Chapter 18

Autoimmune sleep disorders

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Abstract

A number of autoantibodies, some paraneoplastic, are associated with sleep disorders. Morvan syndrome and limbic encephalitis, associated with voltage-gated potassium channel–complex antibodies, principally against CASPR2 and LGI1, can result in profound insomnia and rapid eye movement sleep behavior disorder (RBD). Patients with aquaporin-4 antibodies and neuromyelitis optica may develop narcolepsy in association with other evidence of hypothalamic dysfunction, sometimes as the initial presentation. Central sleep apnea and central neurogenic hypoventilation are found in patients with anti-N-methyl-D-aspartate receptor antibody encephalitis, and obstructive sleep apnea, stridor, and hypoventilation are prominent features of a novel tauopathy associated with IgLON5 antibodies. In addition, paraneoplastic diseases may involve the hypothalamus and cause sleep disorders, particularly narcolepsy and RBD in those with Ma1 and Ma2 antibodies. Patients with antineuronal nuclear autoantibodies type 2 may develop stridor.

Several lines of evidence suggest that narcolepsy is an autoimmune disorder. There is a strong relationship with the human leukocyte antigen (HLA) DQB1*06:02 haplotype and polymorphisms in the T-cell receptor alpha locus and purinergic receptor P2Y11 genes. Patients with recent-onset narcolepsy may have high titers of antistreptococcal or other antibodies, although none has yet been shown to be disease-specific but, supporting an immune basis, recent evidence indicates that narcolepsy in children can be precipitated by one type of vaccination against the 2009–2010 H1N1 influenza pandemic.

INTRODUCTION

The 1984 discovery that narcolepsy was tightly linked to the human leukocyte antigen (HLA) haplotype DR2 raised the possibility that some sleep disorders might have an autoimmune origin (Juji et al., 1984; Langdon et al., 1984), and subsequent studies of narcolepsy widely support this, although no specific mechanisms have been demonstrated. In 2001, Morvan syndrome, a rare neurologic disorder with profound insomnia, recognized since the 19th century (Morvan, 1890), was linked to potassium channel–complex antibodies (Liguori et al., 2001). Since then, a range of other autoantibodies have been identified in patients with diencephalic and brainstem encephalopathies that frequently include sleep dysfunction, involving almost all categories of sleep disorders. A brief summary of the sleep disorders associated with autoimmunity follows below (American Academy of Sleep Medicine, 2014).

Narcolepsy is characterized by hypersomnolence and the early onset of rapid eye movement (REM) sleep. About 70% of patients also exhibit cataplexy, a transient weakness of skeletal muscle with emotions such as laughter. More than 90% of patients who have narcolepsy with cataplexy have low cerebrospinal fluid (CSF) hypocretin-1 (orexin-A) levels, a highly specific finding (Bourgin et al., 2008; Liblau et al., 2015). REM sleep behavior disorder consists of loss of normal REM sleep skeletal muscle atonia with excessive motor activity in REM sleep, such as vocalization, arm flailing, and leg kicking (“acting out of dreams”). It is most commonly due to synucleinopathies, such as Lewy body diseases (Boeve et al., 2013). Chronic insomnia disorder

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consists of persistent difficulty initiating or maintaining sleep from a variety of causes. Sleep-disordered breathing includes, among other disorders, obstructive sleep apnea, central sleep apnea, central neurogenic hypventilation associated with brainstem disease, and nocturnal stridor from laryngeal dysfunction. All these conditions have been identified, to varying extents, in association with specific neuronal antibodies, usually in the context of a wider encephalopathy or demyelinating disease.

This chapter will explore the varied sleep manifestations associated with specific autoantibodies and the evidence that idiopathic narcolepsy is an autoimmune disease.

SLEEP MANIFESTATIONS ASSOCIATED WITH SPECIFIC AUTOANTIBODIES (TABLE 18.1)

Voltage-gated potassium channel–complex antibodies

Voltage-gated potassium channel (VGKC)–complex antibodies are a group of autoantibodies targeting neuronal surface antigens that interact with Kv1 subunit VGKCs at or near synapses. At least two proteins have been identified: contactin-associated protein-2 (CASPR2), located at the paranodes, and leucine-rich, glioma-inactivated protein 1 (LGI1), located in the synapse, especially evident in the neuropil of the hippocampus (Irani et al., 2010; Cornelius et al., 2011). These antibodies have been associated with a range of neurologic conditions, including Morvan syndrome (Liguori et al., 2001), limbic encephalitis, and seizure disorders (Tan et al., 2008).

