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Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies

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IMPORTANCE Limbic encephalitis with leucine-rich, glioma-inactivated 1 (LGI1) antibodies is one of the most frequent variants of autoimmune encephalitis with antibodies targeting neuronal surface antigens. However, the neuroimaging pattern and long-term cognitive outcome are not well understood.

OBJECTIVE To study cognitive outcome and structural magnetic resonance imaging (MRI) alterations in patients with anti-LGI1 encephalitis.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional study was conducted at the Departments of Neurology at Charité-Universitätsmedizin Berlin and University Hospital Schleswig-Holstein, Kiel, Germany. Data on 30 patients with anti-LGI1 encephalitis and 27 healthy control individuals matched for age, sex, and educational level were collected from June 1, 2013, through February 28, 2015.

MAIN OUTCOMES AND MEASURES Clinical assessment, cognitive testing, and high-resolution MRI data, including whole-brain, hippocampal and basal ganglia volumetry; white matter integrity (diffusion tensor imaging); gray matter density (voxel-based morphometry); and hippocampal microstructural integrity (mean diffusivity and fractional anisotropy).

RESULTS Of the 30 patients included in the study, 19 were male (63%); mean (SD) age was 65.7 (12.3) years. Patients with anti-LGI1 encephalitis had incomplete recovery with significant and persisting verbal (mean [SE] Rey Auditory Verbal Learning Test [RAVLT], delayed recall: patients, 6.52 [1.05]; controls, 11.78 [0.56], $P < .001$) and visuospatial (Rey-Osterrieth Complex Figure Test [ROCF], delayed recall: patients, 16.0 [1.96]; controls, 25.86 [1.24]; $P < .001$) memory deficits. These deficits were accompanied by pronounced hippocampal atrophy, including subfields cornu ammonis 2/3 (CA2/3) and CA4/dentate gyrus (DG), as well as impaired hippocampal microstructural integrity. Higher disease severity correlated with larger verbal memory deficits (RAVLT delayed recall, $r = -0.40$; $P = .049$), decreased volumes of left hippocampus ($r = -0.47$; $P = .02$) and left CA2/3 ($r = -0.41$; $P = .04$) and CA4/DG ($r = -0.43$; $P = .03$) subfields, and impaired left hippocampal microstructural integrity ($r = 0.47$; $P = .01$). In turn, decreased volume of the left CA2/3 subfield (RAVLT delayed recall, $r = 0.40$; $P = .047$) and impaired left hippocampal microstructural integrity (RAVLT recognition, $r = -0.41$; $P = .04$) correlated with verbal memory deficits. Basal ganglia MRI signal abnormalities were observed in only 1 patient, but a longer duration of faciobrachial dystonic seizures correlated with a reduction of pallidum volume ($r = -0.71$; $P = .03$). In contrast, no abnormalities of cortical gray matter or white matter were found. The latency between disease onset and initiation of immunotherapy was significantly correlated with verbal (RAVLT recall after interference, $r = -0.48$; $P = .02$) and visuospatial (ROCF delayed recall, $r = -0.46$; $P = .03$) memory deficits.

CONCLUSIONS AND RELEVANCE Anti-LGI1 encephalitis is associated with cognitive deficits and disability as a result of structural damage to the hippocampal memory system. This damage might be prevented by early immunotherapy.

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Editorial
Supplemental content

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Encephalitis associated with leucine-rich, glioma-inactivated 1 (LGI1) antibodies belongs to a newly discovered group of autoimmune encephalitides with antibodies targeting neuronal surface antigens.[1,2] Patients with LGI1 antibodies develop limbic encephalitis and typically present with memory impairment, confusion, behavioral changes, and temporal lobe seizures. Faciobrachial dystonic seizures (FBDS), presenting as short, stereotyped dystonic movements of the face and the ipsilateral arm and/or leg, frequently precede the onset of anti-LGI1 encephalitis.[3] Early recognition and immunosuppressive treatment of FBDS can prevent progression to limbic encephalitis and development of cognitive deficits.[4,5]

Characteristic imaging features of autoimmune encephalitides associated with different antibodies are increasingly recognized.[6] For example, advanced imaging analyses, including resting-state functional magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and volumetry, have revealed reduced hippocampal functional connectivity, widespread white matter damage, and hippocampal atrophy in encephalitis associated with *N*-methyl-D-aspartate receptor (NMDAR) antibodies despite normal results of clinical MRIs in most of these patients.[7,8] Thus, these advanced analyses can provide relevant clinical and pathophysiologic information in autoimmune encephalitis. In anti-LGI1 encephalitis, results of clinical MRI at the stage of FBDS are frequently unremarkable, although basal ganglia abnormalities have been observed in some patients.[4,9-11] During the limbic encephalitis stage of the disease, most patients develop T2 hyperintense signal alterations of the medial temporal lobes.[1-3] However, to our knowledge, no previous study has examined imaging correlates of anti-LGI1 encephalitis and their association with cognitive deficits and clinical outcome in detail.

In the present study, we investigated the effect of anti-LGI1 encephalitis on clinical and cognitive outcomes as well as the structure and function of the hippocampus and the basal ganglia in a cohort of 30 patients. We report (1) findings of routine clinical MRI; (2) neuropsychological outcome; (3) results of whole-brain, hippocampal, and basal ganglia volumetry; assessment of white matter integrity using DTI; gray matter morphology using voxel-based morphometry; and hippocampal microstructural integrity; and (4) correlation of structural imaging markers and onset of treatment with clinical and cognitive outcomes.

