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DG, JH and SR designed the study

GP, VR, BJ, SMC and JH collected data at the French Reference Center of Paraneoplastic Neurological Syndromes

DG, LC, VN and SR extracted and analyzed data

ABS and NS reviewed MRI data

All authors participated to the writing and revision of the manuscript.

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ABSTRACT

Objective: To characterize the evolution of epilepsy in patients with leucine-rich glioma inactivated 1 antibody-associated (LGI1ab) limbic encephalitis, including factors associated with drug-resistant epilepsy (DRE).

Methods: Retrospective analysis of patients with LGI1 encephalitis managed at two tertiary epilepsy centers between 2005 and 2019 and whose samples were confirmed by the French Reference Center of Paraneoplastic Neurological Syndromes. Raw clinical, biological, EEG, and MRI data were reviewed. Two endpoints were defined: (i) Epilepsy remission: patients seizure free and in whom anti-seizure medications (ASM) have been stopped for at least 1 year at the last follow-up visit (ii) DRE: patients with persistent seizures at the last follow-up despite at least two ASM used at efficacious daily dose.

Results: 39 patients with LGI1 encephalitis were included with a median follow-up duration of 42 months (range 13-169). All of them reported seizures at the acute phase, with faciobrachial dystonic seizures (FBDS) in 23 (59%) and other focal seizures in 38 (97%), including 4 patients (10%) with de novo status epilepticus. At the last follow-up visit, 11 patients (28%) achieved epilepsy remission. Among the 28 patients with persistent epilepsy, eight (29%) fulfilled criteria of DRE. The only factor significantly associated with epilepsy remission was the time from clinical onset of the encephalitis to initiation of the first immunomodulatory treatment, with longer delay in patients with persistent epilepsy (7.5±8.9 vs 2.4±1.7 months, p=0.006). Evolution to DRE was only driven by MRI evolution. Eight of the 15 patients (53 %) who developed hippocampal atrophy (p=0.007) also suffered from drug-resistant seizures at the last follow-up.

Significance: In patients with LGI1 encephalitis, rapid initiation of immunomodulatory treatment favors long-term epilepsy remission. Evolution to DRE might primarily reflect the anatomical lesion of limbic structures. Determining what modalities of immune treatment may alter these outcomes requires prospective studies with long-term follow-up.

INTRODUCTION

Focal seizures (FS) are one of the main features of LGI1 encephalitis[1–3]. They consist in seizures of mesial temporal lobe origin and faciobrachial dystonic seizures (FBDS) [4, 5]. In LGI1 encephalitis, the efficacy of antiseizure medication (ASM) is modest, particularly for FBDS [6], whereas early immunotherapy showed striking responses on these manifestations[7, 8]. Several studies described the natural course of LGI1 encephalitis[3, 5, 7, 9, 10], but data are lacking about the long-term evolution of seizures. Although a majority of patients may achieve seizure freedom[6, 11, 12], particularly considering "acute symptomatic seizures"[13] happening early in the disease course, some patients suffer from "autoimmune-associated epilepsy"[13], sometimes drug resistant. Some of the latter even underwent epilepsy surgery[14, 15]. Yet, the factors contributing to long-term persistence of epilepsy and evolution to drug resistant epilepsy (DRE) in LGI1 encephalitis remain unclear. Particularly, whether initial or follow-up clinical, biological, or imaging features could help to determine the future evolution of epilepsy have poorly been investigated.

To tackle this issue, we studied a cohort of patients with LGI1 encephalitis focusing on early and follow-up clinical, electrophysiological, and MRI features to assess their potential association with the long-term epilepsy outcome.

METHODS

The study was performed according to the STROBE guidelines for cohort studies (Supplemental text S1).