Morvan syndrome, originally named Morvan’s fibrillary chorea (Morvan, 1890; Josephs et al., 2004), is a rare disorder affecting both the peripheral and central nervous systems. Peripheral nerve hyperexcitability is manifest by myokymia, fasciculations, and neuromyotonia. Profound insomnia, fluctuating encephalopathy with hallucinations, and dysautonomia (especially hypotonia) characterize the central nervous system symptoms (Josephs et al., 2004). Men comprise about 90% of reported cases (Josephs et al., 2004; Irani et al., 2012: 29 cases; Lee et al., 2013). Approximately 50% of cases are associated with neoplasms, especially thymomas (Cornelius et al., 2011; Lee et al., 2013). Associations with myasthenia gravis and hypothyroidism have been reported (Josephs et al., 2004; Lee et al., 2013). Both CASPR2 and LGI1 antibodies have been found in patients with Morvan syndrome (Irani et al., 2012), although CASPR2 antibodies tend to be higher titer.

Insomnia is prominent and profound. Polysomnography and wrist actigraphy often show no sleep or marked reduction in total sleep time (Fischer-Perroudon et al., 1974; Murri et al., 1976; Liguori et al., 2001; Cornelius et al., 2011). REM, slow-wave, and stage N2 sleep are markedly reduced or absent with undetectable sleep spindles or K-complexes (Liguori et al., 2001). Background electroencephalogram shows disorganized, predominantly theta activity (Cornelius et al., 2011). When REM sleep is present, muscle atonia is lost. Behavior at night is characterized by agitation and apparent dream enactment, a state known as agrypnia excitata (Liguori et al., 2001; Cornelius et al., 2011; Lugaresi et al., 2011). Despite the intensely disrupted night sleep, daytime hypersomnia is not prominent (Cornelius et al., 2011). The anatomic and physiologic substrate of the sleep disturbances is unknown, especially as magnetic resonance imaging (MRI) scans are usually normal, but disturbance of thalamo-limbic circuitry has been postulated (Josephs et al., 2004). The sleep manifestations of Morvan syndrome are very similar to those seen in

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VGKC, voltage-gated potassium channel complex; NMDA, N-methyl-D-aspartate; ANNA, antineuronal nuclear autoantibody; CSA, central sleep apnea; OSA, obstructive sleep apnea.

*Also abnormal motor behavior in nonrapid eye movement sleep.
familial fatal insomnia, a prion disorder characterized by thalamic atrophy (Montagna et al., 2003).

The insomnia in Morvan syndrome is usually refractory to treatment with conventional hypnotics. In 2 patients, opioid medication provided some benefit (Josephs et al., 2004). In contrast, immunotherapy, including plasma exchange, intravenous immunoglobulin (IVIG), corticosteroids, and cyclophosphamide resulted in marked improvement in insomnia and dream enactment behavior (Lee et al., 1998; Josephs et al., 2004; Cornelius et al., 2011) and other clinical features (Irani et al., 2012).

Limbic encephalitis associated with VGKC–complex antibodies is characterized by seizures, confusion, and memory loss in association with increased MRI T2 signal in the medial temporal lobes and often an abnormal CSF (Vincent et al., 2004; Irani et al., 2010). Antibodies to LGI1 are most frequently present (Irani et al., 2010; Lai et al., 2010). Tumors have been reported in some patients, including adenocarcinoma of the prostate and colon (Cornelius et al., 2011), but tumors are not common. Some of these patients have sleep disturbances similar to those seen in Morvan syndrome. REM sleep behavior disorder with loss of REM sleep atonia and dream enactment behavior can occur (Fig. 18.1) (Iranzo et al., 2006; Irani et al., 2010) and profound insomnia associated with agrypnia excitata has been described (Cornelius et al., 2011; Peter-Derex et al., 2012). In some patients hypersomnia may be present (Irani et al., 2010). The neurologic and sleep manifestations in some patients overlap between Morvan syndrome and limbic encephalitis, blurring the distinction between the two conditions. Sleep disturbances in limbic encephalitis are often very responsive to immunotherapy (Iranzo et al., 2006; Cornelius et al., 2011; Peter-Derex et al., 2012).