Key Points

Question What are the neuroimaging characteristics and the cognitive long-term outcome in encephalitis with leucine-rich, glioma-inactivated 1 (LGI1) antibodies?

Findings In this cross-sectional study of 30 patients with anti-LGI1 encephalitis, significant bilateral atrophy of the hippocampus and its subfields, as well as significantly impaired hippocampal microstructural integrity, was observed. This structural damage was correlated with persistent verbal and visuospatial memory deficits; early immunotherapy was associated with better memory outcome.

Meaning Anti-LGI1 encephalitis is associated with pronounced structural damage of the hippocampus that causes persisting impairments of verbal and visuospatial memory.

Methods

Patient Cohort

Thirty patients (11 women, 19 men; mean [SD] age, 65.7 [12.3] years) with anti-LGI1 encephalitis from 2 centers using a unified study protocol were included in this study (eTable 1 in the Supplement) (Charité-Universitätsmedizin Berlin, Germany, 19 patients; University Hospital Schleswig-Holstein Kiel, Germany, 11 patients). Patients were recruited after the acute stage of limbic encephalitis (latency after disease onset: median, 23.3 months; interquartile range [IQR], 6.4-35.4 months). Three patients were not eligible for MRI studies, and imaging analyses were therefore restricted to 27 patients. Fludeoxyglucose F 18-positron emission tomography data on 4 patients were previously published.[12,13] The imaging and neuropsychology control group comprised 27 healthy individuals without a history of psychiatric or neurologic disease. The control participants were individually matched to patients with respect to study site, sex, educational level, and age (9 women, 18 men; mean [SD] age, 64.3 [2.3] years). There were no significant differences between patients and controls regarding age and years of formal education. The study was conducted from June 1, 2013, through February 28, 2015. The study was approved by the ethics committees of the Charité-Universitätsmedizin and the University Hospital Schleswig-Holstein. All participants provided written informed consent, and all received financial compensation.

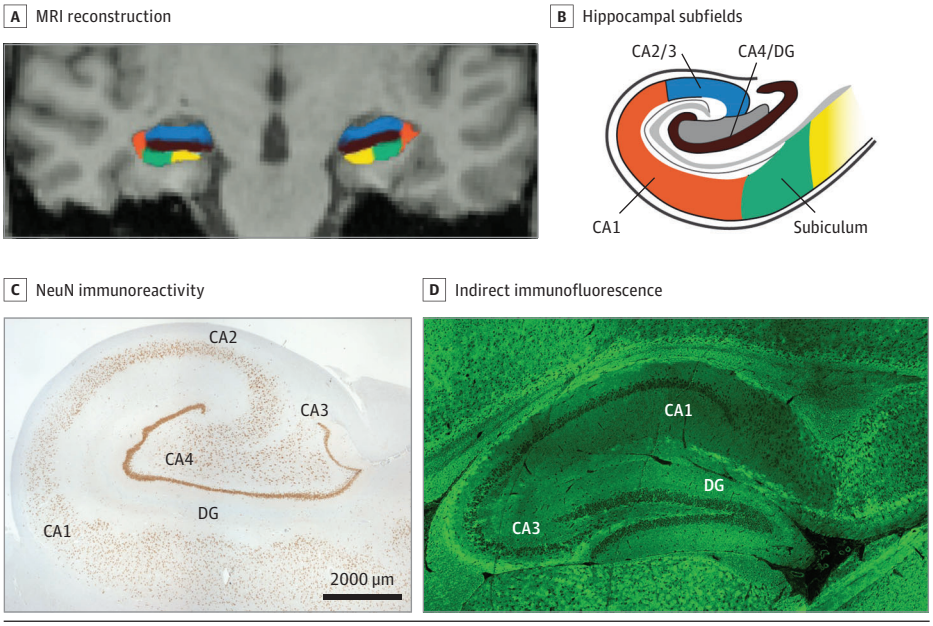
Clinical Assessment

Neurologic disability and dependence in daily activities were scored using the modified Rankin Scale (mRS)[14] by 3 experienced neurologists (C.F., H.P., and T.B.). The scale is scored as 0, no symptoms; 1, no significant disability, able to carry out all usual activities despite some symptoms; 2, slight disability, able to look after own affairs without assistance but unable to carry out all previous activities; 3, moderate disability, requires some help but able to walk unassisted; 4, moderately severe disability, unable to attend to own bodily needs without assistance and unable to walk unassisted; 5, severe disability, requires constant nursing care and attention, bedridden, incontinent; and 6, death due to the condition. Latency from disease onset to treatment was calculated as the time between the onset of the first symptoms (eg, FBDS or autonomic seizures) and initiation of the first immunotherapy, and follow-up time was defined as the interval between the onset of the first symptoms and the time of the study (eTable 1 in the Supplement).

