INVITED REVIEW

Recognizing New-Onset Sleep Disorders in Autoimmune Encephalitis Often Prompt Earlier Diagnosis

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Summary: Sleep/wake disorders are common in patients with autoimmune encephalitis, sometimes the most prominent or sole initial symptom, then delaying diagnosis. Sleep/wake disorders in autoimmune encephalitis vary and include severe sleeplessness, hypersomnia, central and/or obstructive sleep apnea, rapid eye movement sleep behavior disorder, indeterminate sleep/wake states, and loss of circadian sleep/wake rhythms. N-methyl-D aspartate receptor encephalitis (NMDAR) is often associated with insomnia, then hypersomnia and sleep-related central hypoventilation. Profound sleeplessness and rapid eye movement sleep behavior disorder are seen in patients with voltage-gated potassium channel–complex antibodies. Fragmented sleep and hypersomnia are common in paraneoplastic syndromes associated with anti-MA protein encephalitis; rapid eye movement sleep behavior disorder in those with antibodies against leucine-rich glioma inactivated protein (LGI1) or contactin-associated protein 2 (CASPR2) antibodies. Antibodies against a cell adhesion protein IGLON5 may result in obstructive sleep apnea, inspiratory stridor, disorganized nonrapid eye movement sleep, and excessive movements and parasomnias fragmenting nonrapid and rapid eye movement sleep. Recognizing a particular sleep/wake disorder is often a presenting or prominent feature in certain autoimmune encephalitis permit for earlier diagnosis. This is important because reduced morbidity and better short- and long-term outcomes are associated with earlier diagnosis and immunotherapies.

Key Words: Autoimmune encephalitis, REM behavior disorder, Inspiratory Stridor, Anti-IgLON5 disease.

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Sleep/wake disorders (SWDs) are common in patients with autoimmune encephalitis (AIE), sometimes the prominent initial or even sole symptoms then delaying diagnosis. Early recognition, diagnosis, and immunotherapy of AIE appear to improve or lessen relapse and improve outcomes.[1–4] Sleep/wake disorders in AIE vary and include hypersomnia, severe sleeplessness, rapid eye movement (REM) sleep behavior disorder behavior disorder (RBD), central and/or obstructive sleep apnea (OSA), indeterminate sleep/wake states, and/or loss of circadian sleep/wake rhythms. A recent retrospective case series found that new sleep complaints were reported in 73% of 26 patients with AIE (median age, 53; range, 18–83), including snoring/gasping (47%), insomnia (29%), hypersomnia (21%), dream/wake confusional states (11%), and dream enactment behavior (11%).[5]

RISING PREVALENCE AND INCIDENCE OF AIE

Until recently, most confirmed causes for acute encephalitis were infectious. However, a 2015 population-based epidemiological study found that prevalence and incidence rates for AIE now match those for infectious encephalitis (13.7 vs. 11.6/100,000 and 0.8 vs. 1.0/100,000 person years, respectively), even though the incidence and prevalence of infectious encephalitis has not increased between 1995 and 2015.[6] The increased incidence of AIE reflects development of neural markers, which detect the pathogenic autoantibodies of AIE against neuronal cell-surface or synaptic proteins. Autoantibodies of AIE were first recognized as being associated with certain tumors and paraneoplastic syndromes. Knowing these associations remain important, and Table 1 summarizes different autoantibodies associated with AIE, which are associated with particular tumors.[4,7,8]

The disease burden of either autoimmune or infectious encephalitis is severe: averaging hospitalizations of 20,258 cases per year in the United States between 1998 and 2010, fatal in 5.8%, and costing an estimated $2.0 billion in 2010.[9] However, the disease burden for AIE may be greater because relapses and recurrent hospitalizations are much more common for patients with AIE than for those with infectious encephalitis.[6]

CONSTANTIN VON ECONOMO FIRST TO DESCRIBE SLEEP DISORDERS IN ENCEPHALITIS

The Austrian neuroscientist Von Economo was the first to report sleep disturbances as a pathognomonic sign of encephalitis. He reported the first seven cases of what was encephalitis lethargica at a meeting of the Viennese Psychiatric and Neurological Society in April 1917.[10,11] Sleep was severely disturbed in 85% of patients. Most exhibited extreme hypersomnia, often sleeping 20 or more hours per day, arising only to eat and drink. Hypersomnia in them lasted well into the chronic phase of the disease. Others had severe sleeplessness (insomnia) which he termed *agrypnia* (a Greek word meaning a total inability to sleep).