Aquaporin-4 antibodies

Neuromyelitis optica (NMO) is a demyelinating disorder characterized by relapsing optic neuritis and longitudinally extensive myelitis (Wingerchuck et al., 2007). In contrast to multiple sclerosis, CSF pleocytosis is often present but CSF oligoclonal bands are unusual. The disorder is nine times more frequent in women than men. About 75% of patients with NMO have a serum autoantibody (NMO-IgG) directed against the water channel protein, aquaporin-4, found in astrocytic foot processes (Lennon et al., 2005 #392). MRI scans of the brain are usually normal or show nonspecific changes, but 10% of seropositive patients show a distinctive pattern of increased T2 signal in the hypothalamus and periventricular areas around the lateral, third, and fourth ventricle, areas known to especially express aquaporin-4 (Pittock et al., 2006).

Fig. 18.1. Patient with voltage-gated potassium channel antibodies and rapid eye movement sleep behavior disorder. Patient on admission; coronal T2-weighted brain magnetic resonance imaging shows bilateral, more pronounced on the right, mesial temporal hyperintensity sparing the brainstem (A), and polysomnography demonstrates increased phasic electromyographic activity in the limbs during rapid eye movement sleep (B). A, ear; C, central electroencephalogram (EEG); Chin, chin surface electromyogram (EMG); EKG, electrocardiogram; LAT, left anterior tibialis surface EMG; L Bic, left biceps surface EMG; LOC, left electrooculogram; Nasal, nasal airflow; O, occipital EEG; RAT, right anterior tibialis surface EMG; R Bic, right biceps surface EMG; ROC, right electrooculogram; Thor, thoracic breathing efforts. (Reproduced from Iranzo et al., 2006.)
A small number of cases of narcolepsy in association with NMO-IgG antibodies and symmetric hypothalamic lesions on MRI scans have been described (Baba et al., 2009; Kanbayashi et al., 2009; Nozaki et al., 2009; Nakano et al., 2011; Sekiguchi et al., 2011; Deguchi et al., 2012; Suzuki et al., 2012). All but one (Carlander et al., 2008) of these patients were Japanese, a population known to have a relatively higher prevalence of NMO compared with populations of European origin. Additional patients with hypothalamic involvement and excessive daytime sleepiness from other ethnic groups have been described, but without adequate testing to characterize them as having narcolepsy (Poppe et al., 2005; Viegas et al., 2009; Samart and Phanthumchinda, 2010).

These patients with well-defined narcolepsy showed a relatively consistent clinical picture. In 5 of 8 patients, hypersomnolence preceded other manifestations of NMO and in 3 cases hypothalamic features remained the only signs of the disorder. In 1 patient, hypersomnolence was recurrent. Cataplexy was not present in any patients. Other signs of hypothalamic dysfunction were common, including hypothermia, dysautonomia, and the syndrome of inappropriate antidiuretic hormone secretion. CSF examination revealed pleocytosis. CSF hypocretin-1 concentration was low (<110 pg/mL) in 5 of 8 cases. The multiple sleep latency test showed sleep-onset REM sleep periods (SOREMPs) in all 3 cases in which the test was performed. In 2 patients, HLA testing did not show the typical antigens associated with idiopathic narcolepsy. Intravenous and subsequent oral steroids resulted in improvement in sleepiness in 4 of 5 patients. This was associated with increase in CSF hypocretin-1 levels and resolution or improvement of hypothalamic signals on MRI scans. The results of therapy and the intermediate levels of CSF hypocretin-1 in most cases suggest that the hypothalamic dysfunction is often partial and potentially reversible, and may be associated with neuronal dysfunction rather than cell death.

