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IgLON5 DISEASE RESPONSIVE TO IMMUNOTHERAPY

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A 45-year-old man was seen with a history of confusion and disorientation for 1 year, during which time he was unable to identify relatives. He was unable to cope at his work as a plasterer, noticed neck pain, dysphagia, and unexplained weight gain. His family reported that his sleep pattern had changed, describing his sleep as disturbed with episodes consistent with stridor, myoclonus (the video at Neurology.org/nn), and semipurposeful movements.

At his initial examination, he appeared mildly confused with a depressed affect. He was obese (body mass index of 33 kg/m^2) and was noted to be centrally cyanosed (figure e-1). He had mild gait ataxia, bulbar dysarthria, and dysphagia. The rest of his examination was normal. He was found to have established ventilatory failure and sleep-disordered breathing. EEG demonstrated a baseline of theta waves with α rhythm intermixed. CSF analysis was abnormal, suggesting inflammation (table). MRI of the head and neck was normal. Inpatient polysomnography with video was extremely limited by the patient's limited sleep duration and nocturnal behavioral problems. The awake period evaluation revealed intermittent runs of theta wave activity suggesting an increased homeostatic sleep drive. Frequent spontaneous desaturations were noted, some of which were central in nature. The sleep period evaluation demonstrated an increased sleep onset latency and reduction in non-REM stage 2 sleep and a complete absence of REM sleep (figure e-2). His apnea-hypopnea index was 25, confirming moderate obstructive sleep apnea. Nocturnal noninvasive ventilation was issued for long-term use, but initial adherence was poor.

The patient was initially treated with prednisolone and immunoglobulins. This was associated with improvement in behavior mirrored by improvement in CSF parameters, and he became well enough to be discharged home. However, he was admitted 6 weeks later with aspiration pneumonia and ventilatory failure requiring intensive care support. His sleep disorder was still prominent clinically and required further treatment with plasmapheresis followed by another course of IV immunoglobulins, which led to a rapid improvement over a few weeks. A repeat CSF analysis confirmed raised protein suggestive of persistent inflammation, and further IV-pulsed cyclophosphamide was given. After 2 pulses, his behavior normalized and sleep pattern improved with return of dreams, and resolution of neck pain and dysphagia.

Serum antibodies to IgLON5 returned positive using indirect immunofluorescence (Euroimmun). CSF testing for the antibody was also positive (figure e-3). The patient continued treatment with cyclophosphamide, and he has received 8 pulses so far. His human leukocyte antigen (HLA) genotyping confirmed HLA-DQB1*05:01 and HLA-DRB1*10:01 alleles.

At his last review (2 years from the onset of his initial symptoms), he continues to improve. He exhibited no evidence of cognitive impairment or abnormal behavior, and there were no involuntary movements. His gait remains mildly ataxic. Noninvasive ventilation has been established with improvement in his arterial blood gases. His spouse reports better sleep patterns.

Discussion. A recent report suggested treatment with immunotherapy for a patient with IgLON5 encephalitis.[1] Here, we provide further evidence of an IgLON5-associated disorder that has shown sustained response to immunotherapy.

IgLON5 antibody–associated encephalopathy was first described in 2014.[2] Sleep disturbance was characteristic in all these patients' presentations. Other features including gait ataxia, bulbar dysarthria, and dysphagia[2] were also present. Movement disorders associated with IgLON5 syndrome, including orofacial and limb chorea,[1] dystonia, hypomimia, bradykinesia, and myoclonus.[3] Cognitive decline featuring impaired executive function, visuospatial dysfunction, and episodic memory loss has been reported.[4] Brain imaging is typically normal. The youngest patient reported in the literature was 52 years old.[2]

The physiologic role of IgLON5 is unknown, but other members of the IgLON family are involved in synaptic and neuronal formation during brain development.[5] Antibodies to IgLON5 have been originally linked with a tauopathy when they were detected in 8

Supplemental data at Neurology.org/nn

Table CSF analysis confirmed a pleocytosis (100% lymphocytes) with raised protein suggestive of CSF inflammation

	December 2015	January 2016	March 2016	July 2016
Red blood cell count, per mm^3	0	1,920	3	4
White blood cell count, per mm^3	14	3	1	1
Total protein, g/L	0.84	0.77	0.82	0.84
CSF glucose, mmol/L	4.0	6.5	6.6	6.2
Plasma glucose, mmol/L	3.5	5.8	6.9	6.4
Oligoclonal bands	Negative	Negative	Negative	Negative

patients with a similar clinical presentation.[2] IgLON5-associated disorder provides an interesting link between neurodegeneration and autoimmunity. All patients who were HLA genotyped had the same alleles: HLA-DQB1*05:01 and HLA-DRB1*10:01.[2] Autopsy on 6 patients revealed hyperphosphorylated tau protein deposited in the hypothalamus, prehypothalamic region, the tegmentum, and the upper cervical cord.[6] The presence of a pleocytosis on CSF and improvement following immunotherapy in our patient points toward a complex interplay of autoimmunity, genetic predisposition, and neurodegeneration. Furthermore, recent evidence exploring the mechanisms of action of IgLON5 in rat hippocampal neurons suggests that antibodies decreased cell surface IgLON5 clusters with internalization of antibody not reversed once the IgLON5 antibodies were removed from the media.[7] This suggests a pathogenic role of these antibodies in the disease and raises the possibility of a treatable phase of the disease possibly in the early stages.

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