Von Economo performed autopsies on patients who died of encephalitis lethargica and found that those who had

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hypersomnia had rostral lesions in the posterior hypothalamus and its junction with the rostral midbrain; those with agrypnia had caudal lesions at the level of the anterior hypothalamus (preoptic region) and its junction with the basal forebrain.[12] Few today know that Von Economo wrote 14 articles arguing that there were different anatomic centers for sleep and wakefulness in the brain and that sleep was an active (not passive) process, by and for the brain.[11,13] Further research has confirmed that the sleep center in the brain lies in the anterior hypothalamus in the sleep-promoting GABAergic neurons of the ventrolateral preoptic nucleus. Whereas, the wake-promoting center of the brain is the ascending reticular activating system (ARAS), which originates diffusely in the neurons of the brainstem, hypothalamus, and basal forebrain.[14] Ascending reticular activating system activates the thalamus and cerebral cortex and is composed of two major branches: an ascending pathway of cholinergic pedunculopontine and noradrenergic laterodorsal tegmental neurons to the thalamus, and a group of ascending pathways from the locus coeruleus, serotoninergic raphe nuclei, and histaminergic tuberomammillary neurons to the lateral hypothalamus, basal forebrain, and cerebral cortex.[14]

MANY FORMS OF AIE

The first report of an AIE was a syndrome of subacute or fluctuating cognitive impairment, behavioral changes, decreased level of consciousness, seizures, and stroke-like episodes associated with antithyroid antibodies (Hashimoto encephalopathy).[15,16] In the late 1960s, cases of limbic encephalitis with cognitive decline, behavioral changes, and seizures were

TABLE 1. Neurological Syndromes and Cancers Associated With Particular Autoantibodies

Antibodies	Syndrome	Cancer Association	Frequency of Cancer	Comments
Antibodies again synaptic receptors				
NMDA receptor	Anti-NMDA receptor encephalitis	Ovarian teratoma	Varies with sex and age: Ovarian teratomas usually females ages 12–45	Orofacial dyskinesia, choreoathetosis, catatonia, autonomic instability, hypoventilation
AMPA receptor	Limbic encephalitis	Thymoma and small cell lung carcinoma	65%	70% of females with breast or thymus cancers; often recur
$GABA_B$ receptor	Limbic encephalitis	Small cell lung carcinoma	50%	
$GABA_A$ receptor	Encephalitis	Thymoma	<5%	
mGluR5	Encephalitis	Hodgkin's lymphoma	70%	
Dopamine 2 receptor	Basal ganglia encephalitis	—	0%	
Antibodies against ion channels and other cell-surface proteins				
LG/1	Limbic encephalitis	Thymoma	5%–10%	Faciobrachial dystonic seizures common
CASPR2	Limbic encephalitis or Morvan syndrome	Thymoma	20%–50%	Thymoma associated with Morvan syndrome not limbic encephalitis
DPPX	Encephalitis	Lymphoma	<10%	Associated with hyperekplexia and diarrhea
MOG	Acute disseminated encephalomyelitis	—	0%	
Aquaporin 4	Encephalitis	—	0%	
GQ1b	Bickerstaff brainstem encephalitis	—	0%	
Antibodies against intracellular antigens				
GAD	Limbic encephalitis Stiffman syndrome Cerebellar ataxia	Thymoma and small cell lung carcinoma	25%	Tumors more frequent men older than 50 years
MA2	Limbic encephalitis	Testicular seminoma	>95%	With hypothalamic and midbrain involvement
Hu (AANA1)		Small cell lung carcinoma adult, neuroblastoma children	>95%	Clinical presentation often precedes tumor by approximately 4 months; tumor diagnosed first 12%

CASPR2, contactin-associated protein 2; DPPX, dipeptidyl-peptidase–like protein 6; GABA, gamma-aminobutyric acid A/B receptors; GAD, glutamic acid decarboxylase; LGI1, leucine-rich glioma inactivated 1; MOG, myelin oligodendrocyte glycoprotein; NMDA, N-methyl, D-aspartate.

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TABLE 2. Diagnostic Criteria for Possible and Definite Autoimmune Encephalitis

Diagnosis of possible autoimmune encephalitis when all three of the following criteria met

(1) Subacute onset (rapid progression <3 months) of short-term memory impairment, altered mental status (decreased/altered level of consciousness, personality change, or lethargy), or psychiatric symptoms

(2) At least one of the following:

a. New focal CNS findings

b. Seizures not explained by a previously known epilepsy

c. CSF pleocytosis (white blood cell >5 cells per mm^3)

d. Brain MRI or suggestive of encephalitis: hyperintense signal on T2-weighted fluid-attenuated inverse recovery sequences restricted to one/both temporal lobes (limbic encephalitis) or multifocal areas involving grey matter, white matter or both compatible with demyelination or inflammation

(3) Reasonable exclusion of alternative causes

observed associated with a known or occult systemic cancer (ie, a paraneoplastic process).[17,18]

Identification of autoantibodies against neural cell surface and synaptic proteins beginning in the 1980s and 1990s led to understanding that AIE often occurs unrelated to cancer. Diagnostic criteria for possible, probable, or definite AIE were first published in 2016 (and summarized in Table 2).[4]

The focus of this narrative review is not the clinical features of these, but SWDs in AIE as biomarkers, and the diagnostic and therapeutic utility of EEG and polysomnography (PSG) in AIE.

