Distinctive MRI characteristics of LGI1- and CASPR2-antibody encephalitis: independent discovery and validation cohorts

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Key Points

Question: Can MRI features help distinguish LGI1- and CASPR2-antibody encephalitis from other key differentials such as viral encephalitis and Creutzfeldt-Jakob Disease?

Findings: In this retrospective, cross-sectional, case-control study with independent external cohort validation, we identify confinement of T2/FLAIR-hyperintensities to the temporal lobe, without diffusion restriction or contrast enhancement, robustly distinguish LGI1- and CASPR2-antibody encephalitis from key differential diagnoses.

Meaning: These simple MRI features should be utilised within the routine diagnostic process, to help expedite diagnosis and treatment of autoimmune encephalitis.

Abstract

Importance: The rapid and accurate diagnosis of autoimmune encephalitis (AE) encourages prompt immunotherapy initiation, towards improved patient outcomes. However, clinical features and routine investigations may not substantially narrow the differential diagnosis. Also, awaiting autoantibody results can delay immunotherapy administration.

Objective: To identify simple MRI characteristics which accurately distinguish patients with two common forms of AE, LGI1- and CASPR2-antibody encephalitis (LGI1/CASPR2-Ab-E), from two major differential diagnoses, viral encephalitis (VE) and Creutzfeldt-Jakob disease (CJD).

Design: In this retrospective, cross-sectional, blinded analysis, the first available brain MRI from 192 patients with LGI1/CASPR2-Ab-E, VE or CJD were evaluated by two neuroradiologists (discovery cohort; n=87) and validated in an independent cohort by three neurologists (n=105). Groups were statistically compared with contingency tables.

Setting: Two tertiary referral centres: Oxford University Hospitals, UK, and Mayo Clinic, USA.

Participants: 192 participants with available brain imaging and autoantibodies against LGI1 (n=84), CASPR2 (n=26), LGI1 and CASPR2 (n=4), VE (n=32) or CJD (n=46).

Main Outcome(s) and Measure(s): Frequencies of MRI features including T2/Fluid attenuated inversion recovery (FLAIR)-hyperintensities in pre-defined brain regions, swelling or volume loss, presence of gadolinium contrast-enhancement, diffusion-weighted imaging (DWI) changes, haemorrhage, and T1 hyperintensities in the basal ganglia. Correlations with clinical features.

Results: In LGI1/CASPR2-Ab-E, T2/FLAIR-hyperintensities were both less likely to extend outside the temporal lobe (7% vs 94% in VE; P<0.001 and 75% in CJD; P<0.01) and to exhibit swelling (22% of LGI1/CASPR2-Ab-E vs 59% of VE; P<0.001). In LGI1/CASPR2-Ab-E, no diffusion restriction was observed (0%, vs 73% in VE and 80% in CJD; both P<0.001) and contrast-enhancement was rare (5% vs 41% in VE, P=0.013). Findings were similar in the validation cohort, together resulting in an area under the curve of 0.97, sensitivity of 90%

and specificity 95% amongst cases with T2/FLAIR-hyperintensity in the hippocampus and/or amygdala.

Conclusions and Relevance: T2/FLAIR-hyperintensities confined to the medial temporal lobes, without diffusion restriction or contrast-enhancement, are features which robustly distinguish LGI1/CASPR2-Ab-E from key tested differential diagnoses. These straightforward findings from readily available imaging modalities should support rapid clinical decision making towards more expeditious administration of immunotherapies in AE in routine neurology practice.

Data sharing statement

Anonymised data from this study may be shared upon reasonable request from a qualified investigator.

Conflict of interest

SRI has received honoraria/research support from UCB, Immunovant, MedImmun, Roche, Janssen, Cerebral therapeutics, ADC therapeutics, Brain, CSL Behring, and ONO Pharma and receives licensed royalties on patent application WO/2010/046716 entitled 'Neurological Autoimmune Disorder', and has filed two other patents entitled "Diagnostic method and therapy" (WO2019211633 and US-2021-0071249-A1; PCT application WO202189788A1) and "Biomarkers" (PCT/GB2022/050614 and WO202189788A1).

