Neuropsychological and Structural Neuroimaging Outcomes in LGI1-Limbic Encephalitis: A Case Study

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Abstract

Objective: Anti-leucine-rich glioma-inactivated 1 limbic encephalitis (LGI1-LE) is a rare autoimmune condition that affects the structural integrity and functioning of the brain's limbic system. Little is known about its impact on long-term neuropsychological functioning and the structural integrity of the medial temporal lobe. Here we examined the long-term neuropsychological and neuroanatomical outcomes of a 68-year-old male who acquired LGI1-LE.
Methods: Our case patient underwent standardized neuropsychological testing at two time points. Volumetric analyses of T1-weighted images were undertaken at four separate time points and qualitatively compared with a group of age-matched healthy controls.
Results: At the time of initial assessment, our case study exhibited focal impairments in verbal and visual episodic memory and these impairments continued to persist after undergoing a course of immunotherapy. Furthermore, in reference to an age-matched healthy control group, over the course of 11 months, volumetric brain imaging analyses revealed that areas of the medial temporal lobe including specific hippocampal subfields (e.g., CA1 and dentate gyrus) underwent a subacute period of *volumetric enlargement* followed by a chronic period of *volumetric reduction* in the same regions.
Conclusions: In patients with persisting neurocognitive deficits, LGI1-LE may produce chronic volume loss in specific areas of the medial temporal lobe; however, this appears to follow a subacute period of volume enlargement possibly driven by neuro-inflammatory processes.

Keywords: Limbic encephalitis; Cognitive function; Case report; Hippocampus; Magnetic resonance imaging

Limbic encephalitis (LE) is a rare neurological condition characterized by neuroinflammation and dysfunction of the brain's limbic system (Pastuszak et al., 2017; Szots et al., 2017). Patients presenting with LE often experience a subacute onset of neurologic and psychiatric symptoms related to limbic dysfunction (Tüzün & Dalmau, 2007). Although the etiology of LE is not entirely understood, pathological features of the condition are thought to arise from either cancer (i.e., paraneoplastic

syndrome), a preceding autoimmune disorder, or previous infection (e.g., herpes simplex virus; Anderson & Barber, 2008; Tüzün & Dalmau, 2007). Generally speaking, the clinical presentation and prognostic outcomes of infectious forms of encephalitis, such as herpes simplex virus encephalitis (HSVE)—the most common etiology of sporadic cases of encephalitis (Bradshaw & Venkatesan, 2016)—have been well-documented in the literature. In contrast, relatively little is known about the complex neuropsychological and neuroanatomical profile of a rare variant of autoimmune encephalitis, anti-leucine-rich glioma-inactivated 1 limbic encephalitis (LGI1-LE; Griffith, Malpas, Alpitsis, O'Brien, & Monif, 2020; Roberto, Espiritu, Fernandez, & Gutierrez, 2020).

When compared with HSVE, autoimmune forms of LE (e.g., LGI1-LE) are often associated with subacute rather than acute onset of neurologic symptoms and subsequent development of psychiatric symptoms, such as depression and psychosis (Oyanguren et al., 2013). Distinctions between autoimmune and infective encephalitis are shared at both the symptom-level and the neuroanatomic level, as patients with infectious forms of encephalitis, such as HSVE typically present with diffuse changes in the unilateral temporal (Budhram, Leung, Nicolle, & Burneo, 2019; Chow et al., 2015) and extra-temporal structures (Wasay et al., 2005), whereas patients with autoimmune forms of encephalitis, such as LGI1-LE typically present with more focal changes in the bilateral medial temporal lobes (MTLs) (Budhram et al., 2019; Oyanguren et al., 2013).

Like other variants of LE, LGI1-LE is associated with serum antibodies to voltage-gated potassium channels (VGKC; van Sonderen et al., 2016) and is exceptionally rare, with an estimated prevalence of 0.7 per 100,000 persons in 2014 (Dubey et al., 2018) and incidence rate of 0.83 per 1,000,000 persons per year (van Sonderen et al., 2016). Several reports have provided preliminary evidence suggesting that the LGI1 variant is largely non-paraneoplastic (Wang et al., 2017) and responsive to immunotherapy (Buckley et al., 2001; Wang et al., 2017). However, due to the limited literature on LGI1-LE, it is unclear whether the neuroanatomical and neurocognitive changes associated with this variant are progressive, stable, or ameliorated, post immunotherapy.

Neuropsychological findings associated with LGI1-LE

Evidence of the complete neuropsychological sequelae of LGI1-LE has been restricted to a small number of observational studies, case series, and cross-sectional studies. A review by Griffith et al. (2020) compiled the available neuropsychological and neurobehavioral findings of LGI1-LE and found that, on average, patients with this condition experience mild to severe impairments in several cognitive domains, including episodic memory (e.g., Finke et al., 2017 ; Miller et al., 2017), language (e.g., Krastinova, Vigneron, Le Bras, Gasnault, & Goujard, 2012), attention (e.g., Dodich et al., 2016, processing speed (e.g., Krastinova et al., 2012), executive functioning (e.g., working memory; Dodich et al., 2016; Finke et al., 2017; Krastinova et al., 2012), and visual spatial processing (Krastinova et al., 2012). Across these domains, deficits in episodic memory for both verbal and visual information are among the most frequently reported neuropsychological manifestations of LGI1-LE (Griffith et al., 2020). Studies have found that patients diagnosed with the LGI1 variant present with impairments in verbal delayed recall (Finke et al., 2017; Miller et al., 2017), verbal recognition memory (Finke et al., 2017), visual immediate and delayed recall (Finke et al., 2017), and selective episodic autobiographical memory (Miller et al., 2017). The neurobiological underpinnings of these memory deficits, however, are not well understood. Given the central role the MTL plays in subserving episodic memory (Dickerson & Eichenbaum, 2010), it is reasonable to hypothesize that patients with LGI1-LE experience pathological structural changes within various regions of the MTL such as the hippocampus. In addition to cognitive impairment, individuals diagnosed with LGI1 may also present with medical and psychiatric symptoms/manifestations such as hyponatremia, depression, paranoia, anxiety, dysphoria, hallucinations, and faciobrachial dystonic seizures (Ariño et al., 2016; Wang et al., 2017).

