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SLEEP DISORDER, CHOREA, AND DEMENTIA ASSOCIATED WITH IgLON5 ANTIBODIES

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A novel syndrome characterized by a distinctive sleep disorder accompanied by variable symptoms of brainstem involvement and a highly restricted haplotype was recently described in association with antibodies to a neuronal cell adhesion protein named IgLON5. Because of the symptoms and chronic disease progression, most of these patients are primarily seen by specialists in sleep and neurodegenerative disorders. Since the initial description of this encephalopathy in 2014, only 1 additional patient has been reported.¹ In order to improve clinical recognition we report a new patient who presented with the characteristic sleep dysfunction and subsequently developed chorea.

Case report. A 71-year-old right-handed woman was referred for evaluation of chorea. She had been well until 6 years earlier, when she presented with abnormal movements and behavior during sleep. These ranged from simple to complex movements (threading a needle, salting food, dabbing perfume) and were associated with vocalizations, “snoring,” and excessive daytime sleepiness. A polysomnogram (PSG) without video recording detected obstructive sleep apnea (OSA). Treatment with continuous positive airway pressure mask was started, but the nocturnal abnormal movements and behaviors persisted. One year after symptom onset, she developed chorea, progressive memory loss, depression, and mild gait imbalance. An initial neurologic consultation suggested the diagnosis of Huntington chorea, and she was treated with haloperidol, which improved the abnormal movements. On neurologic examination she scored 20 points on the Mini-Mental State Examination. Neuropsychological testing showed impaired executive function (planning, verbal fluency), visuospatial function (clock drawing, Rey Complex Figure Test), and episodic memory (Wechsler Memory Scale-Revised and Rey Auditory Verbal Learning Test). She had restricted upward voluntary gaze and mildly ataxic gait; the chorea predominated in the head and face (video at Neurology.org/nn) and was accompanied by mild motor impersistence and hypotonia. The remainder of the neurologic

examination was normal. Laryngoscopy showed no vocal cord paresis.

Brain MRI was normal and repeat CSF examinations showed mild pleocytosis (ranging from 5 to 9 cells per mm³) and increased protein concentration (ranging from 56 to 62 mg/dL); oligoclonal bands were absent. Testing for antibodies against cell surface proteins showed IgG4 antibodies against IgLON5 in serum (titer 1:2,560) and CSF (1:64) using an immunofluorescence cell-based assay with human embryonic kidney cells expressing IgLON5, as reported.² The human leukocyte antigen (HLA) haplotype was HLA-DRB1*1001 and HLA-DQB1*0501. In a nocturnal video-PSG (under treatment with haloperidol), sleep efficiency was approximately 62% (normal > 75%). There were clear periods of normal N2 and N3 stages (50% of the total sleep time [TST]). REM stage was 8% of the TST, and there were abnormal limb and body jerks. The rest of the sleep (42% of TST) was characterized by diffuse theta activity without sleep spindles, K complexes, delta waves, or REMs. Occasionally during N2 sleep stage the patient had continuous simple limb and body movements. Episodes of OSA were frequent (apnea-hypopnea index: 43 per hour).

Since the diagnosis of IgLON5 encephalopathy the patient has been treated with IV immunoglobulin and rituximab; however, the symptoms remain unchanged.

Discussion. We report a case of IgLON5 sleep disorder associated with chorea and dementia. IgLON5 is the most recently identified antigen within the category of neurologic disorders associated with antibodies against cell surface or synaptic proteins and establishes a new syndrome.² This disorder was first described in 8 patients and differs substantially from previously described autoimmune encephalitis because patients often have a protracted clinical course, the distinctive feature is sleep dysfunction, the disorder is refractory to immunotherapy, and preliminary neuropathologic findings suggest a neurodegenerative process. All of the initial patients had a unique and novel sleep disorder characterized by non-REM and REM parasomnia with abnormal movements and OSA that differed from *agrypnia excitata*.²⁻⁴ Finalistic movements (e.g., elaborated movements clearly resembling an identifiable

daytime activity such as manipulation of objects) were not registered in our patient's video-PSG, although they were clearly present by clinical history.

This disorder provides an intriguing link between autoimmunity and neurodegeneration. Previously reported patients had IgG4 antibodies against IgLON5, and, as in our case, all patients that were HLA genotyped had the same alleles: HLA-DQB1*0501 and HLA-DRB1*1001. An unexpected finding in the autopsy of 2 patients was the detection of neuronal-specific tau deposits in the hypothalamus and tegmentum of the brainstem in a distribution different from known tauopathies^{5,6} and absent signs of inflammation.² Our patient is the first with abnormal CSF findings, although the pleocytosis was mild.

In IgLON5 encephalopathy, the most prominent and usually the first manifestation is the sleep dysfunction, so all medical specialties involved with sleep medicine should be aware of this entity. In addition, chronic progression of symptoms such as chorea, dementia, dysarthria, dysphagia, ataxia, dysautonomia, and vertical gaze paresis, which variably associate with IgLON5 encephalopathy, also occur in neurodegenerative diseases (e.g., multiple system atrophy, progressive supranuclear palsy).⁷ In our experience, if sleep symptoms are overlooked, this disease is usually misdiagnosed.

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1. Högl B, Heidebreder A, Santamaria J, Graus F, Poewe W. IgLON5 autoimmunity and abnormal behaviours during sleep. *Lancet* 2015;385:1590.
2. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol* 2014;13:575–586.
3. Lugaresi E, Provini F. Agrypnia excitata: clinical features and pathophysiological implications. *Sleep Med Rev* 2001;5:313–332.
4. Gaig C, Iranzo A, Santamarí J, Dalmau J, Graus F. Sleep disorder associated with antibodies to IgLON5: parasomnia or agrypnia?—Authors' reply. *Lancet Neurol* 2014;13:864–865.
5. Spillantini MG, Goedert M. Tau pathology and neurodegeneration. *Lancet Neurol* 2013;12:609–622.
6. Ludolph AC, Kassubek J, Landwehrmeyer BG, et al; Reissensburg Working Group for Tauopathies with Parkinsonism. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. *Eur J Neurol* 2009;16:297–309.
7. Fahn S, Jankovic J, Hallett M. Principles and Practice of Movement Disorders: Expert Consult, 2nd ed. Edinburgh, New York: Saunders; 2011.

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