**NMDA receptor antibodies**

N-methyl-D-aspartate receptors (NMDARs) are neuronal surface proteins that bind glycine (NR1 subunits) and glutamate (NR2 subunits) (Dalmau et al., 2008). NMDAR antibodies have been associated with a clinically distinct form of autoimmune encephalitis characterized by early neuropsychiatric symptoms, including agitation, delusional thinking, hallucinations, seizures and memory loss, followed by dysautonomia, orofacial and limb dyskinesia, and decreased consciousness (Dalmau et al., 2008; Irani and Vincent, 2011). Most patients have abnormal MRI scans with abnormalities in multiple areas of the brain. A lymphocytic pleocytosis is usually present. The disorder frequently occurs in childhood or young adulthood and about 90% of patients are female (Dalmau et al., 2008; Poloni et al., 2010; Irani and Vincent, 2011). Neoplasms are present in 20–60% of patients, most commonly ovarian teratoma (Dalmau et al., 2008; Irani and Vincent, 2011). Removal of an associated neoplasm and immunotherapies have resulted in improvement in many patients (Irani and Vincent, 2011).

During the later stages of the illness, central hypventilation occurs in 66% of patients, many requiring ventilator support for periods of 2–40 weeks (Dalmau et al., 2008). Central sleep apnea has been reported in 2 patients (Anderson et al., 2013). Severe insomnia, unresponsive to hypnotics, has been reported during the acute phase of the illness in 2 patients (Poloni et al., 2010) and prominent sleep disturbances (hypersomnia and inversion of sleep patterns) have been noted in 27% of patients after recovery (Dalmau et al., 2008).

In a series of 10 children with a phenotype of encephalitis lethargica and positive NMDAR antibodies, 6 were reported to have insomnia and 2 sleep inversion during the course of their disease. This contrasts with 10 similar patients without NMDAR antibodies, of whom 5 exhibited hypersomnolence, 3 sleep inversion, and only 1 insomnia (Dale et al., 2009). Further systematic clinical and polysomnographic studies of the sleep disturbances in different phases of the disorder are needed.

**IgLON5 antibodies**

IgLON5 is a neuronal cell adhesion molecule, part of the immunoglobulin superfamily (Sabater et al., 2014). IgLON proteins may be involved in synaptic formation (Hashimoto et al., 2009). Serum and CSF antibodies to IgLON5 have been detected in 8 patients with a unique clinical and pathologic syndrome but in only 1 of 298 controls with neurologic or sleep disorders (Sabater et al., 2014). The 8 patients developed symptoms at a median age of 59 years. Six followed a slow progressive course over 2–12 years, whereas 2 progressed subacutely over 2 and 6 months.

The neurologic picture consisted of bulbar symptoms (dysarthria and dysphagia), dysautonomia (hypersalivation, hyperhidrosis, bradyarrhythmias, and urinary urgency), gait ataxia, eye movement abnormalities and chorea, but no parkinsonism. Sleep disturbances were prominent and were the presenting feature in 4 of the 6 patients with a chronic course. Moderate to severe obstructive sleep apnea, nocturnal stridor, and abnormal sleep motor behaviors were present in all patients. Polysomnography revealed simple and complex vocalizations and movements in stage N2 and simple limb...
movements in REM sleep. Intrusion of REM into stage N2 sleep was noted and muscle tone was abnormally increased in REM sleep, but stage N3 sleep was normal. Periodic limb movements of wakefulness and sleep were present and total sleep time and sleep efficiency were reduced. Four of the 8 patients, including both with a subacute course, developed central neurogenic hypoventilation, and 6 died suddenly, 2 during sleep. Immuno-therapy was unsuccessful in 7 patients; one improved temporarily but died soon thereafter.

Brain MRI scans and CSF examination were normal in all patients. CSF hypocretin-1 levels were normal in the 3 patients tested. All 4 patients tested had the HLA DQBI*0501 and HLA DRBI*1001 alleles, findings uncommon in the Spanish population. No other antibodies commonly detected in autoimmune encephalopathies were found. Autopsy findings in 2 patients showed hyperphosphorylated tau protein in neurons in the hypothalamus and tegumentum of the brainstem, including the periaqueductal gray matter, pedunculopontine nuclei, magnocellular nucleus, and nucleus ambiguus. Deposits of α-synuclein and features of inflammation were absent.

Several other similar patients have been reported but without testing for IgLON5 antibodies. One patient with dysphagia, chorea, gait instability, and respiratory failure (Kaphan et al., 2008), and one with dysphagia, stridor, and central hypoventilation (Pretnar-Obilak et al., 2010) were found to have tauopathies at autopsy. A patient with dysphagia, stridor, dysautonomia, diplopia, and central hypoventilation was found to have serum and CSF antibodies to the gamma-aminobutyric acid (GABA)-B receptor (Batocchi et al., 2001). The differential diagnosis for the disorder includes progressive supranuclear palsy (a tauopathy) and multiple-system atrophy (a synucleinopathy with stridor a prominent feature).