Neuroimaging findings associated with LGI1-LE

Neuroanatomical changes to the MTL following LGI1-LE have been documented in the literature. In a study that examined magnetic resonance imaging (MRI) data (Wang et al., 2017) LGI1-LE patients, on average, had scans showing abnormally high T2 and/or fluid-attenuated inversion recovery (FLAIR) signal intensities in the left hippocampus (Barajas, Collins, Cha, & Geschwind, 2010; Liu, Li, Li, Zhou, & Zhang, 2016; Shen et al., 2014), bilateral hippocampus (Hanert et al., 2019; Heine et al., 2018; Szots et al., 2014; Wang et al., 2016), and bilateral MTL (Barajas et al., 2010; Krastinova et al., 2012; Rodríguez Cruz, Pérez Sánchez, Alarcón Morcillo, & Velázquez Pérez, 2016; Wang et al., 2016). In a case series of 57 patients diagnosed with VGKC-LE, ~84% had brain MRI scans indicating increased T2 signal in the unilateral and/or bilateral MTL (Lai et al., 2010).

To date, only a few studies have examined the neuroimaging outcomes of LGI1-LE in each of the six major hippocampal subfields (i.e., CA1, CA2, CA3, CA4, dentate gyrus, subiculum). Evidence of atrophy affecting one or more of the hippocampal subfields may help explain the distinct neuropsychological sequalae of LGI1-LE, as emerging research suggests that each of the hippocampal subfields innervate specialized functions in various hippocampal-dependent memory processes

(e.g., Bartsch et al., 2010; Bartsch, Dohring, Rohr, Jansen, & Deuschl, 2011; Travis et al., 2014). Finke et al. (2017) examined the association between hippocampal atrophy and neuropsychological deficits in a group of 30 patients with anti-LGI1 LE and found that volumetric decreases in the left CA2 and left CA3 hippocampal subfield were correlated with patients' observed deficits in delayed verbal memory recall, recall after interference, and recognition, whereas volumetric decreases in the left presubiculum, left CA2, and left CA3 subfield were associated with patients' observed impairments in recognition. Together, these findings suggest that the severity and location (i.e., widespread vs. focal) of hippocampal atrophy may be important in predicting the subsequent neuropsychological functioning (i.e., diffuse vs. domain-specific impairment) of patients diagnosed with LGI1-LE.

In the current study, we hope to extend the existing literature on LGI1-LE by examining the long-term neuropsychological and neuroanatomical outcomes of an individual who acquired LGI1 LE. Based on the previous literature, we predict that (i) the patient will exhibit noticeable improvement in episodic memory following immunotherapy (Ariño et al., 2016; Zangrandi et al., 2019), (ii) hippocampal subregions will show a differential pattern of volumetric change, and (iii) following immunotherapy, the grey matter (GM) volume of structures within the MTL will remain relatively stable over time (Finke et al., 2017; Miller et al., 2017).

Case report

The current study was approved by the University of Manitoba's Research Ethics Board and Shared Health Manitoba. In accordance with our approved ethics protocol, the following information has undergone several steps of deidentification to uphold the patient's privacy and anonymity.

Background information

The patient is a 68-year-old retired mechanic, who is an English-speaking, right-handed, male with ∼11 years of education and a medical history of hypothyroidism, hyperlipidemia, and remote head trauma (i.e., sustained when he was 18 years old) from which a full recovery was made.

Patient presentation

Collateral interviews from the patient's family members revealed that in the 3 months leading up to his hospitalization, the patient was experiencing ongoing confusion and difficulty with his memory. The patient presented to the emergency department after experiencing symptoms of confusion and sustaining a head trauma secondary to a fall. The patient recalled that he had fallen and struck his head on a cupboard door. Computed tomography (CT) brain imaging revealed a right frontal lobe hemorrhagic contusion with small intracerebral hemorrhage (1.9 × 0.8 cm), left frontal and cerebellar contusions, and a tiny acute right subdural hemorrhage. Further investigations revealed that the patient was suffering from new onset focal seizures. To uncover the etiology of his seizures, the patient underwent a series of neurologic investigations over the course of 3 months. Through this period, he was on a medication regimen that included prednisone, lacosamide, and levetiracetam. He continued taking levothyroxine for known hypothyroidism and atorvastatin for hyperlipidemia.

Starting ∼ 1 month after his initial CT scan, the patient underwent MR imaging at four separate time points to assess and monitor structural changes in the brain (i.e., MRI 1 = ∼5 weeks post-hospitalization, MRI 2 = ∼6 weeks post-hospitalization, MRI 3 = ∼11 weeks post-hospitalization, MRI 4 = ∼55 weeks post-hospitalization). Initial MRI findings revealed increased signal intensity in the hippocampal formation bilaterally, as well as the uncus and amygdala bilaterally, greater on the right. One month later, he received a follow-up MRI which revealed that the hippocampus had decreased in size, suggesting the presence of edema attributable to neuroinflammation on the prior MRI. EEG findings demonstrated seizure activity.

While under the care of an attending neurologist, the patient underwent several diagnostic tests, including bloodwork, lumbar puncture, and clinical imaging (as aforementioned). The results from his lumbar puncture revealed that his cerebrospinal fluid was positive for LGI1 autoimmune encephalitis. In combination, the findings from his brain imaging, lumbar puncture, and clinical history (i.e., focal seizures) were used to make a definitive diagnosis of LGI1-LE. The final diagnosis was made by his attending neurologist. After receiving one course of cyclophosphamide—an immunotherapeutic agent used to treat LGI1-LE—the patient was admitted to an Acquired Brain Injury inpatient rehabilitation program. Seven months after being discharged from the hospital (∼10 months after receiving his last MRI), he received a follow-up MRI to assess structural brain changes. Findings from this MRI revealed persistent FLAIR signal abnormality in the bilateral hippocampi and frontal lobes, representative of gliosis.

In accordance with the clinical services offered by our Adult Neuropsychology Service, our patient first underwent a neuropsychological screening assessment, shortly after receiving immunotherapy to assess his post-treatment level of cognitive

functioning. Approximately 9 months later, the patient underwent a follow-up, more comprehensive neuropsychological assessment to generate a more comprehensive profile of his cognitive strengths and weaknesses for long-term treatment planning. The selection of tests in each assessment was based on the assessment's intended purpose (i.e., briefer measures used during the screening assessment) and with the aim of minimizing any practice effects. Standardized scores for performance on the Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998), California Verbal Learning Test-Revised (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000), Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997), Rey-Osterrieth Complex Figure Test (RCFT; Rey, 1941), Delis–Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001), Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 2011), Kaplan Baycrest Neurocognitive Assessment (KBNA; Leach, Kaplan, Rewilak, Richard, & Proulx, 2000), Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997a), Wisconsin Card Sorting Test (WCST; Berg, 1948), Wechsler Test of Adult Reading (WTAR; Wechsler, 2001), Test of Premorbid Cognitive Functioning (TOPF; Pearson, 2009), Controlled Oral Word Association Test (FAS/Animals; Benton, de Hamsher, & Sivan, 1983), Wechsler Memory Scale (WMS-III; Wechsler, 1997b; WMS-IV; Wechsler, 2009) are corrected for age and years of education.