Neuropsychological Assessment

Patients and controls were tested using a comprehensive neuropsychological test battery on verbal episodic memory (Rey Auditory Verbal Learning Test [RAVLT], 25 participants), with learning and recall trials scored from 0 to 15 (sum score, 0-75)[15]; visuospatial memory (Rey-Osterrieth Complex Figure [ROCF],

Figure 1. Hippocampal Subfield Anatomy and Pathophysiology in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 (LGI1) Antibodies



A, Magnetic resonance imaging (MRI) reconstruction of the hippocampus with a representative subfield segmentation. B, Schematic overview showing the different hippocampal subfields. C, NeuN immunoreactivity showing histologic subfield morphology. D, Detection of anti-LGI1 autoantibodies with indirect immunofluorescence. Patient serum with antibodies against LGI1 was incubated with frozen sections of mouse hippocampus. Bound antibodies were visualized using a fluorescence-labeled secondary antibody. CA indicates cornu ammonis; DG, dentate gyrus.

23 participants), with copy and recall trials scored from 0 to 36[16]; and working memory (forward and backward digit span test, 26 participants). We assessed attention and executive functions using the Trail-Making Test A and B (n = 11)[17] and a computerized test battery (simple response time [subtest alertness], n = 25; Go/No-Go and dual-task performance [subtest divided attention], n = 24), naming and conceptual knowledge (Regensburg Word Fluency Test, n = 22),[18] and interference (Stroop test, 16 participants). To estimate the premorbid general intellectual ability, 25 patients performed the German equivalent of the National Adult Reading Test, scored from 0 to 37.[19] General reasoning abilities were evaluated using the German version of the Raven's Progressive Matrices (Leistungsprüfsystem, subtest logical thinking, 15 participants), scored from 0 to 40.[20] The Montreal Cognitive Assessment test was administered for cognitive screening in 11 patients.

Antibody Testing

Serum samples and cerebrospinal fluid of the patients were tested for LGI1 antibodies by indirect immunofluorescence using a biochip mosaic containing, as antigenic substrates, frozen sections of rat hippocampus, rat and monkey cerebellum, and formalin-fixed HEK293 cells that expressed recombinant membrane-bound LGI1 (Euroimmun AG; Lübeck, Germany) (**Figure 1**).

MRI Analyses

Detailed information about MRI acquisition and analysis is available in the eMethods in the Supplement. Imaging data were acquired at both study sites using 3-T MRI scanners. For the clinical study, previous brain MRIs (4-9 serial MRIs in all patients) were reevaluated with specific regard to hippocampal and basal ganglia signal changes by a neuroradiologist or experienced neurologist (C.F. and T.B.) blinded to the patient's diagnosis. Whole-brain DTI analysis using tract-based spatial statistics, hippocampal microstructural integrity analysis, and voxel-based morphometry were performed as described previously[7,8] using the FMRIB Software Library (FSL, version 5.0; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) (Figure 1). Volumes of the basal ganglia, whole hippocampus, and hippocampal subfields were determined using FreeSurfer, version 5.1 (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer has been shown[21,22] to provide reliable and valid subcortical volumes, including hippocampal subfield segmentation, and to be more accurate than other automated methods in comparison with manual tracing. All volumes were adjusted within subject for intracranial volume.

Statistical Analysis

Psychometric test results were compared between groups using unpaired, 2-tailed *t* tests for independent samples or, if required, the Welch *t* test. Multivariate analyses of variance, with group as factor, age as covariate, and the 6 subfield volumes as dependent variables, were performed to analyze left and right hippocampal subfield volumes. Separate multivariate analyses of variance were used to assess whole left and right hippocampal volume and hippocampal mean diffusivity (MD). Bivariate correlation analyses were performed using parametric Pearson correlation for interval or ratio-scaled data and nonparametric Spearman rank correlation for ordinal data.

Results

Clinical Features

Clinical, laboratory, and electrophysiologic data of all patients are provided in the **Table** and eTable 1 in the Supple-

Table. Clinical Features of 30 Patients With Anti-LGI1 Encephalitis

Characteristic	No. (%)
Sex	
Male	19 (63)
Female	11 (37)
Age, mean (SD), y	65.7 (12.3)
Time after disease onset, median (IQR), mo	23.3 (6.4-35.4)
Tumors present[a]	3 (10)
Clinical diagnosis of limbic encephalitis	29 (97)
Time from symptom onset to immunotherapy, median (IQR), mo	1.6 (0.8-4.4)
Amnesia	30 (100)
Confusion, irritability	18 (60)
Behavioral and mood disturbances	11 (37)
Sleep disturbances	6 (20)
Modified Rankin Scale score, mean (SD)[b]	1.7 (1.1)
Death[c]	1 (3)
Unilateral or bilateral faciobrachial dystonic seizures[d]	16 (53)
Pilomotor and/or autonomic seizures	6 (20)
Complex partial or generalized seizures	12 (40)
Electroencephalogram (n = 27)	
Epileptiform activity	7 (26)
Focal or generalized slowing	12 (44)
Antiepileptic treatment[e]	26 (87)
Acute immunotherapy	29 (97)
IV corticosteroids	27 (90)
Plasma exchange	10 (33)
Immunoglobulins	11 (37)
Long-term immunosuppression	
Oral corticosteroids	20 (67)
Azathioprine	10 (33)
Rituximab	5 (17)
Methotrexate sodium	1 (3)
Cyclophosphamide	1 (3)
Acute clinical imaging	
Hippocampal/MTL T2/FLAIR hyperintensities[f]	22 (73)
Follow-up clinical imaging (n = 26)	
Hippocampal atrophy	25 (96)
Hippocampal sclerosis	13 (50)
Hyponatremia[g]	21 (70)
Antibodies against LGI1	
During acute phase[h]	30 (100)
During follow-up	20 (67)

Abbreviations: FBDS, faciobrachial dystonic seizures; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; IV, intravenous; LGI1, leucine-rich, glioma inactivated 1; mRS, modified Rankin Scale; MTL, medial temporal lobe.

