

Understanding anti-IgLON5 disease

OPEN

Francesc Graus, MD,
PhD
Joan Santamaría, MD,
PhD

Correspondence to
Dr. Graus:
fgraus@clinic.ub.es

*Neurol Neuroimmunol
Neuroinflamm*
2017;4:e393; doi: 10.1212/
NXL.0000000000000393

The unambiguous characterization of antibodies against neural antigens has been critical to understand the interplay between the immune system and the brain, allowing in some instances the discovery of clinical entities that had been previously unrecognized or lumped with other syndromes under generic names.¹ The best example is anti-NMDA receptor encephalitis, a relatively common disease that before the discovery of NMDA receptor antibodies was unrecognized or defined with nonspecific terms, such as non-herpetic encephalitis, or confused with Hashimoto encephalopathy or encephalitis lethargica.² A similar scenario applies to anti-IgLON5 disease in which the identification of antibodies against IgLON5, a neural cell adhesion molecule of unknown function, has led to the characterization of a new disorder.³ Before the discovery of IgLON5 antibodies, the disease of these patients was defined with descriptive terms or labeled as “atypical early progressive supranuclear palsy (PSP)” or “brainstem tauopathy” (for review, see reference 4), indicating that it could not be classified among well-defined CNS disorders. However, the comprehensive evaluation of the initial patients with IgLON5 antibodies disclosed a common clinical core of symptoms that included a complex sleep disorder with abnormal behaviors and vocalizations during non-REM and REM sleep along with sleep-disordered breathing, gait instability, more typical of disequilibrium than cerebellar ataxia, and bulbar symptoms such as stridor, dysphagia, or central hypoventilation.³ These symptoms were found to evolve over months to years, and unlike other CNS disorders associated with antibodies against neural surface antigens, patients with IgLON5 disease did not respond to common immunotherapies. With the identification of more patients, 4 clinical presentations were characterized according to predominant symptoms: prominent sleep disorder, progressive bulbar dysfunction, gait instability with abnormal eye movements reminiscent, but not typical

of PSP, and cognitive deterioration sometimes associated with chorea. Independently of the form of presentation, most patients described a sleep disorder when directly questioned about symptoms of sleep apnea and other alterations of sleep or when they were studied with video-polysomnography (V-PSG).⁵

One potential bias of these initial studies is that they emphasized the sleep dysfunction, and therefore, patients could have been selected for IgLON5 antibody screening. Recently, the article by Honorat et al.⁶ published in this issue of *Neurology*[®] *Neuroimmunology and Neuroinflammation* contributes to clarify this issue. These authors re-examined 367 archived serum or CSF samples that showed a pattern of mice brain immunostaining similar to that reported for IgLON5.³ Most of the samples had been sent for antibody testing before the discovery of IgLON5 antibodies. Using a commercial cell-based assay, they eventually found that 26 of the samples had IgLON5 antibodies. For 20 of these patients, clinical information was available, including 15 who had detailed Mayo Clinic records. The findings confirmed that brainstem and sleep disorders are the predominant manifestations of anti-IgLON5 disease. Twelve of 15 patients developed sleep dysfunction, mainly sleep apnea. The frequency of abnormal movement and behaviors was lower, but most of the patients were not assessed by V-PSG, which in our experience is critical for full assessment of this disease. In addition, 14/20 (70%) patients showed gait instability and 12 dysphagia or stridor. Unlike previous series, 7 (35%) patients had symptoms of central or peripheral nervous system hyperexcitability, including hyperekplexia, fasciculations, cramps, or stiffness. Therefore, this study confirms that the core symptoms of anti-IgLON5 disease include the sleep disorder along with gait instability and bulbar dysfunction and draws attention to investigate for this disease in patients with symptoms that suggest, but are unusual for, stiff-person syndrome spectrum disorder.⁷

From the Neuroimmunology Program (F.G.), August Pi Sunyer Biomedical Research Institute (IDIBAPS); and Service of Neurology (F.G., J.S.) and Multidisciplinary Sleep Disorders Unit (J.S.), Hospital Clínic, Barcelona, Spain.