Behavioural observations

Across both assessments, the patient's speech was fluent and coherent with no overt evidence of word-finding problems. He exhibited a flexible range of affect. Throughout the clinical interview, the patient demonstrated significant memory-related difficulties while answering questions. For instance, he was unable to recall whether he had been married, if he had any children, or his correct phone number. Vision and hearing were deemed adequate for testing. Across both assessments, the patient exhibited intact comprehension of verbal test instructions. During the initial screening assessment, the patient exhibited increased perseverations on tests of verbal memory and verbal fluency. These perseverative errors appeared to decrease at the time of reassessment. Despite reporting a general frustration with his memory difficulties, the patient did not exhibit any overt signs of frustration or emotional dysregulation across both assessments. There was also no overt evidence of marked psychiatric symptoms, such as psychosis.

Comparison to healthy controls

To evaluate LGI1-LE-associated neuroanatomical changes in the MTL, the patient's T1-weighted brain MRI scans were compared intraindividually and qualitatively to the T1-weighted brain MRI scans of $n = 12$ healthy age-matched controls (i.e., aged 60 years or older) obtained from Marrie et al.'s (2021) Comorbidity, Cognition and Multiple Sclerosis (C-COMS) study. One healthy control was excluded from the volumetric analysis due to a corrupted image file. At the time of their scans, the healthy controls were on average 67.9 (7.88) years old and had obtained 16.7 (3.15) years of education. Of the 12 healthy older adult controls, five were male and seven were female. Due to variability in clinical imaging across sites, MR scans for the patient were acquired using different sequences and scanning parameters. A full list of the scanning parameters, including field strength, matrix size, spatial resolution, repetition time, echo time, inversion time, and flip angle, can be found in the attached Appendix.

GM volume of the MTL and subfields of the hippocampus were estimated by running an automated volumetric analysis using the Computational Anatomy Toolbox (CAT12; www.neuro.uni-jena.de/cat/) for SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/). The Hammers Atlas (Hammers et al., 2003) was used to extract volumes for MTL structures and the CoBrA Atlas (Park et al., 2014) enabled us to additionally extract specific volumes of the hippocampal subfields (i.e., HCA1, subiculum, CA4/dentate gyrus, CA2/3, stratum radiatum/stratum lacunosum/ stratum moleculare) and extrahippocampal regions (i.e., fornix, fimbria, mammillary body, alveus).

A full list of the GM volumetric data extracted from the Hammers and CoBrA atlases for the patient's four MRI scans and 12 healthy controls baseline MRI scans can be found in Tables 2 and 3.

Results

Neuropsychological findings

Results from both neuropsychological assessments can be found in Table 1. At the time of his initial screening assessment, on tests of overall intellectual functioning and premorbid functioning, our case study performed within the average range for his age. Similarly, he performed within normal limits in the areas of passive attention, auditory working memory, information processing speed, visual construction, language (expressive vocabulary, phonemic fluency, and semantic fluency), and executive

functioning (inhibitory processing, alternating attention/mental set-shifting, non-verbal abstract reasoning, judgment in practical situations, and planning and organization).

Despite performing within normal limits on tasks involving attention, executive functioning, visuospatial ability, and language, our patient exhibited marked impairments in episodic memory. In general, his skills in encoding fell within normal limits for both verbal and visual information; however, he exhibited significant levels of forgetting after a delay and this was especially pronounced for verbal information. On a word-list learning test, his skills in delayed recall fell in the severely impaired for his age and cues at recognition provided no benefit (severely impaired for his age).

At follow-up, the patient was re-evaluated with a more comprehensive neuropsychological assessment. On tests of overall intellectual functioning and premorbid functioning, the patient again performed within the average range for his age. He also performed well within expectation in the areas of bilateral fine motor dexterity, passive attention, auditory working memory, information processing speed, language, visual construction, and executive functioning. His endorsement of mood and anxiety symptoms on the Hospital Anxiety Depression Scale (HADS; Zigmond & Snaith, 1983) fell within normal limits.

At follow-up, testing revealed that our patient continued to exhibit severe impairments in verbal episodic memory. Although performance related to encoding was generally preserved, his skills in delayed recall fell in the severely impaired range for his age. On tests of visual memory, our patient's skills in encoding, immediate recall, and delayed recall fell within normal limits. Discrimination on one test of visual recognition fell below expectation as he failed to endorse a significant number of target items. Overall, at follow-up, the patient continued to exhibit focal impairments in episodic memory with more pronounced deficits in memory for verbal versus visual information.

Our patient's focal deficits in memory are highly consistent with his diagnosis of LGI1-LE. It is unlikely that the patient's initial fall would have significantly contributed to his neuropsychological profile as his impairments were highly consistent with focal damage to the MTL, and this was supported by comprehensive MR imaging. The extent of injury arising from the patient's fall (e.g., small/tiny hemorrhage in frontal and cerebellar areas) would not be expected to produce such focal and pronounced deficits in episodic memory.

Structural MRI Volumetry

MTL (Hammers' atlas).

Intraindividual comparison. In general, our case exhibited a general trend of volumetric increase in areas of the MTL such as the right hippocampus and bilateral amygdala between MRI 1 and MRI 2, followed by a progressive decrease in volume between MRI 2 and MRI 4 (see Table 2). Other regions such as the para hippocampus and ambient gyrus exhibited no consistent differences over time, fluctuating between MRI 1 and MRI 4 (see Table 2).

Qualitative comparison to healthy controls. Compared with a reference group of healthy controls, our case study appeared to exhibit increased total cortical GM volume in the bilateral temporal lobes. More specifically, when examining our case study's MRI 2 volumetric findings, there appears to be enlargement of the bilateral hippocampus and bilateral amygdala as compared with the healthy controls (i.e., greater than one standard deviation above the mean). In contrast, volumetric findings from our case study's MRI 4 revealed marked reduction (i.e., greater than one standard deviation below the mean) in certain medial temporal areas such as the right hippocampus and left parahippocampus and ambient gyrus, as compared with healthy controls.

Hippocampal subfields (CoBrA atlas).

Intraindividual comparison. In general, between MRI 1 and MRI 2, the patient exhibited volumetric increases in the right hippocampal subfields (i.e., HCA1, CA2/CA3, CA4/dentate gyrus, subiculum, stratum radiatum/stratum lacunosum/stratum moleculare) which was then followed by progressive GM volumetric decrease between MRI 2 and MRI 4 (see Fig. 1A). Subregions within the left hippocampus did not show such an observable trend.

