mg/d, with little benefit. She eventually required assistance with all activities of daily living. The motor and sensory examinations remained essentially unchanged except for the increasing prominence of frontal release signs. The patient died in July 1998.

POSTMORTEM FINDINGS

The postmortem examination was limited to her brain, which weighed 1020 g. On gross examination, there was regional cerebral atrophy, most prominent in the anterior frontal and anteromedial temporal lobes, with moderate to marked ex vacuo hydrocephalus, most prominent in the temporal horns and third ventricle.

Microscopic examination demonstrated widespread but variable areas of astroglial and microglial reaction, most prominent in layers 1 through 3 of the cortex. There were small glial nodules that included pleomorphic microglia and histiocytes with scattered lymphocytes or plasma cells. In addition to these nodules, there was perivascular lymphocytic infiltration that was also seen in deep cerebral white matter, most prominently in frontal, insular, and temporal regions. Inflammatory cells were also seen around leptomeningeal, subpial, and superficial cortical blood ves-

sels. In deeper cortical layers, rodlike microglia were seen in association with reactive astrocytes. Hippocampal pyramidal neurons, particularly in CA1, were frequently eosinophilic with inflammatory changes similar to those observed in the neocortex. Examination of the amygdalae revealed a residual spongy tissue composed of reactive astroglia with rare surviving neurons; however, no residual inflammation or microglial reaction was present. The surrounding white matter was atrophic and gliotic with prominent corpora amylacea. Basal ganglia and thalami appeared to be spared, but the midbrain tectum, periaqueductal gray, paramedian pontine tegmentum, and ventral paramedian medulla showed the same glial and perivascular changes. Cerebellar gray and white matter were minimally affected with a few pleomorphic microglia in the roof nuclei. There was no evidence of cortical beta amyloid immunoreactivity. No neurofibrillary degeneration (tau immunoperoxidase) or Lewy bodies (ubiquitin immunoperoxidase) were present. Luxol fast blue and periodic acid–Schiff stain revealed no evidence of demyelination. Frozen specimens of the cerebellum sent to Gambetti’s laboratory for prion protein analysis were negative.

Table 1. Serum and Urine Laboratory Values Associated With Rare Causes of Dementia and Insomnia*  

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Patient Serum Level</th>
<th>Normal Serum Level</th>
<th>Patient Urine Level</th>
<th>Normal Urine Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine gold, µg/L† ‡</td>
<td>640</td>
<td>&lt;2.5</td>
<td>310</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Melatonin, pg/mL</td>
<td>86</td>
<td>20-80</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>284 pg/mL</td>
<td>110-410 pg/mL</td>
<td>43 µg/24 h</td>
<td>11-86 µg/24 h</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>&lt;14 pg/mL</td>
<td>&lt;30 pg/mL</td>
<td>3 µg/24 h</td>
<td>0-15 µg/24 h</td>
</tr>
<tr>
<td>Dopamine</td>
<td>28 pg/mL</td>
<td>&lt;87 pg/mL</td>
<td>217 µg/24 h</td>
<td>100-440 µg/24 h</td>
</tr>
<tr>
<td>Total catecholamines</td>
<td>312 pg/mL</td>
<td>120-450 pg/mL</td>
<td>263 µg/24 h</td>
<td>&lt;540 µg/24 h</td>
</tr>
<tr>
<td>Ceruloplasmin, mg/dL</td>
<td>34</td>
<td>21-53</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Copper</td>
<td>88 µg/dL</td>
<td>70-155 µg/mL</td>
<td>22 µg/24 h</td>
<td>15-50 µg/24 h</td>
</tr>
<tr>
<td>Bismuth</td>
<td>NA</td>
<td>NA</td>
<td>Not detected</td>
<td>&lt;5 µg/L</td>
</tr>
<tr>
<td>Prolactin, ng/mL</td>
<td>35.8 (Midafternoon)</td>
<td>0-20</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Human growth hormone, ng/mL</td>
<td>&lt;1.5 (Midafternoon)</td>
<td>≤1.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>27.6 (8 AM)</td>
<td>6-23 (8 AM)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>3.5 (8 PM)‡</td>
<td>0-9 (8 PM)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA indicates not available.
†Normal gold levels are <0.5 µg/L for urine and <2.5 µg/L for serum, with therapeutic levels of 3000 to 8000 µg/L (from National Medical Services, Inc, Willow Grove, Pa).
‡Normal diurnal variation.