[a] One neuroendocrine tumor of the jejunum, 1 breast cancer, and 1 esophageal adenocarcinoma.

[b] Explained in the Clinical Assessment subsection of the Methods section.

[c] One patient died of infectious complications (sepsis and multiorgan failure).

[d] Sixteen of 30 patients (53%) experienced unilateral or bilateral FBDS before the onset of the acute limbic phase of the encephalitis. All but 1 patient with FBDS developed limbic encephalitis.

[e] Including carbamazepine, levetiracetam, valproic acid, clonazepam, pregabaline, and phenytoin.

[f] Transient diffusion restriction of bilateral posterior cortex in 1 patient (3%) and no specific abnormalities in 7 patients (23%).

[g] Hyponatremia (sodium level <135 mEq/L); mean (SD) sodium level, 129.3 (4.5) mEq/L; the remaining patients showed a low-normal serum sodium concentration of 137.6 (1.5) mEq/L (to convert to mmol/L, multiply by 1).

[h] In serum and cerebrospinal fluid, titer range 1:10-1:1000.

ment. Sixteen of 30 patients (53%) experienced unilateral or bilateral FBDS. In addition, 5 patients (17%) reported pilomotor and/or autonomic seizures (eg, shivers or flushing),[23,24] and 1 patient (3%) experienced both FBDS and autonomic seizures (in total, 6 patients [20%]). All except 1 patient with isolated FBDS developed limbic encephalitis with typical clinical features (ie, amnesia, confusion, behavioral and mood disturbances, sleep disturbances, and/or complex partial or generalized seizures). In summary, 28 of 30 patients (93%) experienced FBDS and/or other types of seizures. Immunotherapy was initiated in 29 patients (97%) (Table). Most patients initially received intravenous corticosteroids followed by plasma exchange and/or immunoglobulins (first-line treatment) and long-term immunosuppression (second-line treatment: azathioprine, cyclophosphamide, rituximab, or methotrexate sodium). Clinical outcome was moderate, with a median mRS score of 2 (IQR, 1-2). One patient died of infectious complications.

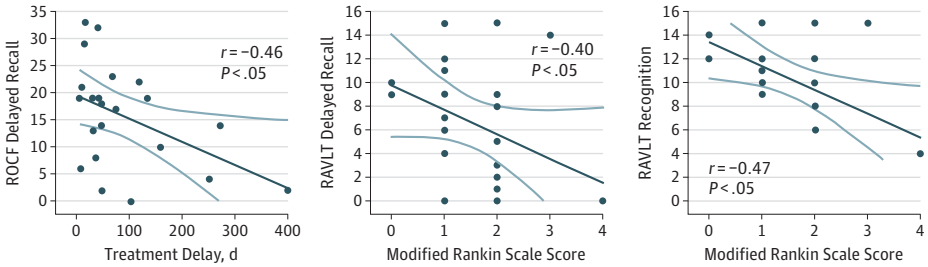
Cognitive Outcome

Patients with anti-LGI1 encephalitis showed pronounced episodic verbal memory deficits. Performance in the patients, reported as mean (SE), was significantly impaired across all 5 learning trials of the RAVLT compared with that of the healthy controls (patients, 40.64 [2.88] vs controls, 54.59 [1.67], $t_{50} = -4.27$; $P < .001$) during the retrieval after the interference list (patients, 6.88 [0.99] vs controls, 11.70 [0.48], $t_{50} = -4.48$; $P < .001$) and delayed recall (patients, 6.52 [1.05] vs controls, 11.78 [0.56], $t_{50} = -4.51$; $P < .001$), as well as in the recognition of target words (patients, 10.24 [0.76] vs controls, 13.69 [0.34], $t_{50} = -3.46$; $P = .001$) (**Figure 2** and eFigure 1 and eTable 2 in the Supplement). Moreover, patients showed significant visuospatial memory deficits (ROCF: immediate recall, patients, 16.62 [2.14] vs controls, 25.16 [1.21], $t_{27} = -3.64$; $P = .001$; delayed recall, patients, 16.0 [1.96] vs controls, 25.86 [1.24], $t_{48} = -4.17$; $P < .001$) and impaired working memory (digit span forward, patients, 6.92 [0.47] vs controls, 8.12 [0.35], $t_{50} = -2.04$; $P = .047$; digit span backward, patients, 5.73 [0.58] vs controls, 7.42 [0.43], $t_{50} = -2.42$; $P = .02$). Furthermore, patients had impairments of executive function and attention as well as impaired semantic and phonemic fluency (eTable 2 in the Supplement).