The question arises whether the IgLON5 antibodies in this distinctive condition are causative or secondary to neurodegeneration. The presence of tau pathology, the absence of inflammatory changes in the CSF, on MRI scans or at autopsy, and the lack of response to immuno-therapy would mitigate against a primary autoimmune encephalopathy. However, the HLA pattern seen in 4 of the patients suggests the possibility of a genetic predisposition to autoimmunity (Balint and Bhatia, 2014). Further work will be needed to determine the exact nature of the disorder.

Ma antibodies

Ma-1 and Ma-2 antibodies are found in a range of tumors, especially carcinoma of the lung (Hoffmann et al., 2008). Combinations of limbic, diencephalic, and brainstem paraneoplastic syndromes have been described, with about a third of patients having diencephalic symptoms, especially narcolepsy (Dalmau et al., 2004).

Of 22 reported cases of Ma antibody-associated narcolepsy (Landolfi and Nadkarni, 2003; Dalmau et al., 2004; Overeem et al., 2004; Blumenthal et al., 2006; Compta et al., 2007; Rojas-Marcos et al., 2007; Adams et al., 2011; Dauvilliers et al., 2013a), all had hypersomnia and 6 (27%) had cataplexy. REM sleep behavior disorder was reported in 2 patients (Compta et al., 2007; Adams et al., 2011). Most also had symptoms related to the limbic system, including seizures (Landolfi and Nadkarni, 2003; Overeem et al., 2004), and some to the brainstem, including supranuclear gaze palsies (Adams et al., 2011). Hypothalamic endocrine abnormalities have been reported (Dalmau et al., 2004; Adams et al., 2011). Associated tumors included testicular, lung, and tonsillar neoplasia.

Nocturnal polysomnography in 4 patients showed reduced sleep efficiency, absent sleep spindles (1 patient), and absent slow-wave sleep (1 patient) (Landolfi and Nadkarni, 2003; Compta et al., 2007; Adams et al., 2011; Dauvilliers et al., 2013a). REM sleep without atonia was reported in 3 patients (Compta et al., 2007; Adams et al., 2011; Dauvilliers et al., 2013a). Multiple sleep latency tests showed results typical of narcolepsy with reduced mean sleep latencies and multiple SOREMPs. CSF hypocretin-1 levels were measured in 12 cases and were low or undetectable in all, but HLA typing in 2 patients did not show the typical antigens associated with idiopathic narcolepsy (Landolfi and Nadkarni, 2003; Compta et al., 2007). CSF protein concentrations, white cell counts, or both were raised in 4 of 5 patients.

The brain MRI scan was abnormal in 8 patients but showed diencephalic involvement in only 4. Histologic examination of the hypothalamus in 1 case showed hypothalamic gray-matter inflammation with perivascular cuffing, astrocytic gliosis, and CD8+ T cells infiltrating neural tissue (Dauvilliers et al., 2013a). Effects of immunomodulation or treating the primary tumors were variable and the small numbers of cases reported do not allow any definitive conclusions to be reached.

Antineuronal nuclear autoantibody type 2 (ANNA-2) (anti-Ri antibody)

The paraneoplastic antibody ANNA-2 IgG binds to Nova-1 and Nova-2 antigens, neuron-specific RNA nuclear proteins, widely distributed in the brain (Yang et al., 1988;
Pittock et al., 2003). Opsoclonus-myoclonus syndrome is the most characteristic clinical association of these antibodies, but they are also found in patients with multifocal dysfunction of the brainstem, cerebellum, and spinal cord, including gaze palsy and dysphagia. Associated malignancies include breast carcinoma, and small cell and nonsmall cell lung carcinoma.