1. Patients' selection

Patients' screening was performed within the French Reference Centre on Paraneoplastic Neurological Syndromes which collects the main clinical data and biological samples of patients diagnosed in France with limbic encephalitis, including LGI1 encephalitis (Lyon, France). However its database has not been designed to specifically assess LE-related epilepsy. Accordingly, it does not include detailed information about long-term evolution of epilepsy, seizure type observed during the follow-up, management of antiseizure drugs. In this context, the objectives of the current study could not be addressed without reviewing the clinical, EEG and MRI raw data of all patients. To tackle this issue, we focused this study on patients diagnosed and managed in two specific centers which combine expertise both in LE and in epilepsy (Neurological Hospital of the Hospices Civils de Lyon and at the Pitie Salpetriere Hospital in Paris), ensuring raw data of high quality.

We thus identified from the database French Reference Centre on Paraneoplastic Neurological Syndromes, 41 patients with positive serum and/or CSF for LGI1 antibody diagnosed and followed for at least 1 year between August 15th, 2005 and August 1st, 2019 at the Neurological Hospital of the Hospices Civils de Lyon and at the Pitie Salpetriere Hospital in Paris. All of them were also included in a recent study reporting other outcomes at the whole database level [16]. Two patients with additional antibodies suggesting other syndromes than pure LGI1 encephalitis were excluded (one patient with both LGI1, CASPR2 and GAD antibodies, one with LGI1 and CASPR2 antibodies), and 39 were included in the present study.

2. Biological collection and LGI1Ab detection

All serum and/or CSF samples were centrally collected and stored in the NeuroBioTec biobank (Hospices Civils de Lyon, France, n° 0033–00046, AC-2013–1867, NFS96-900). LGI1Ab were detected in CSF using immunofluorescence on rat brain sections and confirmed by specific cell-based assay, as previously described; in serum, LGI1ab were detected only by cell-based assay [16]. Brain sections and CBA were used because in our detection set we use systematically both technics. Brain section were systematically performed because this approach allow to screen for other autoantibodies at the same time.

3. Standard protocol approvals and patient consents

All patients gave their written informed consent. This study was approved by the institutional review board of the Hospices Civils de Lyon and registered online (NCT04106765).

4. Data collection

The medical charts of all included patients were retrospectively reviewed and clinical, biological, EEG and MRI data were collected. The variables collected for the purpose of the study are detailed in supplementary table 1.
MRI were reviewed blind to clinical data both by epilepsy experts (DG, LC, VN, SR) and, independently, by two neuroradiologists (ABS, NS). Hippocampal morphology was visually analyzed and scored using Scheltens classification, with hippocampal atrophy considered as an Scheltens score ≥ 2, and evolution of hippocampal atrophy during the follow-up when the Scheltens' score was increased by at least 1 point between initial and last MRI. In case of disagreement between the epilepsy experts and the neuroradiologist, MRI was reviewed and a consensus was reached.

5. Study endpoints

According to the seizure evolution during follow-up and the outcome at last visit, we defined three epilepsy endpoints:

- Complete epilepsy remission: seizure freedom with all ASM stopped for at least 1 year at the last follow-up visit. This group primarily included patients who had never reported seizures and those who only suffered from acute symptomatic seizures [13]. However, patients who were seizure free at the last follow-up visit but still treated with at least one ASM were not considered in complete remission.
- Seizure freedom on ASMs: patients who developed autoimmune-associated epilepsy [13] but who were seizure free at the last follow-up visit but still treated with at least one ASM
- Drug-resistant epilepsy (DRE): patients suffering from autoimmune-associated epilepsy [13] with persistence of seizures despite at least two antiseizure drugs used at efficacious daily dose, as defined by the International League against Epilepsy [17].