SWDS ESPECIALLY COMMON IN PARTICULAR AUTOIMMUNE ENCEPHALITIDES

Sleep disorders are so prominent in four particular AIE as to be phenotypic (and prompt consideration of the diagnosis): NMDAR encephalitis, limbic encephalitis with antibodies against leucine-rich glioma inactivated protein (LGI1) antibodies, anti-MA2 encephalitis, and Morvan syndrome associated with contactin-associated protein 2 (CASPR2) antibodies.

Anti-NMDA Receptor Encephalitis

Anti- N-methyl-D-aspartate (NMDA) receptor encephalitis is associated with IgG antibodies in the CSF against the GluN1 subunit of NMDA receptor (NMDAR).[19] The NMDA receptor is a glutamate receptor and ion channel protein found in nerve cells, which has significant roles in synaptic plasticity and memory function.

NMDAR encephalitis often begins with a viral prodrome lasting up to two weeks (prodromal stage) followed by an agitated schizophrenia-like psychosis with delusions, hallucinations, disorganized thinking, sleeplessness, speech difficulties, and sometimes seizures lasting 1 to 3 weeks (insomnia, psychotic, and seizures phase).[20,21] This often evolves to a stage characterized by akinetic state accompanied by catatonia and central hypoventilation.[21,22] Orofacial limb dyskinesia and autonomic storms and instability characterize the fourth hyperkinetic phase. The last phase of NMDAR encephalitis is gradual recovery over 2 to 5 months. Some are left with residual executive dysfunction, disinhibition, impulsivity, and sleep difficulties. Relapses can occur.

A large observational study found that most patients with NMDAR encephalitis are female (80%) and young (median age, 21 years; 37% <18 years).[23] Tumors, usually ovarian teratoma,[23,24] and herpes simplex encephalitis[25,26] are known triggers of NMDAR autoimmunity. Table 3 summarizes diagnostic clues and Table 4 diagnostic criteria for NMDAR encephalitis.[27]

Different SWDs are observed during different phases of NMDAR encephalitis: often profound insomnia in the acute phase; sleep-related central hypoventilation in the akinetic/catatonic phase; hypersomnia in the recovery phase, and circadian rhythm disorders postrecovery.[21,22,28–32] Hypersomnia is sometimes accompanied by hyperphagia, apathy, irritability, and/or hypersexuality, suggesting hypothalamic dysfunction.[27] Central hypoventilation coupled with autonomic instability often requires intensive care admission and mechanical ventilation for weeks to months.[21,22] After recovery, 27% of patients in one series developed circadian rhythm disorders (especially day/night reversal, awake at night, sleeping in the day).[22]

A 2020 prospective observational case–control study recorded video PSG and evaluated sleep disorders in 18 patients with NMDAR encephalitis.[33] They confirmed the biphasic pattern of sleep disorders in NMDAR encephalitis: insomnia in the acute stage (present in 89%) and hypersomnia during recovery (78%). They further reported frequent often long-lasting confusional arousals from nonrapid eye movement (NREM) sleep during the recovery phase.[33] The hypersomnia persists long after withdrawal of antipsychotics, benzodiazepines, and antiseizure medications, suggesting it is part of the illness.[33]

The EEG is typically abnormal in NMDAR encephalitis.[23,34,35] Again, certain EEG patterns characterize different phases of the illness. A 2019 retrospective analysis of EEG recordings in 24 consecutive patients with NMDAR encephalitis found excessive beta activity (EBA14–20 Hz) in 71%, extreme delta brushes in 58%, and generalized rhythmic delta activity in 50%.[35]

EBA appeared first, followed by extreme delta brushes and then generalized rhythmic delta activity; the median time of appearance of these was 10, 16.5, and 21.5 days, respectively. Extreme delta brushes and generalized rhythmic delta activity occupied an increasing proportion of the EEG as the disease progressed and were associated with abnormal movements but not seizures. Effective immunotherapy led to progressive decrease in generalized rhythmic delta activity and EDB and predated clinical improvement.