Qualitative comparison to healthy controls. Our case study had higher GM volumes (i.e., greater than one standard deviation above the mean) across right hippocampal subfields at MRI 2 as compared with healthy controls (see Fig. 1B). However, at MRI 4, our case study exhibited volume reductions (i.e., greater than one standard deviation below the mean), across the various subregions of the right hippocampus as compared with healthy controls (see Fig. 1C). Thus, when compared with healthy controls, findings from the patient's second and fourth MRI scan are representative of two distinct periods of volumetric change in the hippocampal formation: enlargement at MRI 2 and reduction at MRI 4.

Table 1. Neuropsychological test scores from baseline screening and 9-month follow-up

	Screening			Nine-month follow-up		
	Raw	Standard/Scaled/T Score	Percentile (%)	Raw	Standard/Scaled/T Score	Percentile (%)
Neuropsychological Test						
Memory						
HVLT-R						
Total Recall	20	T = 42	-	17	T = 37	-
Delayed Recall	0	T ≤ 20	-	0	T ≤ 20	-
Retention	0	T ≤ 20	-	0	T ≤ 20	-
Recognition Discrimination	−1	T ≤ 20	-	7	T = 31	-
RCFT						
Copy	33	-	>16	35	-	>16
Time	610	-	<1	155	-	>16
Immediate Recall	13.5	T = 47	38	11.5	T = 43	24
Delayed Recall	11.5	T = 43	24	12.5	T = 45	31
Recognition Total Correct	18	T = 38	12	18	T = 38	12
Recognition True Positive	10	-	>16	6	-	2–5
Recognition False Positive	3	-	6–10	0	-	>16
Recognition True Negative	9	-	6–10	12	-	>16
Recognition False Negative	2	-	>16	6	-	2–5
BVMT-R						
Trial 1	-	-	-	4	T = 45	31
Trial 2	-	-	-	5	T = 38	12
Trial 3	-	-	-	8	T = 47	38
Total	-	-	-	17	T = 43	24
Learning				4	T = 51	54
Delayed Recall				7	T = 46	34
Percent Retained	-	-	-	88	-	>16
Recognition Hit	-	-	-	6	-	>16
Recognition False	-	-	-	0	-	>16
Discrimination	-	-	-	6	-	>16
CVLT-II						
Short-Delayed Free Recall	-	-	-	33	T = 41	-
Short-Delayed Cued Recall	-	-	-	6	z = −0.5	-
Long-Delayed Free Recall	-	-	-	6	z = −1.5	-
Long-Delayed Cued Recall	-	-	-	6	z = −1	-
Total Recognition Discrimination	-	-	-	5	z = −2	-
WMS-IV Logical Memory						
Logical Memory I	-	-	-	26	ss = 11	63
Logical Memory II	-	-	-	4	ss = 2	0.4
Logical Memory II Recognition	-	-	-	24	26–50 cum. %	-
LM Immediate Recall versus Delayed Recall	-	-	-	−9	ss = 1	-
Orientation						
WMS-III Orientation	-	-	-	13/14	-	-
Effort/Performance Validity						
Reliable Digit Span	8	-	-	9	-	-
TOMM	-	-	-	Trial 1 = 50/50 Trial 2 = 50/50		
Global Cognitive Functioning						
WTAR	31	SS = 98	48	-	-	-
TOPF	-	-	-	37	SS = 97	42.1
WASI-II Full Scale IQ-2	102	SS = 102	55	210	SS = 105	70
WASI-II						
VCI	-	-	-	110	SS = 108	70
PRI	-	-	-	100	SS = 100	50
Attention						
WAIS-III						
Digit Span Forward-Longest Span	5	z = −1.03	16	-	-	-
Digit Span Backwards-Longest Span	3	z = −1.23	10	-	-	-
Digit Span Total	12	ss = 7	16	-	-	-

(*Continued*)

Table 1. Continued

	Screening			Nine-month follow-up		
	Raw	Standard/Scaled/T Score	Percentile (%)	Raw	Standard/Scaled/T Score	Percentile (%)
DSC	48	ss = 9	37	-	-	-
DSC Free Recall	0/18	1 cum. %	-	-	-	-
DSC Paired Recall	3/9	1–2 cum. %	-	-	-	-
WAIS-IV						
Digit Span Forward-Longest Span	-	-	-	5	z = −1.29	10
Digit Span Backwards-Longest Span	-	-	-	4	z = 0.58	28
Digit Span Sequencing-Longest Span	-	-	-	8	z = 2.22	99
Digit Span Total	-	-	-	26	ss = 12	75
Coding				58	ss = 11	63
Expressive Language						
WASI-II Vocabulary	36	T = 48	42	-	-	-
FAS Fluency	35	T = 50	50	-	-	-
Animals	13	T = 41	19	-	-	-
D-KEFS Verbal Fluency						
Letter Fluency	-	-	-	37	ss = 10	50
Category Fluency	-	-	-	35	ss = 10	50
Cat. Switching: Tot. Corr. Responses	-	-	-	11	ss = 8	37
Cat. Switching: Total Accuracy	-	-	-	11	ss = 10	50
Visual Ability						
CLOX-1 Free Draw	15/15	WNL	-	-	-	-
Rey-O Copy	33	-	>16%	35	-	>16%
Executive Functioning						
D-KEFS						
Color-Word Inhibition	91	ss = 6	9	53	ss = 13	84
Inhibition/Switching	108	ss = 6	9	55	ss = 13	84
Trails B	49	z = 0.43	66	56	z = 1.22	89
WASI-II Matrix Reasoning	18	T = 54	66	14	T = 45	32
KBNA Practical Problem Solving	10/10	-	-	-	-	-
WCST						
Categories Completed	-	-	-	6/6	-	>16%
Trials to Complete 1st Category	-	-	-	11	-	>16%
Failure to Maintain Set	-	-	-	2	-	11–16%
Learning to Learn	-	-	-	−1.52	-	>16%
Total Errors	-	-	-	13	T = 71	98
Motor Functioning						
Grooved Pegboard[a]						
Dominant (Right Hand)	-	-	-	68	z = 0.75	77
Non-Dominant (Left Hand)	-	-	-	85	z = 0.40	66
Mood Functioning						
HADS-Depression	-	-	-	2/21	-	-
HADS-Anxiety	-	-	-	1/21	-	-

Note. T = *t*-score; z = *z*-score; SS = standard score; ss = scaled score; WNL = within normal limits; HVLT-R = Hopkins Verbal Learning Test-Revised; RCFT = Rey-Osterrieth Complex Figure Test; BVMT-R = Brief Visuospatial Memory Test-Revised; CVLT-II = California Verbal Learning Test-Revised; D-KEFS = Delis-Kaplan Executive Function System; WASI-II = Wechsler Abbreviated Scale of Intelligence; VCI = Verbal Intelligence Index; PRI = Perceptual Reasoning Index; WMS-IV = Wechsler Memory Scale; KBNA = Kaplan Baycrest Neurocognitive Assessment; WAIS-III = Wechsler Adult Intelligence Scale; DSC = Digit Symbol Coding; WCST = Wisconsin Card Sorting Test; WTAR = Wechsler Test of Adult Reading; TOPF = Test of Premorbid Cognitive Functioning; WMS-III = Wechsler Memory Scale; TOMM = Test of Memory and Malingering; HADS = Hospital Anxiety and Depression Scale.
[a]Citation for Grooved Pegboard Test (Matthews & Klove, 1964) can be found in the reference list.