6. Statistical analysis.

In order to take into account the issue of multiple comparisons and the sample size of the cohort, we *a priori* limited the variables of interest for potential association with epilepsy remission and/or seizure freedom on ASMs and/or DRE to:

- Patients' age
- Initial symptoms at LGI1 encephalitis onset:
    - De novo status epilepticus [18], presence of FBDS.
    - Normal MRI; bilateral temporal lobe abnormalities defined as hyperintensity on T2-weighted FLAIR MRI and/or hippocampal atrophy (Scheltens score ≥ 2).
    - Normal EEG or isolated slow waves; bilateral EEG abnormalities defined as bilateral interictal spikes or epileptic discharges.
- Therapeutic management: Time from clinical onset to first immunologic treatment; use of immunosuppressive therapy (intravenous or oral).
- Evolution of MRI data during the follow-up: normal MRI, bilateral temporal abnormalities (hypersignal or hippocampal atrophy) on last MRI; evolution of hippocampal atrophy.

a. Factors associated with epilepsy remission at the last follow-up

All included patients contributed to the analysis. Association between epilepsy remission and variables of interest was assessed by chi-square or Mann-Whitney U test when appropriate.

b. Factors associated with seizure freedom on ASMs and/or DRE at the last follow-up

Only patients with persistent epilepsy at last follow-up contributed to the analysis. As previously, association between seizure freedom on ASMs and/or DRE and variables of interest was assessed by chi-square or Mann-Whitney U test when appropriate.

All statistical analyses were performed with SPSS version 22 software (SPSS Inc., Chicago, IL)

RESULTS

1. Patients' characteristics (Tables 1 and 2)

Overall, 41 patients with CSF and/or serum LGI1Ab were identified in the two participating centers and their diagnosed confirmed by the French Reference Centre on Paraneoplastic Neurological Syndromes. Two patients suffered from isolated peripheral neuropathy and were excluded and therefore 39 patients with LGI1 encephalitis were included in the study.

Their mean ± SD age at LGI1 encephalitis onset was 63±13.6 (Table 1). Twenty-five of them were men (64%). As shown in table 2, the diagnostic of LGI1 encephalitis was confirmed by the positivity of LGI1Ab in the serum in all patients but one, including 26 who were also positive in the CSF, ten who were negative in the CSF and two in whom LGI1 antibodies were not searched in the CSF. For the remaining patient, who was only positive in the CSF, serum was not available in the biobank. Tumor was identified in two patients, including benign thymoma in one (with thymectomy at two months of encephalitis evolution) and pulmonary adenocarcinoma in another, discovered at the diagnosis of LGI1 encephalitis 6 months after cancer diagnosis.

2. Initial features of LGI1 encephalitis

a. Clinical presentation

All but five patients (87%) developed seizures within the first weeks of evolution (Table 2). Seizures consisted

in FS in 38/39 patients (97%), associated with FBDS in 20 of them (49%). The last patient reported isolated FBDS. Four patients suffered from de novo status epilepticus (10%). A total of 31 patients (79%) showed other neurological symptoms to seizures. A total of 17 patients (44%) had both cognitive impairment and behavioral and/or psychiatric symptoms, 13 (33%) isolated cognitive impairment and one (2%) isolated behavioral and/or psychiatric symptoms.

b. EEG data

Initial EEG recordings were available in 36 patients (92%, Table 2). We observed epileptic abnormalities on initial EEG recordings in 19 of them (53%), including 13 who presented clinical and electric temporal discharges, which could be associated with electro-clinical FBDS in six. Isolated inter-ictal spikes were observed in six patients (17%). Isolated focal slow activity without spike was observed in nine patients (25%) whereas EEG was normal in the six remaining patients (17%).

c. MRI data

MRI data were available in all but one patient (97 % of patients) who had a non-MRI-compatible pacemaker (Table 3). The mean ± SD delay between first clinical symptoms and first MRI was 2.9±3.8 months. First MRI was abnormal in 30 patients (79%). We observed medial temporal lobe hyperintensities on T2-weighted FLAIR sequences in 27 patients (71%), which was unilateral in 14 (52%) and bilateral in 13 (48%). In 16 patients (42%), unilateral (n=7) or bilateral hippocampal atrophy (n=9) was already observed on the first MRI. In three of them, who were 86, 69, and 43 years old, the hippocampal atrophy was not associated with T2-weighted FLAIR hyperintensity (Figure 1).