Funding information and disclosures are provided at the end of the article. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was funded by *Neurology: Neuroimmunology & Neuroinflammation*.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

An intriguing aspect of anti-IgLON5 disease is the concurrence of features suggesting an autoimmune disorder (antibodies against a neuronal surface antigen and a robust association with the HLA-DRB1*10:01 genotype) and pathologic evidence of a novel neuronal 3R + 4R tauopathy mainly involving the brainstem and hypothalamus.⁴ This puzzling scenario challenges current concepts about the pathophysiology of autoimmune and neurodegenerative disorders. One possibility is that the neuronal-specific tau accumulation could be antibody mediated, leading to neuronal dysfunction and ultimately neurodegeneration.⁸ In this scenario, early diagnosis and treatment would be crucial to prevent irreversible neuronal damage. The patients described in initial studies did not improve with immunotherapy, but there was a substantial delay (median, 2 years) between symptom onset and diagnosis.⁵ The retrospective study of Honorat et al.⁶ and the case report of Bonello et al.⁹ in this issue of *Neurology Neuroimmunology and Neuroinflammation* also suggest that anti-IgLON5 disease may indeed respond to immunotherapy. Seven of 10 patients in the former study improved after treatment with steroids alone or in combination with other immunotherapies.⁶ These findings, however, must be taken with caution, given the retrospective accrual of information and lack of follow-up in half of the patients. In addition, potential confounding factors such as the use of continuous positive airway pressure therapy to improve the sleep apnea must be taken into consideration at the time of evaluation of response to treatment. The patient described by Bonello et al.⁹ also improved with treatment that started 1 year after disease onset. This patient developed the typical syndrome of anti-IgLON5 disease, but was younger (45 years) than most patients (median age 62 years) with this disorder. If younger patients are more likely to improve is currently unclear because the median age of the 7 patients who improved in the series of Honorat et al.⁶ was similar to that of the whole series.

Future series and single case reports of patients with IgLON5 disease will be important to define the effects of immunotherapy, identify less common clinical presentations, and better understand whether IgLON5 antibodies occur as an epiphenomenon in some neurologic disorders. Preliminary studies suggest that IgLON5 antibodies cause an irreversible antibody-mediated internalization of surface IgLON5 in cultures of hippocampal neurons.¹⁰ The natural next step is to determine whether this antibody effect leads to a disruption of the internal cytoskeletal network and ultimately neuronal tau accumulation.

The field of neurologic sciences is wide and expanding, and the management of patients with

neurologic disorders has driven to the development of multiple neurologic subspecialties, “Autoimmune Neurology” one of the youngest. Specialization is inevitable, but it should not lead to fragmentation of knowledge or tight boundaries; anti-IgLON5 disease is a perfect example that cross-talk between subspecialties is critical to address complex neurologic diseases and, above all, that a solid neurologic background is the key to unlock puzzling clinical scenarios.

AUTHOR CONTRIBUTIONS

Francesc Graus: drafting/revising the manuscript, study concept or design, and study supervision. Joan Santamaria: drafting/revising the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

F. Graus is on the editorial board for *Lancet Neurology*, receives royalties, and holds a patent for IgLON5 as a diagnostic test. J. Santamaria received research support from Fundacio La Marato TV3. Go to Neurology.org/nn for full disclosure forms.

REFERENCES

1. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. *Physiol Rev* 2017;97:839–887.
2. Tan A, Shuey N, Bladin C. A modern perspective on the differential diagnosis between encephalitis lethargica or anti-NMDA-receptor encephalitis. *J Clin Neurosci* 2010; 17:1204–1206.
3. 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.
4. Gelpi E, Höftberger R, Graus F, et al. Neuropathological criteria of anti-IgLON5-related tauopathy. *Acta Neuropathol* 2016;132:531–543.
5. Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. *Neurology* 2017;88:1736–1743.
6. Honorat JA, Komorowski L, Josephs KA, et al. IgLON5 antibody: neurological accompaniments and outcomes in 20 patients. *Neurol Neuroimmunol Neuroinflamm* 2017; 4:e385. doi: 10.1212/NXI.0000000000000385.
7. Martinez-Hernandez E, Ariño H, McKeon A, et al. Clinical and Immunologic investigations in patients with stiff-person spectrum disorder. *JAMA Neurol* 2016;73: 714–720.
8. Leshchynska I, Sytnyk V. Reciprocal interactions between cell adhesion molecules of the immunoglobulin superfamily and the cytoskeleton in neurons. *Front Cell Dev Biol* 2016;4:9.
9. Bonello M, Jacob A, Ellul MA, et al. IgLON5 disease responsive to immunotherapy. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e383. doi: 10.1212/NXI.0000000000000383.
10. Sabater L, Planagumà J, Dalmau J, Graus F. Cellular investigations with human antibodies associated with the anti-IgLON5 syndrome. *J Neuroinflammation* 2016; 13:226.

See Article

See Article