Anti-LGI1 Encephalitis With Co-occurring IgLON5 Antibodies
Clinical Features and Human Leukocyte Antigen Haplotypes

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Neurology Neuroimmunol Neuroinflamm 2023;10:e200126. doi:10.1212/NXI.000000000000200126

Abstract

Objectives
Autoimmune encephalitis (AE) with antibodies against LGI1 and IgLON5 are clinically distinctive but share some particularities such as a strong association with specific human leukocyte antigen (HLA) class II alleles.

Methods
We clinically describe a patient with double positivity for LGI1 and IgLON5 antibodies. In addition, we conducted specific immunodepletion with the patient’s serum and HLA typing and investigated the presence of serum IgLON5 antibodies in a cohort of 23 anti-LGI1 patients carrying the HLA predisposing for anti-IgLON5 encephalitis.

Results
A 70-year-old woman with a history of lymphoepithelial thymoma presented with subacute cognitive impairment and seizures. Investigations included MRI and EEG showing medial temporal involvement, increased CSF protein content, and polysomnography with REM and non-REM motor activity, along with obstructive apnea. Neural antibody testing revealed both LGI1 and IgLON5 antibodies in serum and CSF, and serum immunodepletion ruled out cross-reactivity. The patient carried DRB1*07:01 and DQA1*01:01, DQB1*05:02. Nearly full therapeutic response was obtained after intensified immunosuppressive treatment.

Discussion
We present a case of anti-LGI1 encephalitis with concomitant IgLON5 antibodies. Co-occurring IgLON5 antibodies in anti-LGI1 encephalitis are exceptional, but may appear in genetically predisposed individuals.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

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Whereas limbic encephalitis with leucine-rich glioma-inactivated 1 (LGI1) antibodies is one of the commonest forms of autoimmune encephalitis, the form associated with immunoglobulin-like cell adhesion molecule 5 (IgLON5) antibodies is a rather rare disease.1 Nevertheless, despite obvious clinical differences, including the pathognomonic faciobrachial dystonic seizures in anti-LGI1 encephalitis,2 or the typical combination of sleep, bulbar, and movement disorders in anti-IgLON5 disease,3 some similarities exist between both types of encephalitides, such as their generally nonparaneoplastic nature, frequent predominance of IgG4 antibodies, and strong association with particular human leukocyte antigen (HLA) class II alleles. Nearly 90% of the patients with anti-LGI1 encephalitis carry DRB1*07:014,5 while for anti-IgLON5 disease, the association seems to be more intricate. Although the strongest odds ratio was reported for DRB1*10:01, carried by approximately 60% of the cases, DQA1*01 ~ DQB1*05 were carried by 90% of the patients with these 2 alleles successfully sequenced and were even carried by more than 80% of the non-DRB1*10:01 carriers; altogether, these results could suggest that DQA1*01 ~ DQB1*05 are more relevant than DRB1*10:01.3 We present the clinical manifestations and HLA haplotypes of a patient double positive for LGI1 and IgLON5 antibodies.

Case Report

A 70-year-old woman with a medical history of lymphoepithelial thymoma treated by thymectomy 20 years ago was admitted for mild head trauma. Initial CT scan and EEG were unremarkable. However, her relatives reported confusion, behavioral changes, and memory impairment for several weeks. Neurologic examination showed temporal and spatial disorientation, episodic anterograde amnesia, and executive dysfunction (Montreal Cognitive Assessment, MOCA = 15/30; Frontal Assessment Battery, FAB = 9/18). In addition, she had 2 secondarily generalized temporal focal seizures during hospitalization. Hyponatremia (128 mmol/L) and hypothermia (33–35°C) were observed while CSF analysis only demonstrated hyperproteinorachia (0.72 g/L). Brain MRI showed bilateral temporal FLAIR (fluid-attenuated inversion recovery) hyperintensities (Figure 1) while whole-body PET scan revealed thyroid hypermetabolism, leading to the diagnosis of medullary thyroid cancer. Video polysomnography showed rare and atypical spindles during N2, increased motor activity during non-REM (NREM), decreased REM sleep with frequent loss of atonia and objective jerks, a high arousal index, and obstructive apnea (Table). Indirect immunofluorescence on rat brain slides with the patient’s CSF demonstrated a staining of the granular layers of the hippocampus and cerebellum (Figure 2, panel A), which led to the identification by cell-based assay (CBA) of LGI1 (end-point dilution 1/50) and IgLON5 (1/20) antibodies in the CSF, which were further identified by CBA also in the serum (end-point dilution 1/10,240 for LGI1 and 1/5,120 for IgLON5). Moreover, immunodepletion was performed in the serum to rule out cross-reactivity, confirming the presence of both antibodies (Figure 2, panels B and C). Given this double positivity, we decided to test the HLA of this patient, who carried the haplotypes DRB1*07:01; DQA1*02:01; DQB1*02:02 and DRB1*01:01; DQA1*01:01; DQB1*05:01. We subsequently investigated the presence of IgLON5 antibodies in the serum of 23 anti-LGI1 patients who were also DQA1*01 ~ DQB1*05 carriers (19/23, 83% DRB1*01:01; 0/23 DRB1*10:01) and belonged to a previously reported cohort6; none of them were found to be positive.