Discussion

In this case report, we presented the long-term neuropsychological and neuroanatomical outcomes of a 68-year-old right-handed male diagnosed with LGI1-LE. Neuropsychological test findings revealed focal impairments in verbal episodic memory (verbal delayed recall, retention, and recognition) with little no evidence of improvement 9 months later. At both of his assessments, our patient denied feelings of depression or hopelessness and he did not endorse any thoughts of suicide and/or self-harm. His scores on a self-administered measure of depression and anxiety fell within normal limits, indicating that his

Table 2. Volumetric data of LGI1-LE case report and C-COMS healthy controls (Hammers Atlas)

	LGI1-LE Patient				C-COMS Healthy Controls ($n = 12$)	
	~5-weeks PH GM (cm³)	~6-weeks PH GM (cm³)	~11-weeks PH GM (cm³)	~55-weeks PH GM (cm³)	Baseline GM (cm³)	SEM GM (cm³)
Hammers Atlas[a] Brain Regions						
Left Amygdala	**1.66**	**1.74**	**1.74**	**1.47**	**1.49 (0.154)**	**0.043**
Right Amygdala	**1.63**	**2.21**	**2.10**	**1.81**	**1.62 (0.166)**	**0.046**
Left Anterior Lateral Temporal Lobe	6.93	7.63	7.10	7.58	4.74 (0.499)	0.138
Right Anterior Lateral Temporal Lobe	6.23	6.90	7.01	6.82	4.74 (0.499)	0.138
Left Anterior MTL	4.38	5.34	5.38	4.97	4.76 (0.626)	0.174
Right Anterior MTL	5.91	5.81	5.60	5.45	4.70 (0.515)	0.143
Left Fusiform Gyrus	2.71	3.06	3.15	2.80	2.85 (0.400)	0.111
Right Fusiform Gyrus	3.39	3.29	3.08	3.04	2.81 (0.337)	0.094
Left Hippocampus	**2.39**	**2.37**	**1.73**	**1.65**	**1.84 (0.195)**	**0.054**
Right Hippocampus	**2.36**	**2.56**	**2.00**	**1.42**	**1.91 (0.255)**	**0.071**
Left Medial & Inferior Temporal Gyrus	10.59	10.73	10.76	10.18	7.99 (0.913)	0.253
Right Medial & Inferior Temporal Gyrus	12.72	12.71	12.18	12.44	8.02 (1.061)	0.294
Left Parahippocampus & Ambient Gyrus	3.11	3.81	3.33	3.35	4.70 (0.515)	0.143
Right Parahippocampus & Ambient Gyrus	3.76	3.34	3.00	3.21	3.41 (0.426)	0.118
Left Posterior Temporal Lobe	26.99	28.80	27.14	28.92	21.96 (2.517)	0.698
Right Posterior Temporal Lobe	29.82	30.26	28.71	30.79	21.57 (2.588)	0.718
Left Superior Temporal Gyrus	9.19	9.69	9.33	9.93	6.08 (0.808)	0.224
Right Superior Temporal Gyrus	7.71	7.96	7.71	8.54	6.36 (1.004)	0.279
Total Temporal Lobe	141.47	148.22	141.03	144.39	111.54 (11.586)	3.213

Note. LGI1-LE = leucine-rich glioma-inactivated 1 limbic encephalitis; CCOMS = comorbidity, cognition and multiple sclerosis; PH = post-hospitalization; GM = grey matter; SEM = standard error of the mean. Values within the parentheses denote standard deviation. Bolded values represent regions that demonstrate distinct volumetric course.

[a]Citation for Hammers atlas can be found in reference list.

mood remained stable at reassessment, despite experiencing continued memory difficulties. Structural neuroimaging findings revealed a general trend of an initial volumetric increase in the MTL followed by a period of volumetric decrease. This same trend was observed when examining subregional volumes of the right hippocampus.

Although other studies have documented improved cognitive performance after receiving immunotherapy (Ariño et al., 2016; Qiao et al., 2021; Zangrandi et al., 2019), our case exhibited no discernable improvements in episodic memory over time. This is consistent with literature demonstrating that amongst the group of LGI1-LE patients who do not experience favorable outcomes, persistent memory impairments (van Sonderen et al., 2016) and amnesia (Li et al., 2018) are among the most frequently experienced residual symptoms at follow-up. There are several factors that may influence whether cognitive recovery occurs and the long-term prognosis of LGI1-LE including responsivity to first-line and second-line immunotherapy (Ariño et al., 2016), antibody titre at screening (Butler et al., 2014), and time between symptom onset and treatment (Titulaer et al., 2013). According to our patient's medical records, it took ~ 3 months from his initial symptom onset to make a definitive diagnosis of LGI1-LE. Thus, the amount of time spent between the patient's symptom onset (i.e., recurrent focal seizures) and targeted intervention (derived from appropriate diagnosis) may have adversely affected his long-term outcomes (Titulaer et al., 2013).

Distinctly, our case did not experience any co-occurring neurobehavioral/psychiatric symptoms and/or cognitive deficits in domains other than memory; rather, he exhibited focal, severe impairments in verbal episodic memory. Thus, the patient's longitudinal neuropsychological profile indicates damage to specific memory-dependent structures and existing networks in the brain's limbic system. LGI1-LE-associated memory deficits may be the results of localized neuroinflammation and subsequent atrophy to limbic regions often associated with memory ability, such as the dentate gyrus and CA hippocampal subfields (Travis et al., 2014). Intraindividual analysis of our brain imaging data revealed a pattern of acute GM volume enlargement, followed by chronic GM volume reduction of our patient's MTL including hippocampal subregions. Volumetric findings from our patient's fourth MRI revealed marked GM volume reduction in some left hippocampal subfields (CA4/dentate gyrus) and several right hippocampal subfields: HCA1, CA2/CA3, CA4/dentate gyrus, subiculum, stratum radiatum, stratum lacunosum, stratum moleculare, when compared with healthy controls. Amongst these subregions, the greatest GM volume reduction appeared to be in the CA4/dentate gyrus and CA1. Focal atrophy to the dentate gyrus may be due to the greater expression of the LGI1 transcript observed within the dentate gyrus (Herranz-Pérez, Olucha-Bordonau, Morante-Redolat, & Pérez-Tur, 2010).