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Introduction

Leucine-rich glioma inactivated protein 1 (LGI1)- and contactin-associated protein-like 2 (CASPR2)-antibody encephalitis (LGI1/CASPR2-Ab-E) are two common forms of autoimmune encephalitis (AE), characterised by the acute-to-subacute onset of cognitive impairment, behavioural disturbance and seizures.[1] They can be difficult to distinguish from other causes of encephalopathies or rapidly progressive dementias, such as viral encephalitis (VE) and Creutzfeldt-Jakob Disease (CJD).[2] Delays to immunotherapy administration in patients with AE result in poorer outcomes.[3] Further, autoantibody test results can take several weeks to return. Hence, there is clear practical value in rapidly accessible investigations to assist early diagnosis. Here, we investigate magnetic resonance imaging (MRI)-brain findings to differentiate LGI1/CASPR2-Ab-E from VE and CJD.

Methods

Discovery cohort

Participants

55 people diagnosed with LGI1- or CASPR2-Ab-E, and with locally downloaded MRIs, were identified from existing Oxford Autoimmune Neurology Group cohorts.[3,4] Retrospective data were collected from medical records and research databases, with ethically approved informed consent (Oxfordshire RECA07/Q1604/28 and REC16/YH/0013). 32 people diagnosed with VE or CJD at Oxford University Hospitals between January 2010 and December 2020 were identified from microbiology department and hospital records, respectively (OUH approval #6660).

MRI analysis

Two neuroradiologists, blinded to diagnoses, reviewed participants' earliest available MRIs and reached consensus opinion on features including presence of:

- T2/Fluid attenuated inversion recovery (FLAIR)-hyperintensity in pre-defined brain regions
- Swelling or volume-loss of hippocampus and/or amygdala

- Gadolinium contrast-enhancement
- Diffusion-weighted imaging (DWI) changes
- Haemorrhages
- T1-hyperintensities in the basal ganglia[5]

Analyses

Incidental findings unrelated to diagnosis were excluded from analyses. Statistics were performed using SPSS (v29, IBM) and Prism (v9.4.1, Graphpad). Tables and figures were created using Microsoft Excel (v16.72), Prism and Biorender.com. Chi-square, Mann-Whitney and Fisher exact tests were performed to compare proportional differences between groups (LGI1/CASPR2-Ab-E, VE, CJD), and to identify associations between T2/FLAIR-hyperintensity distribution and clinical features of LGI1/CASPR2-Ab-E. Potentially significant features ($p<0.1$) were entered into stepwise backward logistic regression analyses and receiver operating characteristics (ROC) generated for key findings, excluding missing data.

Validation cohort

The same analyses were performed from MRIs of 105 patients, recruited from Mayo Clinic, USA. MRI interpretation was performed by three blinded neurologists, to assess 'real-world' relevance.

Results

The discovery cohort included 55 participants with LGI1/CASPR2-Ab-E (42 LGI1-antibodies, 9 CASPR2-antibodies, 4 LGI1- and CASPR2-antibodies), 22 with VE (herpes simplex virus 1 (n=18), human herpes virus 6 (n=4)) and 10 with CJD. Supplemental **eTables 1 and 2** summarise their clinical details. 38/51 (75%) LGI1/CASPR2-Ab-E cases were imaged within six weeks of commencing immunotherapy (before or after).