3. Therapeutic management (Table 4)

A total of 38 patients (97%) received at least one immunological treatment (Table 1, table 4), with a mean ± SD delay from clinical onset to first therapy of 6±7.9 months. The first-line therapy was corticosteroids alone in 7 patients (19%), intravenous immunoglobulins alone in 5 patients (14%), or both in 25 (68%). Additionally, two patients received plasmapheresis. Twenty-one patients received a second-line therapy (rituximab and/or cyclophosphamide), including two who had not been treated with first-line therapy. Six patients were treated with chronic oral immunosuppressive treatment (azathioprine and/or mycophenolate mofetil), including three in whom this treatment was initiated immediately after first-line therapy without rituximab and/or

cyclophosphamide.

4. Evolution of LGI1 encephalitis

a. Clinical evolution

The median follow-up duration was 42 months (range 13-169), without difference between patients who achieved epilepsy remission at the last follow-up and those with persistent epilepsy, and, among patients those with persistent epilepsy, between those with or without DRE. At the last follow-up visit, eleven patients (28%) achieved epilepsy remission. Among the remaining 28 patients with persistent epilepsy, 18 were seizure free with at least one ASM (46%), whereas eight (21%) fulfilled criteria of DRE. At the last follow-up, only seven patients (18%) had never demonstrated cognitive impairment. All other patients had reported cognitive impairment during the follow-up, which resolved in 10 (26%) but remained present at last follow-up in 22 (56%). A total of 21 patients (54%), including the seven without cognitive impairment, did not present any behavioral/psychiatric symptoms during the follow-up. Ten (26%) of the 18 remaining were free of behavioral/psychiatric symptoms at the last follow-up. The patient with lung cancer died after a follow-up of 30 months. No other death was reported.

b. MRI evolution

Among the 38 patients with initial MRI data, at least one additional MRI performed during the follow-up was available in 35 (Table 3). The median interval between the LE diagnosis and the last available MRI was 21 months (range 1-133). The last available MRI exhibited temporal T2-weighted FLAIR hyperintensity in 20 patients (57%), which was bilateral in 12 (34%). Hippocampal atrophy was observed in 27 patients (77%), including 17 (63%) with bilateral atrophy. For 18 patients (47%), comparison between the initial and last MRI showed the development (n=12, 33%) and/or aggravation (n=6, 16%) of hippocampal atrophy during the follow-up. The conclusion about the evolution of hippocampal atrophy was driven neither by the interval between LE diagnosis and the last available MRI (29.0 ± 30.4 vs 29.3±21.5 months with or without evolution of hippocampal atrophy; p=0.935) nor by the interval between the first and last IRM were similar whatever (30.6 ± 30.1 vs 29.3 ± 24.1 months with or without evolution of hippocampal atrophy, p=0.525).

5. Factors associated with epilepsy remission at the last visit

No clinical, EEG, or MRI characteristics observed during the acute phase was associated with epilepsy remission

(Table 5). The only factor significantly associated with epilepsy remission was the delay between the LE clinical onset and the initiation of the first immunomodulatory treatment, with a mean ± SD of 7.5±8.9 months in patients with persistent epilepsy and 2.4±1.7 months in those with seizure-freedom (p=0.006). Use of immunosuppressive treatment in addition to corticosteroids or intravenous immunoglobulins was not associated with this epilepsy outcome (p>0.05). After exclusion of ASDs used to treat status epilepticus, the total number of ASDs used at efficacious dosage during the follow-up did not significantly differ between the 28 patients with persistent epilepsy (median 2, range 1-6) and the 11 others (median 1, range 0-2) (p=0.149).

