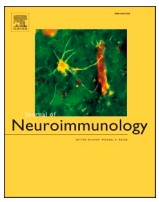
Journal of Neuroimmunology 378 (2023) 578084

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim



Short Communication

# Anti-LGI1 encephalitis: A family affair

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ARTICLE INFO

*Keywords:*
LGI1
Autoimmune encephalitis
Familial
HLA
Genetics

ABSTRACT

Here we describe the second ever-reported case of familial anti-leucine-rich glioma-inactivated protein 1 (LGI1) limbic encephalitis (LE). Two elderly Caucasian sisters presented with psychiatric symptoms and cognitive impairment, followed by faciobrachial dystonic seizures. Anti-LGI1 antibodies were detected in their serum. Considering they had been living in distant regions for decades, environmental factors could be ruled out. Human leukocyte antigen (HLA) genotyping revealed that both carried HLA-DRB1*07, found in 90% of anti-LGI1 encephalitis patients, HLA-DQA1*02:01 and HLA-DQB1*03:03, commonly associated with DRB1*07:01. Considering the exceptional nature of familial cases, as-yet-unknown genetic contributors other than HLA might play a role in our siblings.

## 1. Introduction

Anti-leucine-rich glioma-inactivated protein 1 (LGI1) limbic encephalitis (LE) is the second most common form of autoimmune encephalitis overall and the first one in adults, as elderly males are often affected (Bastiaansen et al., 2017). It generally manifests with the clinical syndrome typical of LE, characterized by the subacute onset of memory impairment, behavioral/mood disorders and epileptic seizures (Dalmau and Graus, 2018). Additional distinctive features such as faciobrachial dystonic seizures (FBDS) and hyponatremia are present in over 50% of the cases, pointing to the involvement of a wide cortico-subcortical network, and also providing physicians with invaluable diagnostic clues (van Sonderen et al., 2017; Morano et al., 2020). The definite confirmation of anti-LGI1 LE relies in the detection of autoantibodies (Abs) directed against LGI1, a trans-synaptic protein secreted by neurons, especially in the hippocampus, and involved in synaptic transmission and neuronal excitability (van Sonderen et al., 2017). As is the case of other antibodies targeting neuronal and/or glial surface antigens, the pathogenic role of anti-LGI1 Abs have been supported by both in vitro and in vivo studies (Geis et al., 2019), and recent findings also hint that Abs specific subclass (IgG4 or, less commonly, IgG1) and binding properties can influence the patients' clinical manifestations and outcome (Thompson et al., 2018; Ramberger et al., 2020). Contrary to anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, no viral trigger has been identified in anti-LGI1 LE, and underlying neoplasms (specifically, malignant thymoma) are revealed in <10% of the cases (Armangue et al., 2018; Gadoth et al., 2017). Conversely, growing evidence suggests that genetic factors – namely, human leukocyte antigen (HLA) alleles – might play a crucial role in the immunopathogenesis of this condition, as already demonstrated for other 'common' autoimmune central nervous system (CNS) disorders like multiple sclerosis (Ramanathan et al., 2023).

Herein we report the case of two sisters presenting anti-LGI1 encephalitis in their late adulthood.

## 2. Case description

### 2.1. Sister#1

The patient was a 64-year-old woman whose past medical history was relevant for Hashimoto thyroiditis and chronic ischemic cardiomyopathy. She developed rapidly progressive disorientation associated with aggressive behavior, delusions and visual hallucinations. Upon admission, blood tests showed $Na^+$ 128 mEq/L, therefore hyponatremic encephalopathy related to a syndrome of inappropriate antidiuretic hormone secretion was initially suspected. A chest CT scan also revealed pulmonary sarcoidosis, histologically confirmed. Considering that no improvement occurred after sodium correction, the hypothesis of Creutzfeldt-Jakob disease (CJD) was then formulated. However, "jerky" movements of the right arm and face later appeared, which did not remit