Extreme delta brushes are thought to be a specific EEG biomarker for NMDAR encephalitis not seen in EEGs of any of 117 patients with other AIE.[34] Extreme delta brushes are most likely not ictal activity.[36] Electrographic seizures characterized by sinusoidal alpha activity from the temporal lobes warrant consideration of NMDAR encephalitis.[37]

A 2018 study found the initial EEG in patients with NMDAR encephalitis may predict the final clinical outcome.[38] A normal dominant posterior rhythm present on the first EEG in

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TABLE 3. Diagnostic Criteria for anti-NMDAR Encephalitis

Probable:
- (1) Rapid onset (<3 months) of at least four of six major groups of symptoms
  - (a) Abnormal behavior or cognitive function
  - (b) Pressured speech, paucity of speech, or mutism
  - (c) Seizures
  - (d) Dyskinesias, rigidity, catatonia, or abnormal postures
  - (e) Decreased level of consciousness
  - (f) Autonomic instability or central alveolar hypoventilation
- (2) And at least one of these laboratory abnormalities
  - (a) Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brushes)
  - (b) CSF with pleocytosis or oligoclonal bands
- (3) Or three of the above groups of symptoms and identification of a teratoma tumor
- (4) Exclusion of a recent history of herpes simplex or Japanese B encephalitis which can result in relapsing immune-mediated neurological symptoms

Definite
- (1) One or more of the six major groups of symptoms and IgG GluN1 antibodies (including presence in the CSF). If only serum is available, confirmation by live neurons or tissue immunohistochemistry in addition to cell-based assay
- (2) Exclusion of a recent history of herpes simplex or Japanese B encephalitis, which can result in relapsing immune-mediated neurological symptoms

71% of 53 patients with NMDAR encephalitis was associated with a 4.7-fold better outcome than a severely abnormal EEG present in 26%. Extreme delta brushes were not observed in first EEG, appeared later in 11% of patients, and only those severely affected. Eight of 14 patients with a severely abnormal first EEG still had a favorable outcome.

Approximately 80% of patients with NMDAR encephalitis improve with immunotherapy and, if needed, tumor removal; recovery is slow, and relapses occur in 15%, albeit milder than at first.[27] Earlier diagnosis and treatment seem to be associated with better outcomes. Early diagnosis, immunotherapy, and removal of tumor if present are associated with a favorable outcome in 80%.

Anti-MA2 Encephalitis Associated with Symptomatic Narcolepsy and REM Behavior Disorder

Encephalitis associated with MA2 antibodies preferentially affects limbic, upper brainstem, and/or diencephalic structures and is usually associated with testicular germ cell tumors (in men younger than 45 years), gastrointestinal or non–small cell lung cancers in women and older men. The median age when patients present was 64 years (range, 53–82 years), and neurological symptoms often precede the cancer diagnosis (62% in one case series).[39] One third of patients with MA2-associated paraneoplastic syndromes present as limbic encephalitis with seizures, memory loss, irritability, and depression.

In one series, progressive hypersomnia with irresistible sleep attacks, weight gain, hyperthermia, and endocrine abnormalities was observed in 38% of patients with anti-MA2 encephalitis.[40] Cataplexy, hypnic hallucinations, and very low/undetectable CSF hypocretin-1 levels were found in a few consistent with a symptomatic narcolepsy syndrome.[41] Narcolepsy symptoms improved after successful treatment of MA2 encephalitis in one patient.[40]

An illustrative case of SWDs in MA2 encephalitis was a 69-year-old man admitted with a 3-month history of progressive severe hypersomnia, memory loss, short attacks of fear, apathy, diplopia, and unsteady gait with frequent falls.[42] Video PSG showed fragmented sleep, markedly reduced sleep efficiency of 48%, absence of sleep spindles, rapid eye movement sleep without atonia (RWA), and dream enactment behaviors (RBD). Figure 1 shows a 30-second of REM sleep without atonia recorded in our sleep laboratory. His multiple sleep latency test showed a shortened mean sleep latency of 7 minutes and 4 sleep-onset REM periods (SOREMPs) consistent with a symptomatic narcolepsy. The level of hypocretin-1 in the cerebrospinal fluid was low (49 pg/mL, normal >110). Brain MRI showed bilateral damage in the dorsolateral midbrain, amygdala, and paramedian thalami.

Another case was a 35-year-old man with anti-MA2 encephalitis and a testicular germ cell tumor who presented with Ehlers–Danlos syndromes worsening over 6 months, sleeping up to 16 hours per day, waking only to seek carbohydrates he craved.[43] EEG awake showed generalized slowing. Dream enactment behavior was observed when sleeping and RWA on PSG. Multiple sleep latency test showed a short mean sleep latency of 2.8 minutes and multiple SOREMPs. He later developed cognitive decline, medically intractable right temporal lobe epilepsy, vertical gaze paresis, and died despite different immunotherapies and bilateral orchidectomy.

Several recent studies report that treatment with immune checkpoint inhibitors can trigger MA2 encephalitis.[39,44,45] One study reported a 112% increase in MA2 encephalitis after implementation of immune checkpoint inhibitors. A case of MA2 encephalitis associated with immune checkpoint inhibitor presented with excessive sleepiness, difficulty with arousal, seizures, cognitive decline, memory loss, and internuclear ophthalmoplegia.[39]

Limbic Encephalitis Associated with LGI1 Antibodies Associated with Insomnia, REM Behavior Disorder, and Excessive Daytime Sleepiness

Encephalitis associated with antibodies against the leucine-rich glioma inactivated protein (LGI1) presents as a limbic encephalitis in middle-aged and older adults with subacute progressive cognitive impairment, confusion, amnesia, hyponatremia, and faciobrachial dystonic seizures.[46] A 2016 case series of 76 patients reported faciobrachial dystonic seizures in 47%, hyponatremia in 60% to 74%, and thymoma in 11%.[46] LGI1 antibodies are found in CSF, and brain MRI often show lesions in hippocampus and basal ganglia. Symptoms may improve or remit with immunotherapy.