Regional T2/FLAIR-hyperintensities

Between 80-91% of the three groups showed MRI abnormalities (LGI1/CASPR2-Ab-E; 44/55. VE; 20/22. CJD; 9/10. **Figures 1, 2A**), more common in LGI1-Ab-E than CASPR2-Ab-E (38/42, 90% vs 4/9, vs 44%; p=0.005. **Figure 2a inset).** T2/FLAIR-hyperintensities were seen in 42/44 (95%) abnormal scans with LGI1/CASPR2-Ab-E, 19/20 (95%) with VE, and only 5/9 (56%) with CJD (**Figure 2B;** p=0.005 and 0.022). These almost universally involved the temporal lobes in LGI1/CASPR2-Ab-E (42/42; 100%) and VE (19/20; 95%) but was confined to the hippocampus/amygdala in all but 8/42 (19%) with LGI1/CASPR2-Ab-E, with occasional involvement of entorhinal cortex (n=6), insula (n=3), parahippocampal gyrus (n=2), piriform gyrus, temporal pole and precuneus (each n=1). By contrast, this confinement was observed in just 1/18 (6%) with VE (p<0.001) and 1/4 (25%; p=0.037) with CJD (**Figure 2C**). Extension beyond the temporal lobe (i.e. insula, cingulate gyrus, frontal lobe, basal ganglia) was even rarer in LGI1/CASPR2-Ab-E (3/42, 7%) versus VE (17/18, 94%; p<0.001) and CJD (3/4, 75%; p=0.005)(**Figure 2D**). No differences were observed in laterality of T2/FLAIR hyperintensities (**Figure 2E**).

Hippocampus/amygdala swelling was more common in VE (13/22; 59%) than LGI1/CASPR2-Ab-E (12/55; 22%; p=0.003) or CJD (0/10; p=0.002) **Figure 2F**). Loss of hippocampus/amygdala volume was not different across 9/55 (16%) LGI1/CASPR2-Ab-E, 3/22 VE (14%) and 1/10 CJD (10%) cases (LGI1/CASPR2-Ab-E vs VE; p=1.0. LGI1/CASPR2-Ab-E vs CJD; p=0.7).

Neither T2/FLAIR nor pre-contrast T1-hyperintensities were seen in the basal ganglia (BG) in LGI1/CASPR2-Ab-E cases. Both were seen in 1/22 (5%) in separate VE cases. Haemorrhage within T2/FLAIR-hyperintense regions occurred in 4/22 (18%) VE, compared to 0/54 LGI1/CASPR2-Ab-E (p=0.006) and 0/9 CJD cases (p=0.07).

Diffusion restriction and contrast enhancement

Strikingly, diffusion restriction with apparent diffusion coefficient (ADC) hypointensities were seen in 16/22 (73%) with VE and 8/10 (80%) with CJD but in 0/50 with LGI1/CASPR2-Ab-E (p<0.001; **Figures 1, 2G**). Furthermore, when performed, contrast-enhancement was observed in only 1/20 (5%) of LGI1/CASPR2-Ab-E cases versus 7/17 (41%) with VE (p=0.014; **Figures 1, 2H**) and 0/2 CJD (p=1.0).

Clinical associations

In LGI1/CASPR2-Ab-E, only seizures were associated with T2/FLAIR-hyperintensities in the hippocampus and hippocampus/amygdala-junction (p=0.022 and p=0.035, respectively). The former remained significantly associated after multivariable regression (OR 12.7; 95%CI 1.3-124.5. P=0.03, **Figure 2I and eFigure 1, Supplement**).

Validation cohort

To validate the radiological findings, three neurologists independently reviewed 105 MRIs blinded to diagnoses of LGI1/CASPR2-Ab-E (n=59), VE (n=10, including HHV1/2, Varicella and West-Nile virus encephalitis) and CJD (n=36; **eTable 4**). Trends were overall similar **(eFigure 2)**, although by comparison to the discovery cohort, those with LGI1/CASPR2-Ab-E showed fewer overall MRI abnormalities and T2/FLAIR-hyperintensities (44/55, 80% vs 27/59 46% and 42/44, 95% vs 16/27 59%; both p<0.001) which more often extended outside of the hippocampus/amygdala (8/42 19% vs 12/15 80%; p<0.001). Yet, extratemporal extension was again rare (3/42, 7%) in LGI1/CASPR2-AB-E compared to VE (6/6, 100%). Diffusion restriction was observed in 0/57 (p=0.002 vs VE, p<0.001 vs CJD) and contrast enhancement in just 1/40 (p=0.003 vs AE, p=1.0 vs CJD).