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https://doi.org/10.1016/j.jneuroim.2023.578084
Received 26 February 2023; Received in revised form 1 April 2023; Accepted 1 April 2023
Available online 5 April 2023

after the administration of valproate (VPA) 1000 mg/day. The patient's EEG tracing was unremarkable, whereas the analysis of paired serum/cerebrospinal fluid (CSF) showed oligoclonal bands (type 3 pattern) and the brain MRI documented T2/FLAIR hyperintensity involving the left mesial temporal structures, the head of the caudate nucleus and the putamen (Fig. 1, Panel A-C). Anti-LGI1 antibodies (Abs) found in the patient's serum confirmed the clinical suspicion of anti-LGI1 LE. She received a course of intravenous (i.v.) methylprednisolone (1 g/day for 5 days) and was switched from VPA to Carbamazepine (CBZ) 400 mg/day, which resulted in marked clinical improvement (i.e. disappearance of both FBDS and behavioral/psychiatric disorders) and allowed the patient to be discharged at home. However, contralateral FBDS and moderate irritability recurred after about 3 months, therefore a course (0.4 g/kg/day for 5 days) of intravenous immunoglobulin (IVIg) was administered, leading to the prompt remission of the symptoms. Despite remarkable cognitive sequelae, no further relapse has been observed to date.

### 2.2. Sister#2

At the age of 76, the patient presented with subacute memory deficits, behavioral changes (tearfulness, apathy) and paranoid delusions. She had no previous condition but hypertension. Blood tests showed mild hyponatremia ($Na^+$ 134 mEq/L). CJD was hypothesized, but the appearance of bilateral FBDS suggested anti-LGI1 encephalitis, confirmed by the detection of anti-LGI1 Abs in both CSF (otherwise unremarkable) and serum. The brain MRI revealed T2/FLAIR hyperintensity of the right hippocampus and amygdala (Fig. 1, Panel D-E). Several standard video-EEG exams and a 24-h ambulatory EEG were performed, documenting bilateral asynchronous temporal interictal epileptiform discharges. The patient received a course of i.v. methylprednisolone, followed by oral prednisone 50 mg/day and CBZ 400 mg/day. However, due to unsatisfactory response and adverse events (insomnia, increase in blood glucose levels), she was switched from steroids to IVIg: FBDS promptly disappeared and both cognitive functions and mood markedly improved.

Our patients were thoroughly screened for malignancies for two years, with negative results, and no oncologic disease ever came up during the whole follow-up period (6 and 3.5 years, respectively). HLA genotyping revealed HLA-DRB1*07 ~ HLA-DQA1*02:01 ~ HLA-DQB1*03:03 alleles in both of them (Table 1). In sister#2 the sequencing of LGI1 gene was also performed, showing that both alleles were wild-type.

## 3. Discussion

In this paper we report the case of two Caucasian sisters who developed anti-LGI1 LE during late adulthood (in their sixties and seventies, respectively), both presenting with subacute severe cognitive impairment and behavioral alterations, later followed by FBDS. This is the second-ever reported 'familial' case of anti-LGI1 encephalitis: in 2022 Ding and colleagues described a pair of Chinese siblings - brother and sister - who were diagnosed with anti-LGI1 LE during their thirties, that is at a much younger age than commonly observed in this condition (Ding et al., 2022). Apart from that, their clinical and radiological features were rather typical, and so were our sisters'. Although so far anecdotal, familial cases of anti-LGI1 encephalitis could be underdiagnosed and under-reported, considering that their clinical presentation appears "unremarkable" compared with sporadic ones, and that physicians might be less inclined to thoroughly enquire about family history in elderly subjects. Moreover, the existence of several comorbidities emerging in late adulthood (e.g. cognitive impairment of different etiology, medication-induced electrolyte disorders etc) could easily hamper the diagnosis of autoimmune encephalitis.

Familial cases of anti-LGI1 LE such as ours highlight the relevance of genetic factors in the immunobiology of this condition. Indeed, in the wake of other autoimmune diseases, recent research has focused on the HLA region, particularly on HLA-DR and -DQ molecules, that are able to present exogenous antigens for recognition by CD4+ T helper cells (Gough and Simmonds, 2007). In a 2021 work by Muñiz-Castrillo and