Faciobrachial dystonic seizures are frequent involuntary episodes of brief (<3 seconds) ipsilateral upper arm spasm and

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TABLE 4. Suspect NMDAR Encephalitis

- Rapid onset days or weeks
- Severe insomnia at disease onset; hypersomnia sometimes coupled with hyperphagia and hypersexuality in recovery phase.
- Disinhibition, wandering, hypersexuality, or manic behavior alternating with depressive behaviors at onset
- Cognitive and memory impairment, distractibility, anhedonia at onset
- Rapid decrease in verbal output at onset may be preceded by pressured speech and progress to mutism
- Temper tantrums, biting, kicking, hitting
- Fluctuating catatonia may alternate with episodes of extreme agitation
- Visual or auditory hallucinations, grandiose
- Religious or persecutory delusions, disorganized thoughts

contraction (dystonia) accompanied by an ipsilateral face twitch.[46,47] Faciobrachial dystonic seizures are often the first symptom, seen in 30% to 50% of patients.[48] Faciobrachial dystonic seizures are quite specific for LGI1 encephalitis, and when coupled with hyponatremia, it suggests the diagnosis.

Insomnia (often severe) is reported in 45% to 65%, usually appears early in the disease, and most often coupled with excessive daytime sleepiness.[46,48,49] Video PSG studies show low sleep efficiency with the absence of sleep in some.[50,51]

An illustrative case of severe insomnia as a presenting symptom of LGI1 limbic encephalitis was a 65-year-old man who was admitted for subacute confusion, anterograde memory loss, and severe insomnia, affecting initiation and maintenance.[50] EEG showed bitemporal slowing. Brain MRI showed hyperintensity in the left mesial temporal lobe on fluid-attenuated inversion recovery. Severely reduced sleep time was recorded on video PSG before treatment with no REM or NREM 3sleep and only a few sleep spindles and K-complexes. Insomnia began to remit, and normal sleep architecture and sleep time were observed on repeat PSG after second infusion cycle of intravenous (IV) immunoglobins.

Rapid eye movement sleep behavior disorder is common in the acute phase of the disease.[48,50–53] REM sleep behavior disorder behaviors with RWA on video PSG was observed in five of six patients with LGI1 encephalitis.[52] CSF hypocretin-1 levels were normal. Rapid eye movement sleep behavior disorder usually resolves, and sleep patterns improve or remit with immunotherapy in patients with LGI1 encephalitis. One study reported milder insomnia with residual complaints of poor sleep quality in 20% of 38 patients for several months after recovery.[54] Seizures usually remit but mild residual cognitive deficits with spatial disorientation common. Relapses were reported to occur in 35%.[54]

CASPR2 Antibodies Associated with Limbic Encephalitis and Morvan Syndrome

Antibodies against contactin-associated protein 2 (CASPR2) have been associated with limbic encephalitis, Morvan syndrome, or neuromyotonia. A large case series of 38 patients (most elderly men) with CASPR2 antibodies found that 77% presented with ≥ 3 of the following symptoms: peripheral nervous system hyperexcitability, dysautonomia, profound sleeplessness, neuropathic pain, encephalopathy/seizures, or weight loss. Twenty-nine percent had Morvan syndrome.

Morvan syndrome is characterized by progressive profound sleeplessness, loss of circadian sleep/wake rhythms, RBD, visual hallucinations, dysautonomia (hyperthermia, hyperhidrosis, cardiovascular instability, urinary incontinence, erectile dysfunction), and peripheral nerve hyperexcitability (neuromyotonia, fasciculations, myoclonus, muscle cramping).[55]

Insomnia affects 90% of patients with Morvan syndrome, and often, it is the first symptom. Insomnia initially is often initially partial but within weeks to a few months evolves to complete inability to initiate or sustain sleep accompanied by severe autonomic and motor hyperactivity (the symptom combination termed *agrypnia excitata*).[48,56,57] As the disease progresses, circadian rhythms are lost and distinctions between wakefulness, NREM, and REM sleep blur (termed *status dissociatus*) and prolonged dream enactment behaviors and hallucinations (called by some *oneiric stupor*) occur.[58–62]

Video PSG recordings in patients with Morvan syndrome show them performing simple and complex behaviors mimicking daily life behaviors (such as eating, dressing, buttoning pajamas).[62,63] When severe, patients exhibit nearly continuous dream enactment behaviors, which can emerge from relaxed wakefulness, REM, or NREM sleep. During these, their eyes may be open or closed, and they may respond to questions while continuing to perform their dream enactment behaviors.