6. Factors associated with seizure freedom on ASM

Among patients who still suffered from epilepsy at the end of the follow-up, those who achieved seizure freedom on ASMs were significantly older than those who continued to suffer from seizure (64.9 ±12.2 years vs 55.2 ± 14 years old, p=0.01). None of EEG or MRI characteristics at the acute phase was associated with seizure freedom on ASMs. Regarding the evolution of MRI, normal MRI during the follow-up was only observed in 5 of the 18 patients who achieved seizure freedom (31%). However, the only MRI variable significantly associated with seizure freedom on ASM was evolution to hippocampal atrophy on MRI. This MRI evolution was observed in six of the 18 seizure free patients on ASMs (38%) and in nine of the ten patients who were not seizure free (90%, p=0.014)

7. Factors associated with evolution to DRE

As observed for previous endpoints, initial clinical or EEG characteristics were not associated with evolution to DRE. Patients with evolution to DRE were non significantly younger than the patients without DRE (55.0 ±15.9 years vs 64.20 ± 12.0 years old, p=0.099). Although, none of the eight patients with DRE exhibited a normal initial MRI compared to 7/19 (37 %) patients without DRE, this association did not reach statistical significance (p=0.068). In contrast, the evolution of MRI significantly differed between patients with and without DRE. None of the five patients with normal MRI during the follow-up suffered from DRE, whereas the eight patients with DRE all demonstrated hippocampal atrophy on the last MRI. Thus, development and/or aggravation of hippocampal atrophy was significantly associated with DRE (p=0.007). No significant association between the therapeutic management and evolution to DRE was observed (Table 5).

DISCUSSION

Seizures are a major clinical component in LGI1 encephalitis, and FS with or without bilateral tonic-clonic evolution or FBDS are usually observed during the acute phase[3, 7]. Although it has been reported that acute symptomatic seizures secondary to autoimmune encephalitis evolution is often positive, with most patients achieving seizure freedom[6–8, 11, 19] some patients can develop autoimmune-associated DRE [6, 20]. The main objective of the present study was to investigate the long-term evolution of epilepsy in patients with LGI1 encephalitis and to assess which factors were associated with the long-term seizure outcome. We primarily observed: (i) In line with previous studies[6, 9, 21], the long-term prognostic of epilepsy was overall good with 74% of patients achieving long-term seizure freedom, including 28% in whom ASM could be withdrawn. However, 21% of patients developed autoimmune-associated DRE. (ii) The only factor associated with epilepsy remission was the delay from LE onset to immunotherapy initiation, with a shorter delay associated with a greater probability of epilepsy remission. (iii) Evolution to DRE was primarily driven by the development of hippocampal atrophy.

Our study suffered from several limitations, most of them related to its small sample size and retrospective design. Moreover, our minimum follow-up of 13 months is quite short to adequately assess the outcome: in a recent study[20], the minimum follow-up to determine epilepsy was 18 months. The number of patients was similar with other recent studies also investigating the long-term evolution of LGI1 encephalitis [6, 9]. Besides, there was no pre-defined patient follow-up modality, and data were highly heterogeneous across patients. Particularly for MRI data, we observed highly variable number of available MRI, sequences, and timing in relation to LE onset. Although we could not formally exclude the hypothesis, the probability of a too-short MRI-follow-up affecting the results appears to be low. We did not observe an association between the development of hippocampal atrophy and the interval between LE onset and last available MRI, nor with the delay between first and last MRI. Furthermore, the duration of those intervals did not differ between patients with or without DRE. Biological follow-up was also heterogenous across patients and serial serum and/or CSF samples for LGI1Ab determination was available in only few of them. Whether or not persistent LGI1Ab are indicative of a chronic active inflammatory process remains an important open question. The patients included in our study did not benefit from repetitive neuropsychological evaluations or from repetitive dedicated psychiatric evaluations. In this context, we could not assess the potential association between epilepsy outcomes and/or hippocampal atrophy and long-term evolution of cognitive profiles. The distinction between FBDS and focal seizures at LE onset, and classification of persistent seizures during the follow-up was based on the detailed description