Clinical Imaging

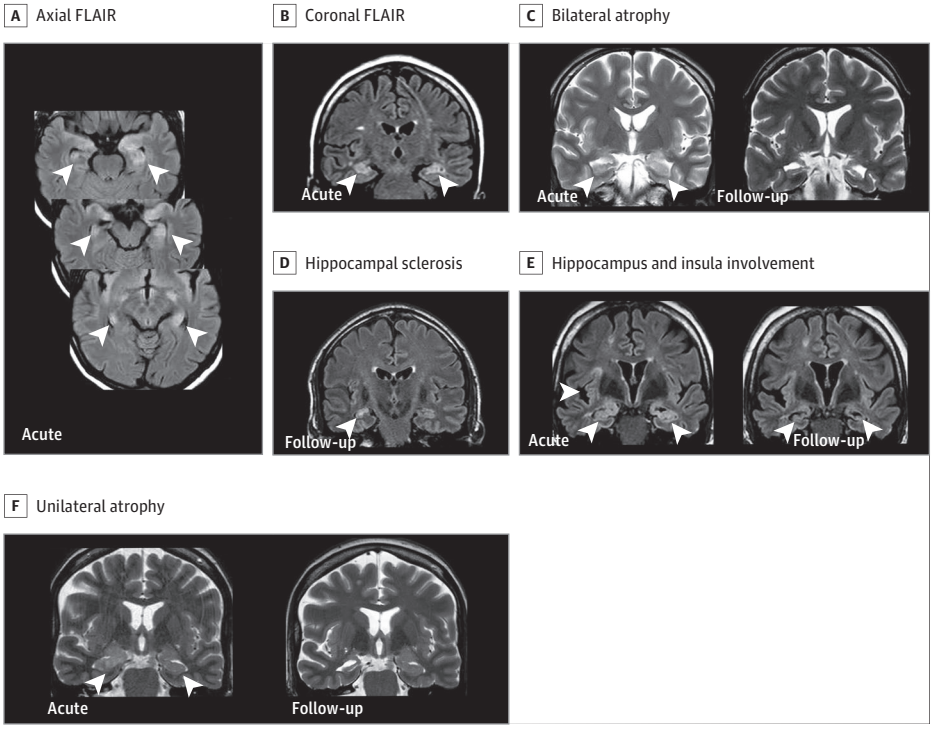
Visual inspection of the acute routine MRI revealed unilateral or bilateral hippocampal T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in 22 of 30 patients (73%), transient diffusion restriction of bilateral posterior cortex in 1 patient (3%), and was normal or showed no specific abnormalities in 7 patients (23%) (median, 17 [IQR, 13-119] days after symptom onset) (**Figure 3** and Table). One patient with normal MRI results exclusively showed FBDS that did not progress to limbic encephalitis. Follow-up routine MRI data were available for 26 patients and showed hippocampal atrophy in 25 patients (96%) on visual inspection (Figure 3). In 13 of 26 patients (50%), hippocampal atrophy was accompanied by T2/FLAIR signal increase and loss of internal laminar architecture indicating hippocampal sclerosis. Serial acute routine and

Figure 2. Cognitive Deficits in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 (LGI1) Antibodies



Delayed treatment and a higher disease severity (modified Rankin Scale score) were associated with more severe visual and verbal memory impairments. RAVLT indicates Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure.

Figure 3. Clinical Magnetic Resonance Imaging (MRI) Findings in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 (LGI1) Antibodies



Representative MRIs of patients with anti-LGI1 encephalitis during the acute stage (median, 17 days after onset) and during follow-up (median, 23.3 months after onset). A, Axial fluid-attenuated inversion recovery (FLAIR) imaging shows signal hyperintensities in both hippocampi and amygdalae during the acute phase. B, Coronal FLAIR image of another patient showing swelling and signal hyperintensity in both hippocampi. C, T2-weighted imaging showing hippocampal edema and enlargement during the acute phase evolving into bilateral hippocampal atrophy. D, Follow-up stage in one patient showing the transition into hippocampal sclerosis of the right hippocampus with gliosis and increased signal in T2. E, Swelling and hippocampal enlargement in one patient showing also an involvement of the right insula and transformation into hippocampal atrophy (follow-up image). F, T2-weighted imaging showing hippocampal edema and enlargement during the acute phase evolving into unilateral hippocampal atrophy. Arrowheads indicate hippocampal and insula imaging changes.