Median time from onset was seven weeks in the LGI1/CASPR2 validation cohort, with no significant differences in other demographic variables when compared to the discovery cohort (**eTable 4**).

Combined predictive values

Finally, two sets of ROC curves incorporated diffusion restriction, contrast enhancement and extratemporal T2/FLAIR-hyperintensities amongst across both cohorts, amongst cases with T2/FLAIR-hyperintensities of the hippocampus/amygdala (**Figure 3A).** The absence of these three factors identified LGI1- and CASPR2-Ab-E with a sensitivity of 90% and specificity of 95%. The same analysis can also performed including all cases (including with normal scans), returning and sensitivity of 93% and specificity of 81% (**eFigure 3**).

Discussion

This study identifies several simply ascertained MRI features which accurately differentiate LGI1/CASPR2-Ab-E from two key differentials.[2,6] Compared to VE and CJD, T2/FLAIR-hyperintensities in LGI1/CASPR2-Ab-E are typically confined to the temporal lobe, without diffusion restriction and only rare contrast-enhancement. These widely accessible MRI sequences should have clear diagnostic utility in the appropriate clinical context, and expedite appropriate immunotherapy administration to patients with these conditions.

Our most frequently observed MRI abnormality was T2/FLAIR-hyperintensities within the hippocampus/amygdala, present in 77% of LGI1/CASPR2-Ab-E cases.[7-9] Importantly, extra-temporal extension of T2/FLAIR-hyperintensities was rare in AE but almost universal in VE. Therefore, the precise distribution of T2/FLAIR-hyperintensities present an opportunity to differentiate LGI1/CASPR2-Ab-E from key differentials. In addition, we identified two other sensitive and highly-specific radiological findings in LGI1/CASPR2-Ab-E: absence of either diffusion restriction or contrast-enhancement. These observations offer fundamental biological insights, suggesting inflammation in LGI1/CASPR2-Ab-E is associated with limited cytotoxic oedema and blood-brain barrier opening. However, outside of this study, we have observed very rare cases with diffusion restriction and contrast-enhancement, often in the hyperacute phase of disease. These observations might be secondary to frequent focal seizures,[10] the only clinical feature we found to associate with hippocampal T2/FLAIR-hyperintensities.

Our findings help contextualise previous studies. An early report suggested diffusion restriction and contrast-enhancement were common in VGKC-antibody-encephalitis,[11] likely relating to the inclusion of patients with clinically-irrelevant VGKC-antibodies without confirmed LGI1/CASPR2-reactivities.[12] Also, we did not observe the T1-hyperintensities reported to specifically associate with faciobrachial dystonic seizures in two previous studies.[5,13] Our findings are more consistent with recent studies[13-15]. In particular, a recent study of all forms of AE identified diffusion restriction, contrast enhancement and extralimbic MRI changes to be predictive of AE-mimics in combination, but not in isolation[15].

Limitations of this study include absence of longitudinal imaging and use of heterogenous imaging protocols employed across hospitals, although this accurately reflects real-world practice. Variable timing of MRIs suggest our data may miss some transient findings.

Nevertheless, 75% of MRIs were performed within six weeks of immunotherapy commencement, in an illness that often takes months, sometimes years to diagnose. Further, we only focused on LGI1/CASPR2-Ab-E, meaning future studies should translate these observations to other forms of AE.

In summary, our study highlights precise anatomical involvement alongside diffusion restriction and contrast-enhancement as imaging findings which, alongside clinical assessment, can help expedite immunotherapy-initiation in LGI1/CASPR2-Ab-E.

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