In addition to subfield specificity, findings from our study suggest that LGI1-LE-associated damage to the hippocampus may be more severe in one hemisphere over the other. Across time, the patient exhibited greater GM volumetric reduction in the right versus the left hippocampus (see Fig. 1D–F). Some researchers have suggested that the observed hemispheric specificity

Table 3. Volumetric Data of LGI1- LE Case Report and C-COMS Healthy Controls (CoBrA Atlas)

	LGI1-LE Patient				C-COMS Healthy Controls ($n = 12$)	
	~5-weeks PH	~6-weeks PH	~11-weeks PH	~55-weeks PH	Baseline	SEM
CoBrA Atlas[a] Brain Regions	GM (cm^3)	GM (cm^3)	GM (cm^3)	GM (cm^3)	GM (cm^3)	GM (cm^3)
Left Hemisphere						
Striatum	5.62	6.10	5.38	6.25	6.22 (0.992)	0.275
Globus Pallidus	0.33	0.41	0.31	0.50	0.21 (0.117)	0.032
Thalamus	**4.41**	**5.05**	**4.26**	**4.11**	**3.39 (0.573)**	**0.159**
Amygdala	**1.57**	**1.70**	**1.65**	**1.39**	**1.38 (0.174)**	**0.048**
HCA1	**1.27**	**1.25**	**0.83**	**0.91**	**0.93 (0.153)**	**0.042**
Subiculum	**0.64**	**0.61**	**0.44**	**0.45**	**0.49 (0.067)**	**0.019**
Fornix	**0.32**	**0.30**	**0.21**	**0.36**	**0.21 (0.065)**	**0.018**
CA4/Dentate Gyrus	**0.75**	**0.80**	**0.50**	**0.51**	**0.60 (0.097)**	**0.027**
CA2/3	**0.28**	**0.25**	**0.14**	**0.14**	**0.17 (0.047)**	**0.013**
Stratum Radiatum/Stratum Lacunosum/ Stratum Moleculare	0.65	0.62	0.40	0.41	0.46 (0.069)	0.019
Fimbria	0.24	0.11	0.09	0.07	0.08 (0.024)	0.007
Mammillary Body	0.05	0.07	0.04	0.05	0.03 (0.992)	0.004
Alveus	0.55	0.43	0.29	0.23	0.31 (0.117)	0.030
Right Hemisphere						
Striatum	6.02	6.33	5.84	6.31	6.29 (0.016)	0.276
Globus Pallidus	0.29	0.32	0.24	0.52	0.16 (0.107)	0.031
Thalamus	**5.84**	**5.78**	**5.59**	**5.70**	**4.13 (0.994)**	**0.205**
Amygdala	**1.48**	**2.01**	**1.81**	**1.60**	**1.40 (0.069)**	**0.053**
HCA1	**1.23**	**1.33**	**0.99**	**0.78**	**0.98 (0.126)**	**0.045**
Subiculum	**0.60**	**0.67**	**0.48**	**0.41**	**0.47 (0.191)**	**0.022**
Fornix	**0.60**	**0.42**	**0.39**	**0.58**	**0.24 (0.162)**	**0.016**
CA4/Dentate Gyrus	**0.71**	**0.81**	**0.59**	**0.35**	**0.58 (0.080)**	**0.030**
CA2/3	**0.28**	**0.27**	**0.19**	**0.14**	**0.20 (0.056)**	**0.012**
Stratum Radiatum/Stratum Lacunosum/ Stratum Moleculare	0.63	0.64	0.46	0.32	0.45 (0.110)	0.022
Fimbria	0.17	0.11	0.08	0.04	0.08 (0.045)	0.006
Mammillary Body	0.05	0.03	0.07	0.05	0.03 (0.079)	0.005
Alveus	0.53	0.51	0.37	0.28	0.35 (0.022)	0.026

Note. LGI1-LE = leucine-rich glioma-inactivated 1 limbic encephalitis; CCOMS = comorbidity, cognition and multiple sclerosis; PH = post-hospitalization; GM = grey matter; SEM = standard error of the mean; CA = cornu ammonis. Values within parentheses denote standard deviation.
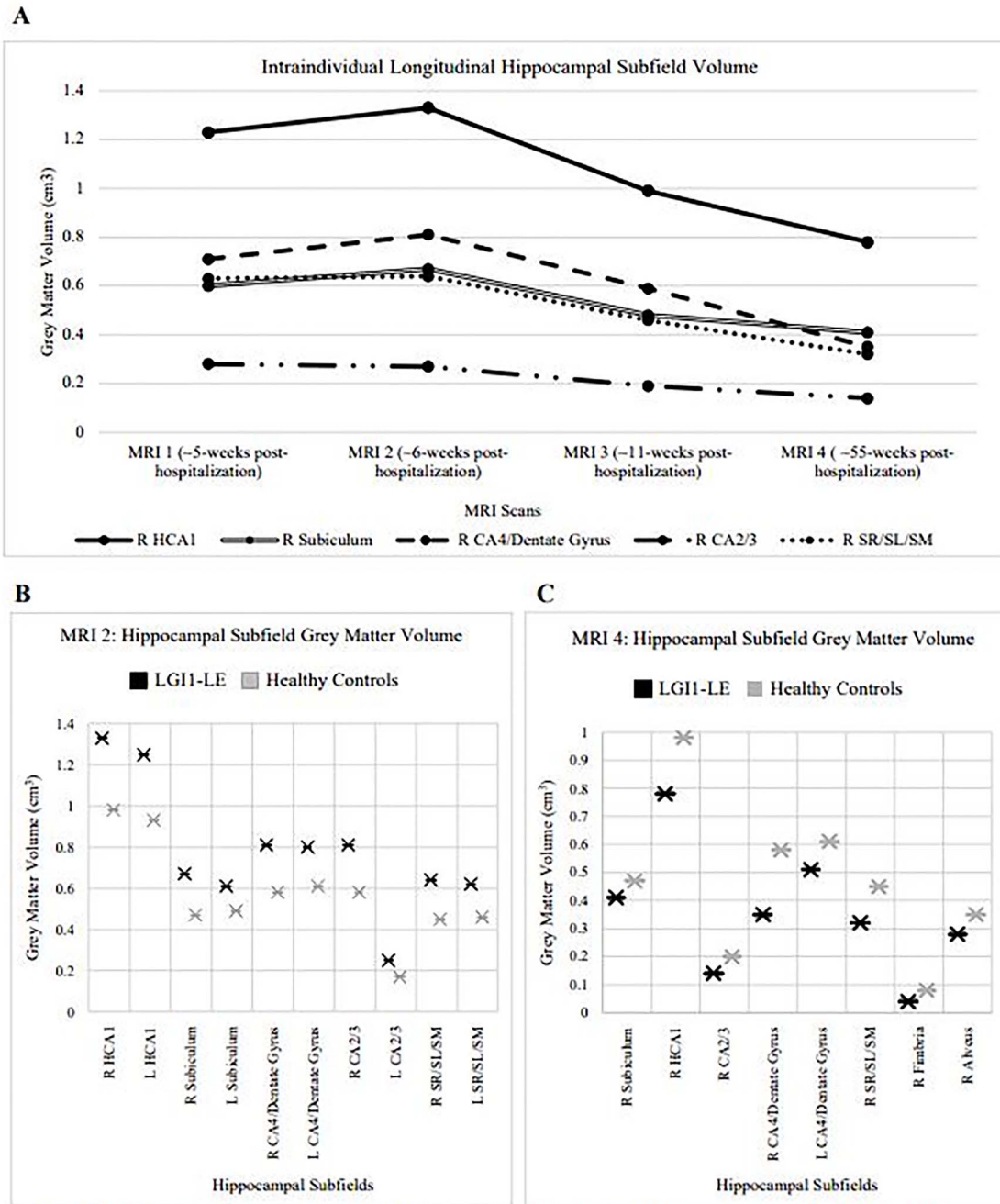
[a]Citation for CoBrA Atlas can be found in reference list. Bolded values represent regions that demonstrate distinct volumetric course.