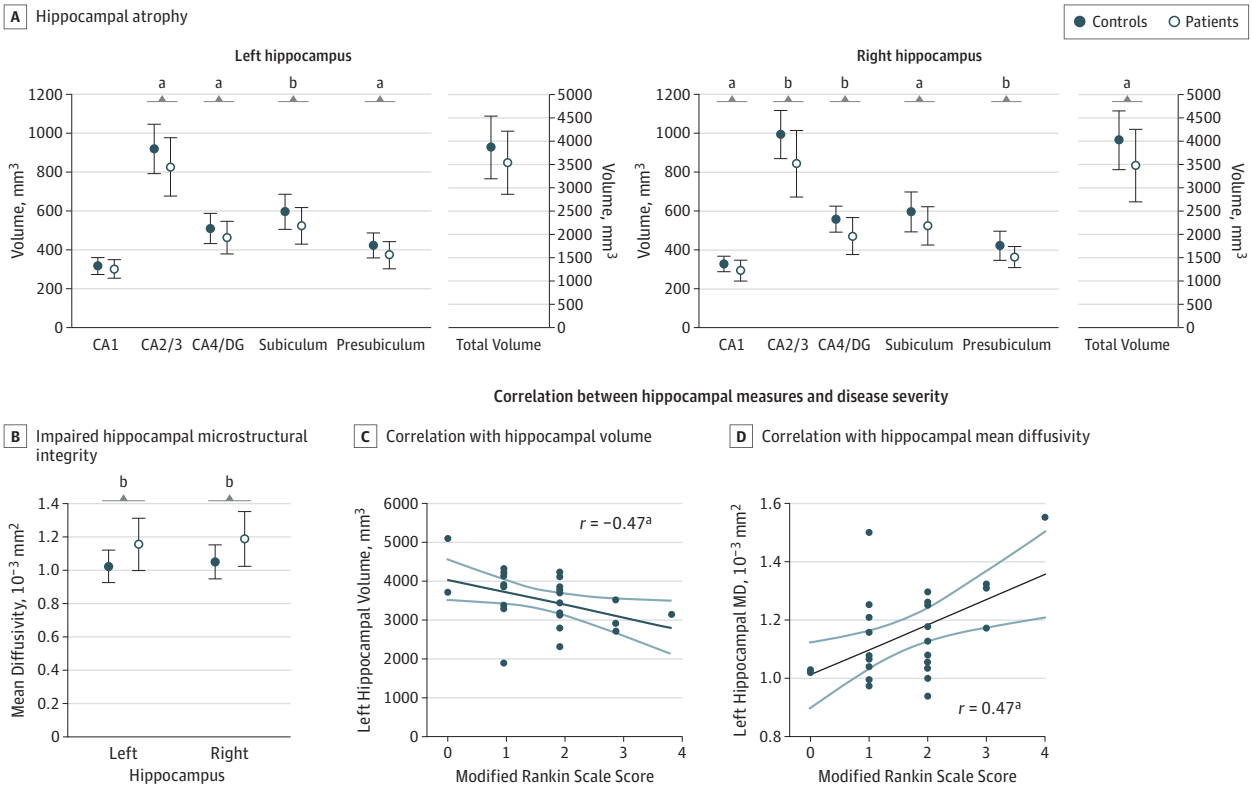
follow-up MRI (T1, T2, FLAIR, and diffusion-weighted imaging; 4-9 MRIs per patient) revealed no signal abnormalities in the basal ganglia except for a small, punctuate T2 hyperintensity in the left pallidum in 1 patient.

Hippocampal Volumetry

Patients had a significantly reduced whole bilateral hippocampal volume in comparison with controls (eTable 2 in the Supplement). A multivariate analysis of variance of the left and right hippocampal volumes and their corresponding subfields revealed a significantly reduced volume of the right hippocampus in the patient group (Figure 1, **Figure 4**, and eFigure 2 in the Supplement). Significant reductions of hippocampal subfield volumes in patients were observed bilaterally for cornu ammonis 2/3 (CA2/3), CA4/dentate gyrus (DG), presubiculum, and subiculum (Figure 4 and eTable 2 in the Supplement).

A decreased volume of the left CA2/3 subfield correlated significantly with deficits in the recall of the verbal memory material after interference (r = 0.40, P = .048) and delay (r = 0.40, P = .047) as well as during recognition (r = 0.42, P = .04) (Figure 4 and eFigure 2 in the Supplement). Impaired recognition was also associated with a decreased vol-

Figure 4. Hippocampal Volumetry and Microstructural Integrity Analyses



A, Reduced volumes of the left and right hippocampus and their corresponding subfields. Error bars indicate SD. B, Mean diffusivity (MD) of the left and right hippocampus is increased in patients with encephalitis with leucine-rich, glioma-inactivated 1 (LGI1) antibodies. C, Higher disease severity (modified Rankin Scale Score) is associated with lower hippocampal volumes. D, Higher disease severity (modified Rankin Scale Score) is associated with more severely impaired microstructural integrity of the hippocampus.

[a] $P < .05$.

[b] $P < .01$.

ume of the left subiculum ($r = 0.42$, $P = .04$). Patients with lower CA4/DG volumes were additionally more prone to commit intrusion errors during the recognition part of the RAVLT ($r = -0.59$, $P = .03$).

Hippocampal Microstructural Integrity

Patients had increased MD of both the left and right hippocampus (diffusivity left: patients, 1.155 [0.030] × 10^{-3}; controls, 1.028 [0.019] × 10^{-3}, $F_{1,34} = 12.99$; $P = .001$; right: patients, 1.186 [0.031] × 10^{-3}; controls, 1.045 [0.019] × 10^{-3}, $F_{1,34} = 14.78$; $P < .001$) (Figure 4 and eTable 2 in the Supplement). The MD of the left hippocampus was negatively correlated with recognition performance of verbal episodic memory material on the RAVLT ($r = -0.41$, $P = .04$). Increase of right hippocampal MD correlated significantly with the number of intrusion errors during the RAVLT recognition ($r = 0.57$, $P = .03$). No significant hippocampal fractional anisotropy differences were observed.

Basal Ganglia Volumetry

Basal ganglia volumes were not significantly different between the patients and controls (eTable 2 in the Supplement). Right pallidum volume was negatively correlated with duration of FBDS (ie, days that FBDS persisted: $r = -0.71$, $P = .03$), with longer FBDS duration associated with smaller pallidum volume. The same trend was observed for all investigated basal ganglia volumes (all $r < -0.30$).

Voxel-Based Morphometry and DTI

Voxel-based morphometry analysis revealed no differences in cortical gray matter volume between the patient and control groups. No abnormalities in white matter microstructure were observed in the patient group compared with the control group with regard to the diffusion parameters fractional anisotropy, MD, axial diffusivity, and radial diffusivity.