The patient was initially treated with lacosamide and prednisone (1 mg/kg/d). However, given the lack of response, 2
monthly courses of IV immunoglobulin (2 g/kg) were administered with a spectacular clinical effect: no seizure recurrence, cognitive improvement (MOCA score 23/30), and normalization of the natremia and body temperature. Then, to consolidate this improvement, 2 infusions of rituximab (1 g, 15 days apart) were administered, followed by monthly courses of cyclophosphamide (1 g) for 6 months. The patient almost completely recovered, showing cognitive improvement (MOCA = 27/30, FAB = 16/18) and disappearance of all sleep disorders but obstructive apnea syndrome, which later improved with a positional device (Table).

Discussion
We report here a patient double positive for LGI1 and IgLON5 antibodies who also carried the HLA class II haplotypes strongly associated with these 2 types of autoimmune encephalitides. Although indirect immunofluorescence with the patient’s CSF was more compatible with LGI1 antibodies, serum and CSF CBA clearly showed the co-occurrence of IgLON5 antibodies, which was further confirmed by immunodepletion. Accordingly, despite most of the clinical picture being closer to what is known for anti-LGI1 encephalitis, with prominent clinical (amnesia, temporal seizures, psychiatric symptoms) and radiologic (MRI) limbic involvement,2 the slightly disorganized N2 and mild motor activity during NREM could resemble some characteristics of NREM sleep described in anti-IgLON5 disease.7 However, we did not observe abnormal sleep initiation with absent N1 and undifferentiated NREM sleep accompanied by intense vocalizations and complex motor activity typical of anti-IgLON5 disease.7 In addition, other sleep features, such as reduced sleep time, sleep efficiency, and REM sleep, as well as REM behavioral disorder and REM sleep without atonia, have been described in both types of encephalitides.7-9 It is likely that the LGI1-related manifestations led to a prompt diagnosis and treatment that contributed to the immunotherapy response, which is usually less favorable in anti-IgLON5 disease, although improvement of sleep disturbances and other manifestations has previously been reported.7-9
It is well-known that the most common neural antibodies co-occurring with LGI1 antibodies are those directed against contactin-associated protein-like 2 (CASPR2), especially in the context of Morvan syndrome with malignant thymoma.10 Furthermore, this subset of patients frequently shows a wider autoimmune response that includes antibodies against the acetylcholine receptor (with clinically overt myasthenia gravis) and netrin 1 receptor.10 On the contrary, only 2 cases with co-occurring LGI1 and IgLON5 antibodies have previously been reported, although no clinical description was provided for one of them and the other one had a clear anti-IgLON5 phenotype; no HLA genotyping was performed.9,11 Our patient has a history of thymoma, although given the long delay between the tumor diagnosis and the clinical picture, and the lack of signs suggesting recurrence, it seems unlikely to be involved in the pathogenesis of the disease. Similarly, thyroid cancer is not typically associated with LGI1 or IgLON5 antibodies12 and probably represents just a coincidental finding. Conversely, the patient carried the HLA class II haplotypes strongly associated with both encephalitides, reflecting that these particular haplotypes, or other more uncommon ones, are necessary for the development of LGI1 or IgLON5 antibodies. Nevertheless, other factors may modulate this predisposition, as reflected by the absence of IgLON5 antibodies in a cohort of anti-LGI1 patients who were also DQA1*01~DQB1*05 carriers.

It is of interest that the clinical picture of our patient was dominated by features of anti-LGI1 encephalitis, which is congruent with the results of the immunofluorescence and the higher titers determined for LGI1 antibodies. Previously, gamma aminobutyric acid B receptor (GABABR) antibodies with no apparent clinical relevance were also detected in 2 different patients with LGI1 and IgLON5 antibodies, respectively; the GABABR antibodies were, however, only identified in serum, and no tissue-based assay was performed.13,14 These findings highlight the importance of tissue-based assays not only to avoid false-negative and negative results obtained by currently available commercial CBAs but also to support the clinical relevance of the detected antibodies.15

In conclusion, we describe a unique case of anti-LGI1 encephalitis with co-occurring IgLON5 antibodies presenting with predominant limbic manifestations with some complex sleep disturbances and combined HLA associations, the latter being necessary but not sufficient for immune tolerance breakdown.

Acknowledgment
The authors thank the patient for consenting to the publication of this case report, Dr Valérie Dubois (EFS Auvergne-Rhône-Alpes) for HLA genotyping, and NeuroBioTec Hospices Civils
de Lyon BRC (France, AC-2013-1867, NFS96-900) for banking sera and CSF samples.

**Study Funding**
This work is supported by a public grant overseen by the Agence nationale de la recherche (ANR; French research agency) as part of the “Investissements d’Avenir” program (ANR-18-RHUS-0012). This study was performed within the framework of the LABEX CORTEX of the Université Claude Bernard Lyon 1, within the program “Investissements d’Avenir” (ANR-11-LABX-0042) operated by the ANR.

**Disclosure**
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

**Publication History**
Received by Neurology: Neuroimmunology & Neuroinflammation January 27, 2023. Accepted in final form March 31, 2023. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

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**References**

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*Neurol Neuroimmunol Neuroinflamm* 2023;10;
DOI 10.1212/NXI.0000000000200126

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