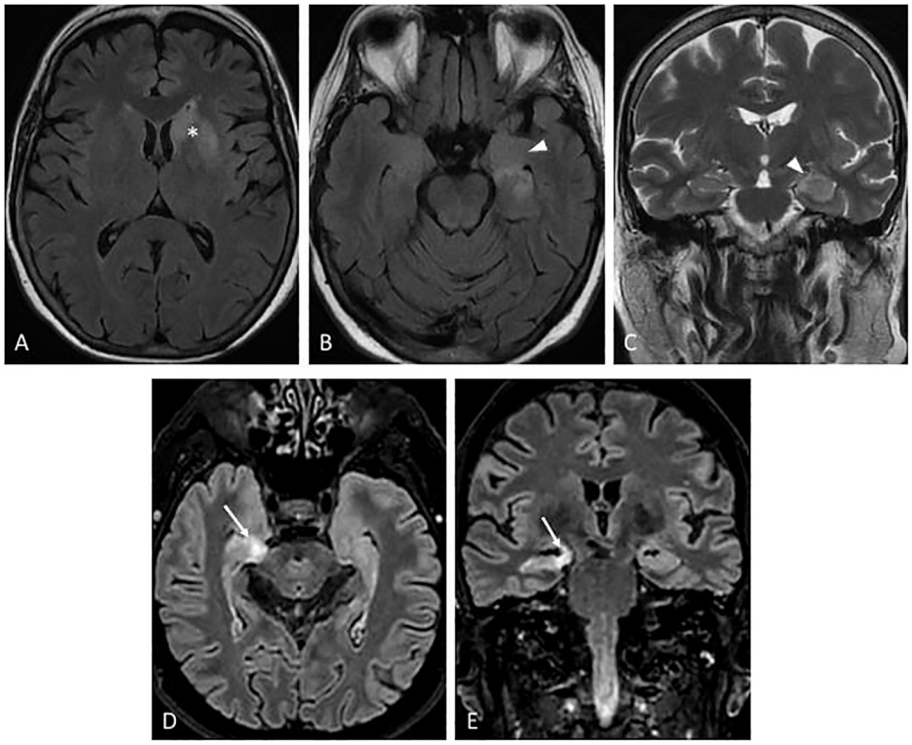


**Fig. 1.** *MRI of Sister #1*. Axial FLAIR image (A) showing left striatum hyperintensity (star). Axial FLAIR (B) and coronal T2 (C) scans showing left hippocampus hyperintensity and swelling (arrowhead). *MRI of Sister #2*. Axial (D) and coronal (E) FLAIR scans showing right hippocampus hyperintensity (arrow).

**Table 1**
Comparison between the clinical and para-clinical features of the two siblings.

| Patients' characteristics | Sister#1 | Sister#2 |
|---|---|---|
| **Age at LE onset (years)** | 64 | 76 |
| **Relevant medical history** | | |
| Autoimmune comorbidities | Hashimoto thyroiditis, sarcoidosis | No |
| Neoplasms | No | No |
| **LE features** | | |
| Early signs | Rapid cognitive impairment, aggressive behavior, psychosis | Weight loss, memory deficits, behavioral changes, delusions |
| Clinical manifestations | | |
| FBDS | Yes | Yes |
| Cognitive impairment | Yes | Yes |
| Behavioral disorders | Yes | Yes |
| Acute symptomatic seizures | No | No |
| Sleep alterations | Yes | Yes |
| Dysautonomia | No | No |
| Movement disorders | No | No |
| **Laboratory findings** | | |
| $Na^+$ level (mEq/L) | 128 | 134 |
| CSF analysis | Unremarkable | Unremarkable |
| OCB | Present (mixed pattern) | n.a. |
| Anti-LGI1 Abs | Serum+ (CSF not tested) | Serum+, CSF+ |
| **Neuroimaging/neurophysiological exams** | | |
| MRI at onset | ↑T2/FLAIR and ↑ volume of L mT lobe, ↑T2/FLAIR head of the caudate nucleus and putamen | ↑T2/FLAIR of the R mT (hippocampus and amygdala) |
| EEG findings | | |
| Interictal | No | Bitemporal asynchronous IEDs |
| Ictal correlate of FBDS | n.a. | No |
| **HLA genotype** | HLA-B*15/50<br>HLA-C*06/07<br>HLA-DRB1*07/11<br>HLA-DQA1*02:01/05:01<br>HLA-DQB1*03:01/03:03 | HLA-B*15/38<br>HLA-C*07/12<br>HLA-DRB1*01/07<br>HLA-DQA1*01/02:01<br>HLA-DQB1*03:03/x |
| **LGI-1 sequencing** | n.a. | Wild-type |
| **Treatment and FU** | | |
| IT | 1^: i.v. MTP → corticosterone acetate<br>Relapse: IVIg | i.v. MTP → prednisone → IVIg (2 courses) |
| ASMs | VPA → CBZ | CBZ |
| Response to IT | Partial | Incomplete response after steroids; marked clinical improvement after IVIg |
| Relapse | Yes (3 months) | No |
| FU duration (years) | 6 | 2 |
| Long-term immunomodulation | No | No |
| Clinical manifestations at last FU | Cognitive impairment | Mild cognitive impairment |
| FU MRI | Normal | ↑T2/FLAIR and ↓ volume of both mT > R |