of LGI1-LE-associated hippocampal damage may be due to the asymmetric expression of the LGI1 gene in the hippocampus (Jang et al., 2018). Interestingly, researchers have found that lateralized damage to the hippocampus, is more common in the left versus right hemisphere (Jang et al., 2018; Wang et al., 2017). Although our patient's right hippocampus exhibited greater volumetric change over time (i.e., between MRI 1 and 4), his neuropsychological findings nonetheless suggest that sufficient damage was inflicted by the left hippocampus given his pronounced deficits in verbal memory. Our case study suggests that LGI1-LE-associated damage to the hippocampus may be asymmetric (i.e., greater damage to one hemisphere compared with the other) and more severe in some subfields (e.g., CA subfields, dentate gyrus) than others (e.g., subiculum).

To date, few researchers have examined the longitudinal MRI outcomes of LGI1-LE from initial disease onset to subsequent recovery. Wagner, Weber, and Elger (2015) compared the volumetric findings between a group of patients with "early" (<2 years after the disease onset) and "late" (greater than 2 years after the disease onset) VGKC-LE. They found that "early" VGKC-LE patients exhibited whole hippocampal GM volume enlargement, whereas "late" VGKC-LE patients exhibited whole hippocampal GM volume reduction. Indeed, our case study demonstrated a similar trend with an increase in hippocampal GM volume between MRI 1 and MRI 2 (~10 days), followed by a progressive decrease in hippocampal GM volume between MRI 2 and MRI 4 (~11 months). This distinct volumetric course may be due to the onset of specific cellular processes associated with the subacute and convalescent phase of LGI1-LE (i.e., cellular swelling followed by acute cell death; Bien et al., 2012; Wagner et al., 2014).
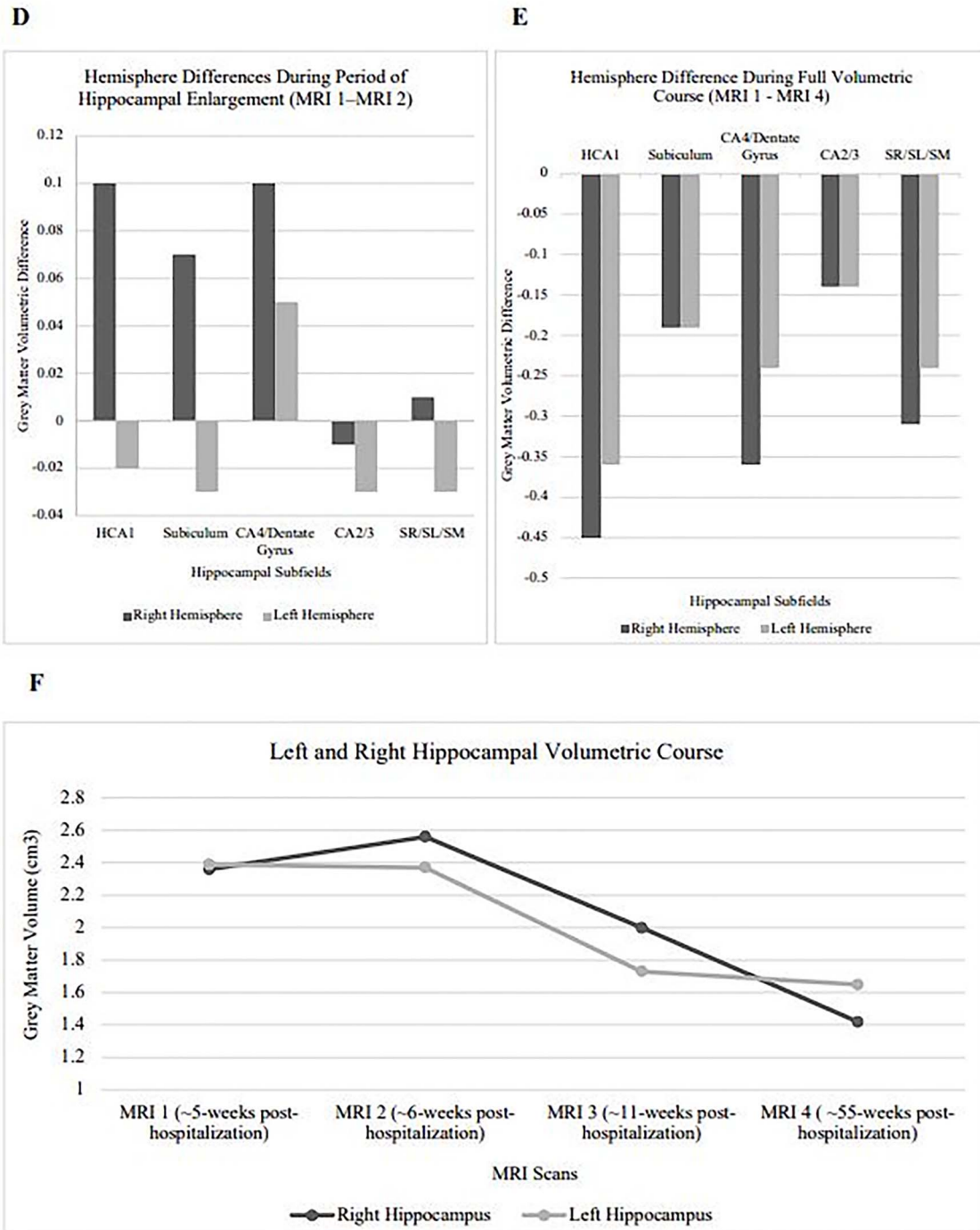
More specifically, volumetric enlargement observed during the subacute phase of LE may be due to parenchymal swelling triggered by the release and breakdown of chemicals during the body's initial inflammatory response (Wagner et al., 2014). Hippocampal atrophy observed in cases of chronic LE (Irani et al., 2013) may be due to acute cell death triggered by the body's