Table 2. Comparison of Serum and Urine Gold Levels for the Patient and Spouse Over Time*  

<table>
<thead>
<tr>
<th>Gold Level</th>
<th>Specimen</th>
<th>12/16/95</th>
<th>1/11/96</th>
<th>2/2/96</th>
<th>5/17/96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Urine</td>
<td>550-650</td>
<td>240</td>
<td>310</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>640</td>
</tr>
<tr>
<td>Spouse</td>
<td>Urine</td>
<td>NA</td>
<td>NA</td>
<td>470</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>NA</td>
<td>NA</td>
<td>610</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Data are given in micrograms per liter. NA indicates not available; ND, none detected. Normal gold levels are <0.5 µg/L for urine and <2.5 µg/L for serum, with therapeutic levels of 3000 to 8000 µg/L (from National Medical Services, Inc, Willow Grove, Pa).

COMMENT

Compared with age-matched controls, patients with dementia have a greater disruption of sleep, with more frequent arousals and decreased sleep efficiency, and may have increased stage 1 and decreased SWS.1-3,10 Patients with Alzheimer disease often have dysregulation of their circadian rhythms, sleep excessively during the day, have nighttime awakenings, and may have alteration of REM latency.3,10 Patients with Lewy body dementia may have REM behavioral disorder.3 The sleep disorder described in this patient is not associated with degenerative dementias, such as Alzheimer, Lewy body, or Pick disease, because the absence of SWS and REM atonia and the presence of sleep onset–REM periods are not characteristic of these degenerative dementias. The postmortem examination was also not compatible with these dementias.
As in this patient’s case, patients with Parkinson disease may have persistence of muscle tone, leading to loss of REM atonia.11-14 and patients with progressive supranuclear palsy may present with horizontal and vertical gaze palsies. Although patients with Parkinson disease and the Parkinson-plus syndromes may have a reduction of SWS and REM sleep, they have not been reported to have absent SWS. In addition, the postmortem examination did not demonstrate degranulation of the substantia nigra, and no neurofibrillary tangles were noted.

This woman demonstrated a supranuclear gaze palsy and complained of excessive flatus and loose stools, which have been reported in patients with Whipple disease.19 Our patient, however, did not demonstrate other signs associated with Whipple disease, including uveitis, arthralgias, malabsorption, fevers, and lymphadenopathy.15,16 The dementia of Whipple disease has been described as progressive short-term memory difficulties, with diffuse abnormalities on neuropsychological testing.16 Whipple disease is caused by *Tropheryma whippelii*, diagnosable on polymerase chain reaction analysis of CSF.27 Unfortunately, this test was not available when we evaluated this patient, but the absence of periodic acid–Schiff stain–positive macrophages in CSF, on a small bowel biopsy, and in postmortem tissue is not consistent with the diagnosis of Whipple disease.

Niemann-Pick type C is a progressive disorder that may have a late onset and may also present with vertical supranuclear ophthalmoplegia. This disorder is often associated with psychiatric disease, progressive dementia, dystonia, dysarthria, ataxia, and hepatosplenomegaly.18,19 Of the greatest relevance to our patient is the description of 7 patients with a combination of cataplexy and variants of Niemann-Pick disease.20 However, our patient’s bone marrow and postmortem examination findings were not compatible with this diagnosis.

Morvan fibrillary chorea is a rare condition manifested by severe insomnia, hallucinations, and loss of REM sleep, with frequent arousals.21 Our patient, however, had excessive sleepiness and loss of SWS. Chronic gold and mercury exposure has been implicated in the pathogenesis of Morvan fibrillary chorea. Initial gold levels were high in our patient but were later also noted to be elevated in her asymptomatic husband (Table 2). No source of gold for ingestion or other intake was discovered, and the levels returned to normal 6 months later, without any sign of clinical improvement. Bismuth encephalopathy has also been implicated in a similar sleep disorder, but none was detected on laboratory studies, and there was no evidence for peripheral neuropathy, the most common manifestation of chronic heavy metal toxicity.