Twenty-four hour video PSG recordings in patients with Morvan syndrome show very disorganized sleep/wake patterns with loss of circadian rhythmicity, reduced/absent sleep spindles and K-complexes, brief periods of NREM 3, intrusions, brief fragments of REM sleep, REM sleep without atonia, and rapid shifts between wakefulness, NREM, and REM sleep (later usually without atonia).[56,58,59,63]

In a representative case of Morvan syndrome, the patient would hit and punch his wife while sleeping, fall from bed, sleep talk.[58] His video PSG showed severely fragmented sleep with sleep composed of short periods of NREM 1 and REM sleep without atonia and no NREM 2 or NREM 3 sleep. Continuous motor hyperactivity (with simple flexion–extension movements of all limbs and continuous changes in body position), dream enactment behaviors, confusional arousals, and sleep talking were observed when sleeping. Figure 2 shows a hypnogram from a patient with Morvan syndrome and a normal subject for comparison.

Morvan syndrome should be considered in patients who develop severe acute-onset insomnia, profuse hyperhidrosis, and 24/7 motor hyperactivity with dream behaviors simulating daily life activities, especially when combined with neuromyotonia.[48] Eighty percent of patients with Morvan syndrome have CASPR2 antibodies, sometimes with concurrent LGI1 antibodies.[64] An underlying thymoma is found in approximately half of patients with Morvan syndrome and 20% of the patients with CASPR2 antibodies.[64]

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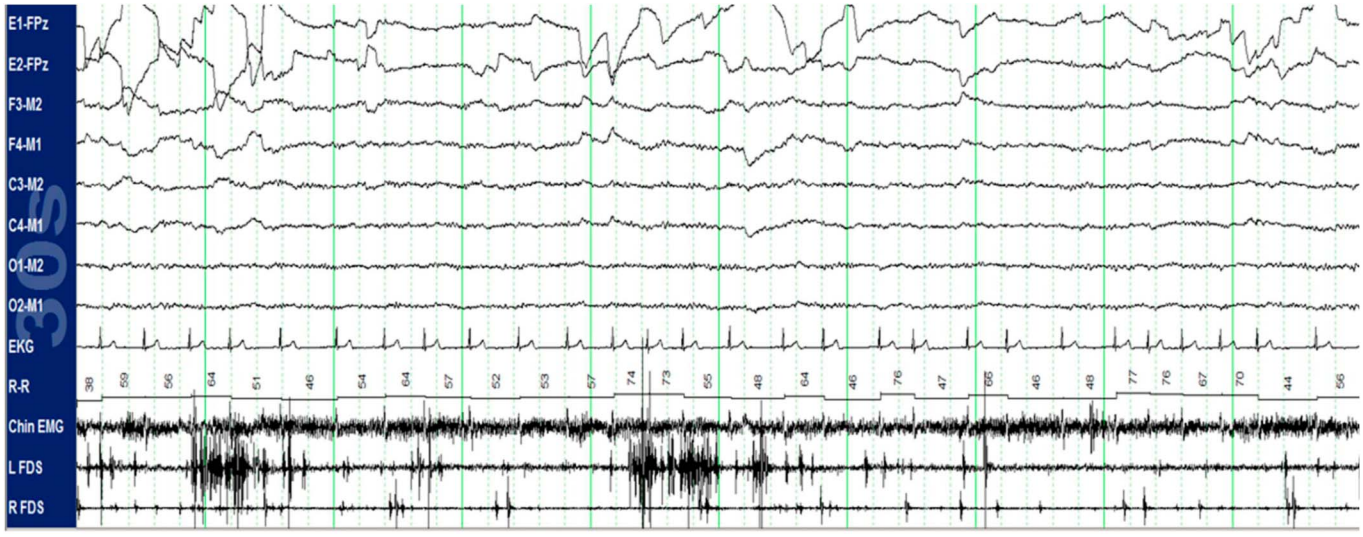

FIG. 1. Thirty-second epoch of REM sleep recorded in an 80-year-old man showing excessive tonic submentalis (chin) muscle activity, and excessive left and right phasic flexor digitorum superficialis muscle activity consistent with REM sleep without atonia. REM, rapid eye movement.