Immunotherapy and Clinical Outcome

The latency between disease onset and initiation of immunotherapy was correlated with worse verbal and visuospatial episodic memory performance (RAVLT recall after interference: $r = -0.48$, $P = .02$; intrusions during recognition: $r = 0.62$, $P = .03$; ROCF: immediate recall, $r = -0.64$, $P = .02$; and delayed recall, $r = -0.46$, $P = .03$) (Figure 2). Higher mRS scores were associated with worse verbal memory performance (RAVLT delayed recall: $r = -0.40$, $P = .049$; recognition: $r = -0.47$, $P = .02$) (Figure 2) and a higher susceptibility to errors on the

Stroop task (r = 0.66, P = .03). Moreover, higher disease severity as indicated by higher mRS scores was accompanied by a volume decrease in left CA2/3 (r = −0.41, P = .04), left CA4/DG (r = −0.43, P = .03), left subiculum (r = −0.47, P = .01), and left hippocampus (r = −0.47, P = .02), as well as an increased MD of the left hippocampus (r = 0.47, P = .01) (Figure 4).

Patients with second-line therapy had significantly worse verbal memory performance (mean [SE] RAVLT delayed recall: 4.07 [1.30] vs 8.15 [1.43], $F_{1,25}$ = 4.48; P = .04) and higher disease severity (mRS: 2.00 [0.26] vs 1.31 [0.21], $F_{1,25}$ = 4.30; P = .048) in comparison with patients with first-line therapy only. Hippocampal volume (3441.0 [162.6] vs 3568.3 [203.7], $F_{1,25}$ = 0.28; P = .60) and integrity (0.00117 [0.00004] vs 0.00116 [0.00003], $F_{1,25}$ = 0.62; P = .81) were equally affected in both groups. Antibody titers and time to follow-up were not significantly correlated with memory performance or structural hippocampal findings.

Discussion

We observed that patients with anti-LGI1 encephalitis had markedly impaired verbal and visuospatial memory in association with significantly reduced hippocampal volumes and impaired hippocampal microstructural integrity. Patients with more severe clinical outcomes had more structural hippocampal damage that in turn predicted worse memory performance. Patients with delayed treatment had worse verbal and visuospatial memory performance. Longer FBDS duration correlated with smaller pallidum volume.

Clinical and Cognitive Outcomes

Patients with anti-LGI1 encephalitis presented with typical clinical symptoms (ie, FBDS and limbic encephalitis) complemented by hyponatremia and characteristic hippocampal MRI signal changes.[1,2,5,25,26] Twenty percent of the patients in our cohort had autonomic (eg, shivers, flushing) or pilomotor seizures.[23,24] Tumors were identified in 3 patients (10%). This observation is in line with findings from the cohorts of Lai et al[2] (6 of 51 patients [12%] with 5 different tumors) and Shin et al[5] (1 of 14 patients [7%]) but contrasts with several studies[1,3,4] that found no tumor associations.

Most patients with anti-LGI1 encephalitis respond to immunotherapy.[4,5,27,28] Almost all of our patients received first- and second-line treatment. Despite this therapy, patients developed substantial verbal and spatial memory deficits.[1,25] These neuropsychological deficits were correlated with disease severity, with higher mRS scores predisposing to worse performance. Memory deficits were more pronounced in patients who received second-line therapy, which likely relates to the higher disease severity in these individuals. Patients with later treatment had significantly worse memory outcomes. These results add to the observation[4] that early identification and immunosuppressive treatment of FBDS can prevent the subsequent development of cognitive deficits and mirror reports[29-31] of a significant correlation between treatment delay and cognitive outcome in NMDAR encephalitis and other autoimmune encephalitides. Consequently, testing for neuronal antibodies should be performed at a low threshold even in patients with normal findings on routine MRI. Our data furthermore suggest that pilomotor and autonomic seizures can be early symptoms of limbic encephalitis, which is in line with previous case reports[32-34] of patients with limbic encephalitis. Although an objective diagnosis of such seizures frequently cannot be achieved, we propose that antibody testing should be considered in patients presenting with paroxysmal shivering, flushing, or pilomotor erection. Despite possible severe adverse effects, all patients in the present study tolerated immunosuppression well, which is in line with findings from previous studies.[5,28]