LGI1-LE Hippocampal Subfield Volumetry

Fig. 1. Line graph (A) represents the patient's intraindividual changes in hippocampal subregions over the course of 11 months. Plots (B) and (C) represent the differences in hippocampal subregions volume between the patient and healthy age-matched controls, at MRI 2 and MRI 3, respectively. Bar graphs (D) represent the hemispheric differences in volumetric changes of hippocampal subregions between MRI 1 and MRI 2 (period of volumetric enlargement). Bar graphs (E) represent the hemispheric differences in volumetric changes of hippocampal subregions between MRI 1 and MRI 4 (full volumetric course). Line graph (F) illustrates the differences in the volumetric course of the patient's left and right hippocampus. R = Right, L = Left, SR = stratum radiatum, SL = stratum lacunosum, SM = stratum moleculare.

D Hemisphere Differences During Period of Hippocampal Enlargement (MRI 1–MRI 2)

E Hemisphere Difference During Full Volumetric Course (MRI 1 - MRI 4)

F Left and Right Hippocampal Volumetric Course

Note. R= Right, L = Left, SR = Stratum Radiatum, SL = Stratum Lacunosum, SM = Stratum Moleculare

Fig. 1. Continued

antibody-mediated and complement-mediated immune responses (Bien et al., 2012). Together, these post-inflammatory immune responses may explain the progressive GM volume loss observed in our patient between MRI 2 and MRI 4.

When considering our results, it is important to examine the possible impact of the patient's head trauma secondary to his fall, on his diagnosis of LGI1-LE, as well as his observed volumetric course. Although it is possible that the patient's presenting

concerns at the emergency department—symptoms of confusion and fall—provided an opportunity to uncover his underlying LGI1-LE, it is unlikely that the head trauma itself would have triggered the autoimmune response underlying his disease course, as he was experiencing symptoms of confusion and problems with his memory, hallmarks of the LE pathology, in the months leading up to his presentation at the emergency department, suggesting that LGI1-LE pathology preceded his head trauma. It is, however, unknown whether the patient's intracranial bleeding brought on by his traumatic brain injury triggered a cellular repair response leading to a widespread autoimmune inflammatory reaction in the brain, contributing to the volumetric enlargement we observed between MRI 1 and MRI 2.

Strengths and limitations

Inclusion of an age-matched healthy control group was a notable strength of our study, as it allowed us to make meaningful volumetric comparisons between our case study and healthy age-matched peers. A second strength of this study is its use of multiple time points for both neuropsychological and MRI data. Through this we were able to conceptualize the patient's cognitive outcomes as well as hippocampal structural integrity throughout the entire disease process (e.g., subacute onset, chronic phase, and convalescent phase). Findings from our case study are certainly limited in generalizability, as we solely reported on the neuropsychological and volumetric course of one patient with LGI1-LE. In addition, intraindividual comparisons of the patient's MRI scans are somewhat compromised as scans were accrued during the patient's clinical work-up and included differing imaging/scanning parameters. Furthermore, as part of this study, we did not include the patient's full immunological and inflammatory profile. Inclusion of inflammatory and immunological data could have helped us better understand the pathogenic mechanisms underlying the patient's full volumetric course.

Conclusions & Implications

In this study, we presented the long-term neuropsychological and neuroanatomical outcomes of a case diagnosed with LGI1-LE—a rare autoimmune condition commonly associated with limbic dysfunction and memory impairment. Across time, our case exhibited focal impairments in episodic memory (more pronounced for verbal than visual information), that did not improve after receiving immunotherapy. Findings from his routine MRI scans revealed GM volumetric enlargement in the bilateral hippocampal subfields during the subacute phase of the disease, shortly followed by GM volumetric reduction during the convalescent phase of the disease. Future studies should include patients' neuroinflammatory profiles as well as recruit a larger sample size to either validate or refute the long-term neuropsychological and neuroanatomical findings presented in this study. As our understanding of LGI1-LE improves, clinicians will be able to utilize neuropsychological testing and structural MRI to help diagnose this condition early in the disease process, reducing the time between disease onset and treatment. Lessening this timeframe could improve patients' both short-term clinical outcomes and long-term prognosis.

Conflicts of Interest

We have no known conflicts of interest to disclose.

Appendix

Imaging parameters associated with each MRI timepoint

	MRI 1	MRI 2	MRI 3	MRI 4
Sequence type	COR T1 MPRAGE iPAT	COR MPRAGE	COR T1 MPRAGE iPAT	COR 3D T1 Flash (Post-Contrast)
Field strength/type of scanner/software version	1.5 T Siemens Avanto Syngo B17	1.5 T Siemens Aera Syngo E11	1.5 T Siemens Avanto Syngo B17	3 T Siemens Verio Syngo B19
Matrix size	$256 \times 192 \times 256$	$256 \times 192 \times 256$	$256 \times 160 \times 256$	$256 \times 160 \times 256$
Spatial resolution	$.98 \times 1.0 \times .98$	$.98 \times 1.0 \times .98$	$.98 \times 1.1 \times .98$	$.98 \times 1.0 \times .98$
Repetition time (ms)	1,560	2,200	1,560	15
Echo time (ms)	2.96	2.67	2.96	5.27
Inversion time (ms)	800	900	800	n/a
Flip angle (degrees)	15	8	15	25

Note. ms = milliseconds; COR = coronal slice; MP RAGE = magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo; iPAT = parallel imaging sequence.

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