Unique Complex Sleep Disturbances Characterize Anti-IgLON5 Disease

Antibodies against immunoglobin-like cell adhesion molecule 5 (anti-IgLON5, a cell adhesion protein on the surface of neurons) is associated with a newly described autoimmune disorder called anti-IgLON5 disease.[65–70] In a case series of 22 patients found by the time of diagnosis, patients had at least one of four syndromes: (1) a sleep disorder with a parasomnia and sleep breathing difficulty, (2) bulbar syndrome (dysphagia, dysarthria, sialorrhea) often accompanied with acute respiratory insufficiency, (3) gait instability and abnormal eye movements, and (4) cognitive dysfunction with chorea.[66]

Sixty cases have been reported in the medical literature as of 2019, and SWDs were present in 83%, heralding the disease in 40%.[71] Cognitive decline with chorea in IgLON5 disease can resemble Huntington disease, the bulbar syndrome with gait instability with gaze palsies progressive supranuclear palsy, and the peripheral nerve hyperexcitability, stiff-person syndrome, but the sleep disorder is so unique and led to discovery of the disease.[72] Video PSG in patients with IgLON5 is different than seen with any other disorder.

Despite their neurological compromise, the dominant posterior alpha rhythm awake is normal.[71] Sleep onset heralded by diffuse theta activity but repeatedly delayed by vigorous repetitive leg movements, which first appear when trying to fall asleep. After a while, a featureless undifferentiated NREM sleep is observed identified by complex motor behaviors and vocalizations, excessive motor activity, and diffuse moderate amplitude of 20 to 50 μV and 4 to 7 Hz theta activity. Poorly differentiated NREM 2 with only a few sleep spindles and K-complexes were seen later in the night accompanied by a variety of vocalizations (talking, laughing, crying), simple motor behaviors (punching, arm raising), and/or complex behaviors (such as eating, picking up imaginary objects). Normal appearing NREM 3 appears inappropriately late in the second half of the night. NREM 2 in the last part of the night is also normal appearing. Obstructive sleep apnea with AHI ranging from 18 to 80 per hour is common. Inspiratory stridor is observed, most often during NREM 2 and 3 sleep. Occasionally central sleep apnea is observed, but the predominant apnea is obstructive in type. Rapid eye movement sleep without atonia and RBD are observed in REM sleep.

Gaig et al.[67] recorded 27 serial video PSG in five patients with anti-IgLON5 disease across the course of their disease. They confirmed that sleep onset (and sleep after reentering after an awakening) was undifferentiated NREM (median 30% of total sleep time) or poorly differentiated NREM 2 (15% total sleep time). In the second half of the night, a median of 12% of total sleep time could be scored as normal appearing NREM 2, 22% NREM 3 sleep. Rapid eye movement sleep behavior disorder, NREM arousal parasomnias, obstructive sleep apnea, and stridor were observed.

Anti-IgLON5 is often associated with HLA-DRB1*10:01 and HLA-DQB1*05:01.[66,73] However, recent study reports suggest that IgLON5 disease may be a neurodegenerative tauopathy, and autopsies finding show abnormal tau hyperphosphorylation and intracellular deposition in neurons in them.[74,75] The majority of patients with IgLON5 disease have been treated with immunosuppressants, most often cycles of IV corticosteroids in combination with IV immunoglobins and/or plasma exchange.[71] Second-line treatments reported include rituximab, mycophenolate mofetil, cyclophosphamide, and azathioprine.

Sleep-disordered breathing and stridor is initially helped by positive airway pressure therapy and Ehlers–Danlos syndrome lessens. However, as the disease progresses, tracheostomy and mechanical ventilation are often needed. Anti-IgLON5 disease has a high mortality, 34% of the 58 patients in the literature so far with definite disease died; the most common cause of death was

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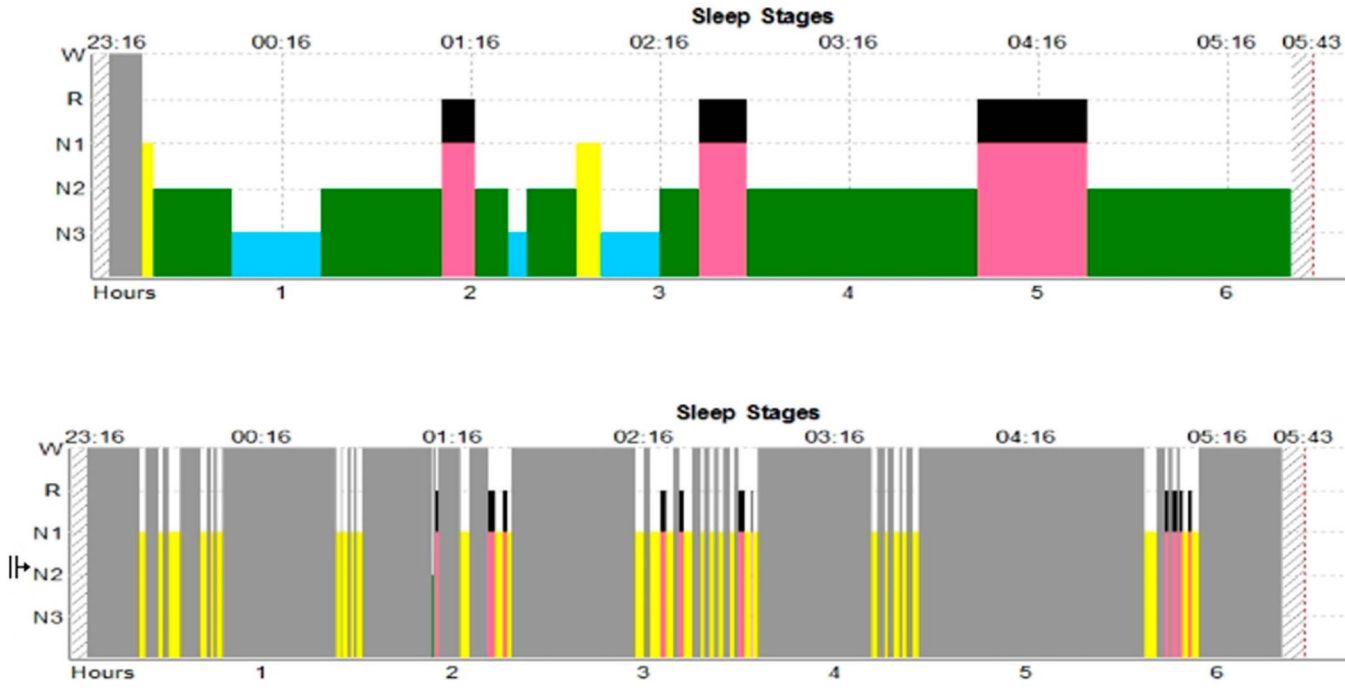