Neuroimaging

The hippocampus shows a selective vulnerability to metabolic and cytotoxic insults and is the major pathogenetic target in limbic encephalitis.[6-8,35,36] In our cohort, 97% of patients experienced memory deficits. Unilateral or bilateral hippocampal hyperintense signal alterations were found on acute and follow-up routine MRI of most patients, but the results of acute imaging were normal or showed no specific alterations in 23% of the patients. On follow-up, almost all patients had developed hippocampal atrophy or sclerosis, suggesting that hippocampal inflammation was present in the acute phase but not detectable by routine MRI.[37,38] Volumetric analyses confirmed these observations and revealed bilateral hippocampal atrophy, thus extending previous observations of smaller whole hippocampal volumes in 8 patients with anti-LGI1 encephalitis[4] and in 15 patients with voltage-gated potassium channel-complex antibodies (3 of 15 with LGI1 antibodies).[39] Furthermore, we observed bilateral volume reductions of all hippocampal subfields except CA1, a finding that contrasts with predominant CA1 abnormalities in other memory disorders, such as transient global amnesia.[40] Pronounced volume loss was observed in CA2/3 and CA4/DG, and patients with more severe disease courses had lower volumes of left whole hippocampus, CA2/3, CA4/DG, and subiculum. Moreover, CA2/3 volume was significantly correlated with several measures of verbal memory performance. This observation is in line with a predominant expression of LGI1 in CA3,[41] a hippocampal subfield that has been implicated in memory encoding[42,43] as well as in pattern completion and pattern separation (ie, hippocampal mechanisms to recover an entire memory from a partial cue and to create distinct, nonoverlapping memory representations).[44,45] During the recognition phase of the verbal learning test (RAVLT), patients were required to distinguish target words from highly similar interference and lure items. Patients recognized fewer target words and were more likely to misclassify interference and lure words as targets, indicating a failure in creating and retrieving nonoverlapping representations in memory. Thus, it is conceivable that impaired pattern separation and completion contribute to the memory deficits in patients with anti-LGI1 encephalitis.

Microstructural integrity of the hippocampus was assessed based on analysis of hippocampal MD, which reflects the mean motion of water molecules that is limited by intact membranes and tissue cytoarchitecture. Thus, MD increases are considered a measure of neuronal disintegration and corresponding structural damage.[46] In anti-LGI1 encephalitis,

hippocampal MD proved to be a sensitive marker of hippocampal damage: MD of both hippocampi was significantly increased and correlated with disease severity and memory deficits in patients. These findings are in line with observations of correlations between increased hippocampal MD and worse memory performance in healthy individuals,[47,48] patients with Alzheimer disease,[49] and patients with anti-NMDAR encephalitis.[7]

In contrast, we observed basal ganglia signal alterations in only 1 patient, and basal ganglia volumes were not reduced in comparison with those in healthy controls. However, longer individual FBDS duration correlated with reduced pallidum volume. This result adds to observations of basal ganglia positron emission tomography and MRI abnormalities and suggests a role for basal ganglia in FBDS pathophysiology.[3,4,10,11,50] We did not observe basal ganglia T1 and T2 hyperintensities that were recently reported in 42% of patients with anti-LGI1 encephalitis and FBDS.[11] This difference in basal ganglia MRI findings might be due to the transient nature of these signal alterations and the different timing of MRI in both studies. For example, T1 hyperintensities were detected a median of 26.5 days after FBDS onset with a median duration of 11 weeks, but T2 hyperintensities were seen after 15 days and lasted only 1 week.[11] Thus, longitudinal studies are needed to reveal the exact time course of these basal ganglia signal changes. Another recent study[50] reported hypermetabolism in the primary motor cortex contralateral to the limb affected by FBDS that normalized when the patients recovered. Using whole-brain voxel-based morphometry and DTI, we found no reduction of gray matter density and whole-brain white matter integrity. Specifically, we detected no structural damage in the motor cortex, corroborating the transient nature of motor cortex involvement in contrast to the severe and persistent hippocampal damage.

Taken together, our MRI analyses provide a characteristic pattern of imaging alterations in anti-LGI1 encephalitis that reveal a more focal and less widespread pathophysiology in comparison with other autoimmune encephalitides.[6] The results particularly contrast with findings in anti-NMDAR encephalitis. The most prominent difference is widespread white matter damage in patients with anti-NMDAR encephalitis that was not observed in those with anti-LGI1 encephalitis despite the typical older age and the presence of microvascular white matter lesions on routine imaging in some of these patients.[8] Furthermore, although whole hippocampal volumes are reduced in both disorders, hippocampal subfields are differentially affected (bilateral atrophy of CA2/3, CA4/DG, subicular complex in anti-LGI1 encephalitis, and CA4/DG and subicular complex in anti-NMDAR encephalitis).[7]

Limitations

This study has limitations inherent to its exploratory and multicenter design. Patients were studied at 2 centers, and some neuropsychological tests were performed only in 1 center. However, major tests assessing memory, attention, and executive function were identical in both centers. Furthermore, a large number of imaging and neuropsychological analyses were performed. Given the exploratory nature of this study, no correction for multiple comparisons was performed across tests. However, corrections for multiple comparisons were performed for individual analyses where applicable (eg, voxel-based morphometry and DTI analyses) (eMethods in the Supplement).

Conclusions

We show that patients with anti-LGI1 encephalitis develop persistent and severe verbal and visuospatial memory deficits in addition to impairments of working memory, attention, and executive functions. Advanced imaging analyses revealed a characteristic pattern of bilateral hippocampal atrophy with predominant effects on the subfields CA2/3, CA4/DG, and the subicular complex and bilaterally impaired hippocampal microstructural integrity. Patients with more severe disease courses had a larger amount of hippocampal damage that in turn predicted worse memory performance. Duration of FBDS was associated with reduced pallidum volume. On clinical evaluation, we observed that 20% of patients presented with pilomotor or autonomic seizures—subtle clinical symptoms that need to be considered as possible signs of limbic encephalitis. Routine MRI during the acute disease stage revealed hippocampal hyperintensities in most patients but was unremarkable in 23% of the patients. Our data show that delayed immunotherapy is associated with more severe memory impairment and thus highlight the need for early diagnosis and rapid treatment in patients with anti-LGI1 encephalitis.

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