available in clinical charts. Because most patients were evaluated by epilepsy specialists in the two participating centers, clinical symptoms and EEG data were sufficiently described in medical files to allow confident classification. In most of them, the symptoms were congruent with seizures of mesial temporal lobe origin, hypothesis confirmed with long-term video-EEG in some patients. However, for the entire cohort, clinical data were insufficiently detailed to formally establish the localization of the epileptogenic zone. The long-term management of ASM might have differed across patients, especially in those who achieved seizure freedom but who still received at least one ASM. The criteria used to define persistent epilepsy (i.e., patient with persistent seizures or, if seizure free, receiving at least one ASM) might have under-evaluated the chance of epilepsy remission.

Our results were in line with the high prevalence of epileptic seizures in LGI1 patients: from sixty-six to 90% for temporal lobe seizures[3–6, 9, 10, 22] during the course of the disease, and 32 to 78% for FBDS[3, 5, 6, 9, 10, 22]. It has even been suggested that seizures related to LE associated with surface antibodies, including LGI1 encephalitis, could be considered as acute and symptomatic[21]. In our study, 21% of all patients eventually suffered from DRE at the last follow-up; which was similar to another recent [9], but greater than reported before[6]. The reasons underlying these discrepancies are unclear. One might speculate that differences in the management of immunotherapy could partly explain these results. But, the significant association between the development of hippocampal atrophy and the risk of developing drug-resistant seizures might suggest the relationship between long-term epilepsy outcome and the anatomical insult at the LE acute phase, which was not observed in another study[9]. Supporting this hypothesis, higher levels of neurofilaments light chains were observed in LGI1 encephalitis patients with epilepsy compared to patients without epilepsy[23]. However, in the absence of a longitudinal study of LGI1ab titers in CSF and/or serum, we cannot exclude chronically active encephalitis in some patients. Data were insufficient to compare patients with and without HLA-DRB1*07:01. Recently, Human Leukocyte Antigen (HLA) and immunoglobulin G isotype were not associated with poor outcome (modified Rankin Scale > 2 at last follow-up)[11]. Nevertheless, this observation might be important for two reasons. First, once hippocampal atrophy is present, continuing immune therapy might have no impact, especially if guided by recurrent focal seizures. Secondly, it might reinforce the pertinence of discussing presurgical evaluation in some patients, as proposed by other groups[14, 15]. It should however be noted that hippocampal atrophy was frequently bilateral with high risk of bitemporal epilepsy. In addition, the poor post-operative outcome reported in patients with drug-resistant epilepsy after infectious encephalitis should be

considered[24].

Shorter time to immunotherapy initiation was associated with greater probability of epilepsy remission. Moreover, in previous studies immunotherapy was the treatment most frequently associated with seizure freedom[6, 12, 19, 22] and delay to its initiation was also associated with late drug resistant epilepsy [20]. However, the best therapeutic protocol remains to be determined, and this association was not found in another study[9]. In our study, we did not observe a significant benefit on seizure outcome with the use of some specific immunosuppressive treatment. However, therapeutic schemes received by our patients were highly variable, strongly limiting the interpretation of these results. We were not able to study the exact relationship between epilepsy outcomes and the modality of immune treatment.

While confirming that seizures are a cardinal symptom of LGI1 encephalitis at the acute phase, our study provided important long-term data which may modulate the benign epilepsy evolution sometimes considered in these patients. About one in five patients did develop DRE, an evolution which may mostly reflect the development of hippocampal atrophy. An important issue in future studies will be to investigate if some therapeutic schemas may be better to limit hippocampal atrophy and, therefore, to prevent evolution to DRE. Determining what modalities of immune treatment may alter long-term epilepsy outcomes requires prospective studies with long-term follow-up.

Acknowledgments and Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Figure legend

Figure 1: MRI data at the acute phase in two patients, who were 86 (A) and 69 (B) years old, in whom the hippocampal atrophy (dashed square) observed on T1- weighted sequences was not associated with T2-weighted FLAIR hyperintensity.

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