Abs: antibodies; ASM: anti-seizure medication; CBZ: carbamazepine; CSF: cerebrospinal fluid; EEG: electroencephalography; FBDS: faciobrachial dystonic seizures; FLAIR: Fluid-Attenuated Inversion Recovery; FU: follow-up; IT: immunotherapy; i.v.: intravenous; IVIg: intravenous immunoglobulin; L: left; LE: limbic encephalitis; LGI1: leucine-rich glioma-inactivated-1; MRI: Magnetic Resonance Imaging; mT: mesial temporal; MTP: methylprednisolone; n.a.: not applicable; OCB: oligoclonal bands; R: right; VPA: valproate.

colleagues, 90% of the individuals with anti-LGI1 LE were found to carry HLA-DRB1*07:01, and these results have been recently replicated in a larger cohort across different ethnicities (Muñiz-Castrillo et al., 2021; Peris Sempere et al., 2022). Moreover, a genome-wide association study (GWAS) performed in a German population found HLA-DQA1*02:01 to be always associated with HLA-DRB1*07:01: the authors revealed that this haplotype (H1, as they called it) was highly specific for anti-LGI1 encephalitis, and speculated that it might be somewhat involved in the dysregulation of IgG subclasses, favoring pathogenic IgG4-LGI1 Abs, although this remains unconfirmed (Mueller et al., 2018). As to our sisters, HLA genotyping revealed DRB1*07, and although only 2-digit level resolution data are available, we can easily presume that it was HLA-DRB1*07:01 based on current knowledge. They also carried HLA-DQA1*02:01 and HLA-DQB1*03:03: the latter has been recently documented in one third of HLA-DRB1*07:01 haplotypes but its additional influence in predisposing to anti-LGI1 LE is still under debate (Peris Sempere et al., 2022). Similarly, in the report by Ding and colleagues the brother too carried HLA-DRB1*07:01 ~ HLA-DQA1*02:01 ~ HLA-DQB1*03:03, whereas the sister could not be tested due to her poor compliance (Ding et al., 2022). Conversely, neither our siblings nor those previously described showed HLA-DRB1*04:02, which has been recently found to be significantly more frequent in both HLA-DRB1*07:01 heterozygous and DRB1*07:01-negative anti-LGI1 LE patients of European ancestry than in controls, and is apparently associated with female sex and younger age at onset, suggesting that independent pathogenic mechanisms might be involved in this disease (Peris Sempere et al., 2022).

Considering that HLA alleles follow the Mendelian inheritance pattern but familial anti-LGI1 encephalitis cases are nothing but exceptional, it could be hypothesized that as-yet-unknown genetic contributors other than HLA haplotype might be at play in our siblings – as already documented in other immune-mediated conditions. For instance, highly penetrant monogenic variants have been identified in rare CNS autoimmune disorders (e.g. in interferonopathies), and GWASs have revealed single nucleotide polymorphisms in non-HLA genes, such as Cathepsin H and Tumor necrosis factor (ligand) superfamily member 4 in narcolepsy (Faraco et al., 2013; Ramanathan et al., 2023). In addition, epigenetic mechanisms (e.g. involving micro-RNAs) have been recently recognized to possibly influence immune responses (Ramanathan et al., 2023). However, none of these scenarios has been yet explored in works focusing on anti-LGI1 encephalitis, so further multicenter studies are warranted.

Finally, it is well acknowledged that environmental factors could act as triggers for autoimmune CNS diseases, as is the case for multiple sclerosis and Epstein-Barr virus infection. With regards to our case, at the time of disease onset our sisters had been living in very distant regions for decades (both in urban areas but of quite different dimensions), which makes an environmental contribution rather unlikely. However, exposure to toxic/infectious agents during their early life could not be specifically investigated since no "exogenous" risk factor has been identified so far in anti-LGI1 LE.

In conclusion, our report shows that, like other autoimmune diseases, anti-LGI1 encephalitis too can "run in the family". Although familial cases appear exceptional, there is a chance that they are, in fact, underdiagnosed, which highlights the need for careful history taking even in elderly patients. In addition, our case suggests the possibility that in anti-LGI1 LE there is much "going on" outside of the HLA region that we still know very little about and should be addressed by future research, possibly broadening our view about the genetic predictors of autoimmune encephalitis.

## Ethical publication statement

The authors confirm that the patients gave their written informed consent for publication.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of Competing Interest

None.

## Data availability

The data that has been used is confidential.

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