A characteristic feature of some patients with the disorder is the presence of stridor. In neurologic disorders, stridor frequently appears during sleep and patients may present to a sleep specialist. In a series of 48 patients with ANNA-2 antibodies, 5 patients (9.6%) had definite and 2 possible episodic laryngospasm, 5 associated with jaw-opening dystonia (Pittock et al., 2010). Two patients lost consciousness during episodes. One patient required tracheostomy, 1 emergency intubation, and 2 others intensive care unit admission. One patient died during an episode of laryngospasm. In at least 1 patient, stridor was reported to occur at night (Pittock et al., 2003). Breast carcinoma was found in 5 patients, small cell lung carcinoma in 1 patient, and cervical carcinoma in 1 patient. Varying degrees of gliosis and perivascular lymphocytic infiltration were found in brainstem nuclei (Pittock et al., 2010). Laryngospasm has also been reported in a single patient with metastatic adenocarcinoma and polyomocyonus, associated with the presence of P/Q and N voltage-gated calcium channel and potassium channel antibodies, but not ANNA-2 antibodies (Lim et al., 2009).

**NARCOLEPSY AS AN AUTOIMMUNE DISEASE**

Converging lines of evidence suggest that autoimmunity directed towards a small group of neurons in the hypothalamus synthesizing hypocretin is the most plausible hypothesis to explain the pathogenesis of narcolepsy. The very strong association with HLA and T-cell receptor polymorphisms clearly implicates the immune system, but to date no specific antibody or T-cell-mediated mechanism has been demonstrated. The HLA haplotype DQB1*06:02, present in about 20% of control subjects, is tightly associated with narcolepsy, being found in 92–98% of patients with narcolepsy and cataplexy (Mignot et al., 2002; De la Herran-Arita and Garcia-Garcia, 2014; Tafti et al., 2014). The odds ratio for the risk conferred by this haplotype is 25:1 (Tafti et al., 2014). Homozygocity increases the risk two- to fourfold (Pelin et al., 1998; Tafti et al., 2014). HLA DQB1*06:02 is found in 48–56% of patients with narcolepsy unassociated with cataplexy (Mignot et al., 2002; Andlauer et al., 2012; De la Herran-Arita and Garcia-Garcia, 2014), but the association increases close to 100% if CSF hypocretin-1 levels are < 110 pg/mL (Andlauer et al., 2012).

CSF hypocretin-1 can be measured by a radioimmunoassay and is low or absent (< 110 pg/mL) in 90–95% of patients with narcolepsy and cataplexy, and in 24–32% of patients with narcolepsy without cataplexy (Mignot et al., 2002; Bourgin et al., 2008; Andlauer et al., 2012). Autopsy studies have demonstrated loss of hypocretin-synthesizing neurons in the hypothalamus in patients with narcolepsy and cataplexy, suggesting that neuronal loss may be the cause of the disorder (Peyron et al., 2000). A number of studies have failed to find antibodies to hypocretin-1, hypocretin-2, preprohypocretin, or hypocretin receptors in the serum or CSF of patients with narcolepsy (Black et al., 2005a, b). Antibodies reactive to rat hypothalamic protein extract were reported in the CSF of HLA DQB1*06:02-positive patients with narcolepsy and low CSF hypocretin-1 levels (Black et al., 2005c), but no specific target was identified.

An increased frequency of narcolepsy in children was noted following the vaccination campaign in the 2009–2010 H1N1 influenza pandemic (Dauvilliers et al., 2010). This was essentially restricted to centers in countries using the Pandemrix vaccine, mainly in northern Europe. A number of epidemiologic studies demonstrated increased incidence of narcolepsy in Sweden, Finland, Norway, France, and China, mainly in children (Han et al., 2011, 2013; Partinen et al., 2012; Dauvilliers et al., 2013b; Heier et al., 2013; Wijnans et al., 2013), with emerging evidence that the rise in cases was transient. Odds ratios compared to before the pandemic ranged between 3:1 and 17:1. In most cases, a relationship to vaccination was noted, but in a retrospective study from China, where vaccination rates were lower, the increased incidence appeared associated with the disease itself (Han et al., 2011). The latency between vaccination and disease onset ranged from days to many months. The vaccine-associated disease was also closely associated with HLA DQB1*06:02, and low or absent CSF hypocretin-1 levels, suggesting that the disease may have only occurred in those individuals who were already susceptible to the disorder. Some studies have attempted delineation of the mechanism of the relationship. In one study, 4 of 13 sera from orexin-negative Pandemrix-associated narcolepsy patients showed antibody binding to both orexin and melanin-concentrating hormone neurons in the hypothalamus but also to other neurons and with no other evidence of autoimmunity (Thebault et al., 2015). In another study, investigators identified a peptide from the influenza vaccine that shared protein residues from a fragment of the hypocretin-2 receptor, and found serum antibodies to hypocretin-2 receptor in 17/20 patients with Pandemrix-associated narcolepsy; however, similar antibodies were found in 11/20 control sera (Ahmed et al., 2015).