FIG. 2. Two hypnograms showing profound differences in sleep architecture between a normal subject and a person with Morvan syndrome. Top graph: normal sleep with NREM sleep. Note the normal sleep stages of NREM I, NREM II, NREM III, and REM sleep. Bottom graph: Example of hypnogram seen in Morvan syndrome. Note markedly reduced sleep efficiency, absence of NREM 2 or NREM 3 sleep. Rapid eye movement sleep occurs in recurrent short episodes and was associated with REM sleep without atonia and REM behavior disorder events. NREM, nonrapid eye movement; REM, rapid eye movement.

sudden death often during sleep (56%) and aspiration (44%).[71] Evaluation of vocal cords for vocal cord paresis is needed. Whether medications, such as melatonin or clonazepam, improve RBD and RWA has not yet been reported. More prospective studies are needed to better understand this devastating autoimmune disease.

Neuromyelitis Optica Spectrum Disorder with Aquaporin 4 Antibodies

Neuromyelitis optica spectrum disorder (previously called Devic syndrome) is an inflammatory disease of the central nervous system associated with aquaporin 4 antibodies, which most often presents with attacks of acute optic neuritis, transverse myelitis, and/or long-lasting episode of hiccups, nausea, and vomiting.[76] Sometimes, it is mistaken for multiple sclerosis; accurate diagnosis is essential because some drugs used for multiple sclerosis can worsen NMSOD.

Aquaporin 4 is the most abundant water-channel protein in the central nervous system. In a subset of patients negative for AQP4-IgG, pathogenetic serum IgG antibodies to myelin oligodendrocyte glycoprotein, an antigen in the outer myelin sheath of central nervous system neurons, are present.

Neuromyelitis optica spectrum disorder in some patients manifests as an acute hypothalamic syndrome with a secondary narcolepsy accompanied by autonomic and endocrine imbalance (hypotension, hypothermia, inappropriate antidiuretic hormone secretion, arrhythmias). Bilateral symmetrical lesions involving the hypothalamus and periependymal surface of the third ventricle were then seen on brain MRI. Several cases of secondary narcolepsy have been reported in neuromyelitis optica spectrum disorder with hypothalamic lesions on brain MRI.[77–80]

Patients then exhibit acute onset hypersomnia (sleeping up to 16 hours per day) with irresistible sleep attacks. Cataplexy is not reported. Low CSF hypocretin levels are reported (which normalize with immunotherapy). The multiple sleep latency test show short mean sleep latency and sleep onset REM periods consistent with narcolepsy. An illustrative case was a 21-year-old woman with bilateral hypothalamic lesions on brain MRI and aquaporin 4 antibodies who presented with hypersomnia, hypothermia, and hypotension.[78] CSF orexin levels were low, and multiple sleep latency test confirmed narcolepsy. Significant improvement in symptoms and MRI was observed following steroid therapy, but cognitive impairment and sleepiness persisted and she subsequently developed obesity.

Steroids and plasma exchange are often effective as a first-line treatment for neuromyelitis optica spectrum disorder attacks.[81] Attack prevention with B cell–depleting immunosuppressants has greatly improved long-term outcomes.

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CONCLUSION

Understanding that SWDs can be the first symptom of AIE is often prominent throughout the course of the disease, sometimes phenotypic of particular AIE, and should prompt screening for AIE. This is important because earlier diagnosis and treatment of AIE may reduce morbidity and improve acute and long-term outcomes.

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