Depressive pseudodementia may be associated with reduced sleep efficiency, SWS, and REM latency.22,23 Reduced REM latency and other REM sleep features have been used to evaluate patients with depression alone and with depression in conjunction with dementia, and sleep onset–REM periods on multiple sleep latency tests have not been consistently reported in depression.25 In addition, the complete absence of SWS and lack of REM atonia during polysomnography in this patient are not typical of depression.

Prion diseases are characterized by deposition of an abnormal isoform of the cellular prion protein. The sporadic forms account for more than three fourths of all cases of spongiform encephalopathy. Lugaresi et al1 initially described a heritable disease that presented with progressive insomnia and dysautonomia, which they called FFI. Subsequent reports have noted phenotypic variability in FFI,24,25 and one would suspect that variability of spontaneous mutations may produce syndromes clinically similar to FFI without the same genotypic findings, including 5 subjects with clinical and histopathological manifestations that were virtually identical to FFI.26 Prion protein PrP(Sc) type 2 was present in all subjects in an amount and a distribution similar to those of FFI. The clinical course and duration were similar, lasting 1 to 24 months. However, PrP(Sc) did not show the striking underrepresentation of the unglycosylated isoform of the protein that is characteristic of FFI. Moreover, none of the subjects had the prion protein gene D178N PRNP mutation, but all were homozygous for methionine at codon 129. The presence or absence of SWS was not reported for the individual patients; however, REM behavioral disorder appeared to be a feature of these cases. The authors concluded that this likely represented a sporadic form of FFI, which they termed sporadic fatal insomnia.26

Whereas patients with FFI may have a loss of SWS and a progressive dementia, as in our patient, this patient did not have the genetic defects associated with this disorder.1,24,27 Analysis of blood for FFI revealed that our patient was homozygous for methionine at codon 129. This is normally a polymorphic site in the prion protein gene, which has associations with sporadic CJD.24,28 but was believed to be a normal variant. The aspartic acid to asparagine mutation at codon 178 associated with FFI was not present in our patient.24 Other differences include the prolonged duration of illness in our patient, lasting at least 7 years.

Precocious loss of physiologic sleep has also been reported in CJD.29 Although FFI has been primarily associated with a pathogenic mutation at codon 178 in the PRNP gene, coupled with methionine at codon 129, a patient has been described with familial CJD who was affected by severe insomnia and was heterozygous for the pathogenic lysine mutation at codon 200 and homozygous for methionine at codon 129 of the PRNP gene.30 At autopsy, the patient had significant involvement of the thalamus, as previously described in subjects affected by FFI with the codon 178 mutation.24 The authors concluded that the case demonstrated the wide variability of the clinical expressions of the codon 200 mutation, which may include insomnia and thalamic pathologic abnormality.30 Further reports have contrasted the phenotypic, genotypic, and pathologic findings between CJD and FFI.24,26

The pathogenesis of FFI would suggest that the limbic thalamus has an integral role in the central autonomic network, which coordinates the limbic cortical regions and the lower brainstem, regulating the body’s homeostasis and sleep-wake cycle in an integrated fashion.1,29,31,32 Fatal familial insomnia characteristically affects the midorsal and anteroventral thalamic nuclei most severely, with the basal ganglia, cerebellum, and brainstem typically unaffected. In this woman, the basal ganglia and thalami appeared to be spared. The midbrain tectum, periaqueductal gray, parmedian pontine tegmentum, and ventral paramedian medulla showed glial and perivascular inflammatory changes. Microscopic examination demonstrated widespread, but variable, areas of astroglial and microglial reaction. Only the amyg-
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Corresponding author: Stephan Eisenschenk, MD, Department of Neurology, McKnight Brain Institute at the University of Florida College of Medicine, 100 S Newell Dr, Room L3-100, Gainesville, FL 32610-0236 (e-mail: eisens@neurology.ufl.edu).

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