Other evidence has further implicated infection in the pathogenesis of narcolepsy. Antibodies to β-hemolytic...
streptococcus antigens (streptolysin O and DNAse B) are present in the serum of HLA DQB1*06:02 patients with narcolepsy and either cataplexy or hypocretin deficiency in the first 3 years after disease onset with odds ratios of 16.1 in the first year and 11.7 in years 1–3, compared to controls (Aran et al., 2009). The finding of Tribbles homolog 2 antibodies in some cases of autoimmune uveitis and then also in the serum of 14–26% of HLA DQB1*06:02 patients with narcolepsy and cataplexy in three series (Cvetkovic-Lopes et al., 2010; Kawashima et al., 2010; Toyoda et al., 2010) was encouraging, but the lack of disease specificity questions their relevance.

Given the highly specific loss of hypocretin-secreting cells, and the HLA association which implies relevance of class II antigen presentation, several important studies have focused on the possible role of cellular immunity in the pathobiology of narcolepsy. In a large controlled study of patients with narcolepsy with varied ethnicity, polymorphisms were detected in the T-cell receptor alpha (TCRA) locus that interacts with the HLA–antigen complex during antigen presentation (Hallmayer et al., 2009). Another study of the same patient sample revealed a narcolepsy-linked polymorphism in the purinergic receptor subtype P2Y11 gene, which modified resistance to ATP-induced cell death in CD8¹ T lymphocytes and natural killer cells (Kornum et al., 2011). A further genomewide association study, using a unique high-density genotyping platform, confirmed the association with the TCRA locus and also identified two other single-nucleotide polymorphisms associated with narcolepsy in the cathepsin H gene and the tumor necrosis factor superfamily member 4 gene (Faraco et al., 2013). Both these proteins are expressed in major histocompatibility complex class II antigen-presenting B lymphocytes.

Based on these varied data, the following hypothesis can be generated. Narcolepsy appears to be a complex autoimmune disorder. In the setting of a specific HLA protein and the presence of perhaps multiple polymorphisms of proteins involved in B-cell–T-cell interactions, environmental antigens associated with infectious agents such as H1N1 influenza or streptococcus may induce an immune response that results in the death of hypocretin-synthesizing neurons (Faraco et al., 2013; De la Herran-Arita and Garcia-Garcia, 2014). Why these cells are the specific target of this presumed process remains to be determined.

Attempts to treat narcolepsy with immunomodulation have been disappointing. Case reports and short open-label series have been reported, most using IVIG within weeks to months after onset of the disorder (Hecht et al., 2003; Dauvilliers et al., 2004; Valko et al., 2008; Knudson et al., 2010, 2012). Subjectively, cataplexy and sleepiness have often appeared to improve, at least transiently, but a single-patient double-blind placebo-controlled study showed equal reductions in the frequency of cataplexy with IVIG and placebo (Fronczek et al., 2007). With a single exception, there have been no convincing reports of significant changes in multiple sleep latency parameters or CSF hypocretin-1 levels. One patient treated with IVIG within a month of onset of cataplexy demonstrated normalization of CSF hypocretin-1 levels after the third infusion (Dauvilliers et al., 2009). It is possible that the largely negative results may be due to administration of IVIG too long after onset of narcolepsy, or alternatively because it is not the best choice of drug; agents affecting cellular immunity could be more suitable.

**FUTURE DIRECTIONS**

Systematic prospective studies are needed to define more accurately the spectrum of sleep disorders associated with autoantibodies. The suggestion that isolated insomnia or REM sleep behavior disorder may occasionally be forms frustes of an autoimmune disorder should be explored (Ju et al., 2011). Further studies of narcolepsy are needed to definitively understand the underlying immunologic mechanisms and their implications for therapy. It has been speculated that the rare condition of Kleine–Levin syndrome (recurrent, self-limiting episodes of hypersomnolence with disinhibition, hyperphagia, altered perception, and cognitive impairment) may be an autoimmune disorder (Dauvilliers et al., 2002). Further studies are needed to confirm or refute this hypothesis.

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