JAMA Neurology | Original Investigation

Magnetic Resonance Imaging Characteristics of LGI1-Antibody and CASPR2-Antibody Encephalitis

Mark J. Kelly, MBBCh BAO, MSc; Eleanor Grant, DPhil; Andrew G. Murchison, BM BCh, MA(Oxon); Sophie Binks, DPhil; Sudarshini Ramanathan, PhD; Sophia Michael, DPhil; Adam E. Handel, DPhil; Lahiru Handunnetthi, DPhil; Christopher E. Uy, MD; John N. Soltys, MD, PhD; Divyanshu Dubey, MD; Gregory S. Day, MD; A. Sebastian Lopez-Chiriboga, MD; Eoin P. Flanagan, MB BCh; Fintan Sheerin, MB BChir, MA; Sarosh R. Irani, MA, DPhil

IMPORTANCE Rapid and accurate diagnosis of autoimmune encephalitis encourages prompt initiation of immunotherapy toward improved patient outcomes. However, clinical features alone may not sufficiently narrow the differential diagnosis, and awaiting autoantibody results can delay immunotherapy.

OBJECTIVE To identify simple magnetic resonance imaging (MRI) characteristics that accurately distinguish 2 common forms of autoimmune encephalitis, LGI1- and CASPR2-antibody encephalitis (LGI1/CASPR2-Ab-E), from 2 major differential diagnoses, viral encephalitis (VE) and Creutzfeldt-Jakob disease (CJD).

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study involved a retrospective, blinded analysis of the first available brain MRIs (taken 2000-2022) from 192 patients at Oxford University Hospitals in the UK and Mayo Clinic in the US. These patients had LGI1/CASPR2-Ab-E, VE, or CJD as evaluated by 2 neuroradiologists (discovery cohort; n = 87); findings were validated in an independent cohort by 3 neurologists (n = 105). Groups were statistically compared with contingency tables. Data were analyzed in 2023.

MAIN OUTCOMES AND MEASURES MRI findings including T2 or fluid-attenuated inversion recovery (FLAIR) hyperintensities, swelling or volume loss, presence of gadolinium contrast enhancement, and diffusion-weighted imaging changes. Correlations with clinical features.

RESULTS Among 192 participants with MRIs reviewed, 71 were female (37%) and 121 were male (63%); the median age was 66 years (range, 19-92 years). By comparison with VE and CJD, in LGI1/CASPR2-Ab-E, T2 and/or FLAIR hyperintensities were less likely to extend outside the temporal lobe (3/42 patients [7%] vs 17/18 patients [94%] with VE; $P < .001$, and 3/4 patients [75%] with CJD; $P = .005$), less frequently exhibited swelling (12/55 [22%] with LGI1/CASPR2-Ab-E vs 13/22 [59%] with VE; $P = .003$), and showed no diffusion restriction (0 patients vs 16/22 [73%] with VE and 8/10 [80%] with CJD; both $P < .001$) and rare contrast enhancement (1/20 [5%] vs 7/17 [41%] with VE; $P = .01$). These findings were validated in an independent cohort and generated an area under the curve of 0.97, sensitivity of 90%, and specificity of 95% among cases with T2/FLAIR hyperintensity in the hippocampus and/or amygdala.

CONCLUSIONS AND RELEVANCE In this study, T2 and/or FLAIR hyperintensities confined to the temporal lobes, without diffusion restriction or contrast enhancement, robustly distinguished LGI1/CASPR2-Ab-E from key differential diagnoses. These observations should assist clinical decision-making toward expediting immunotherapy. Their generalizability to other forms of autoimmune encephalitis and VE should be examined in future studies.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sarosh R. Irani, DPhil, Mayo Autoimmune Neurology Group, Mangurian Building, Mayo Clinic Florida, Level 5, Room 5502, Mangurian Buillding, Jacksonville, FL 32224 (irani.sarosh@mayo.edu).

JAMA Neurol. 2024;81(5):525-533. doi:10.1001/jamaneurol.2024.0126
Published online March 18, 2024.

Leucine-rich glioma inactivated protein 1 (LGI1)-antibody encephalitis and contactin-associated protein-like 2 (CASPR2)-antibody encephalitis (LGI1/CASPR2-Ab-E) are 2 common forms of autoimmune encephalitis (AE), characterized by rapid onset of cognitive impairment, behavioral disturbance, and seizures.[1] They can be difficult to distinguish from other 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 a practical importance in rapidly accessible investigations that can assist early diagnosis. Here, we identify brain magnetic resonance imaging (MRI) findings that differentiate LGI1/CASPR2-Ab-E from VE and CJD.

Key Points

Question Can magnetic resonance imaging (MRI) features help distinguish LGI1-antibody and CASPR2-antibody encephalitis from viral encephalitis and Creutzfeldt-Jakob disease?

Findings This cross-sectional study using validation with an independent external cohort identified that confinement of T2 and/or fluid-attenuated inversion recovery hyperintensities to the temporal lobe, without diffusion restriction or contrast enhancement, robustly distinguished LGI1- and CASPR2-antibody encephalitis from key differential diagnoses.

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

Methods

Discovery Cohort

Using existing Oxford Autoimmune Neurology Group cohorts,[3,4] 55 people with LGI1- or CASPR2-Ab-E and with locally downloaded MRIs were identified. All demonstrated at least 1 of seizures, cognitive impairment, psychosis, and behavioral disturbance, consistent with encephalitis. Two participants with purely peripheral features (neuropathic pain, neuromyotonia) were excluded. Retrospective data were collected from medical records and research databases, with patients granting informed written consent as approved by ethics committees (Oxfordshire RECA07/Q1604/28-REC16/YH/0013). Thirty-two people with VE or CJD diagnosed at Oxford University Hospitals were identified from microbiology department and hospital records, respectively (Oxford University Hospitals approval 6660). This cross-sectional study was designed in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Two neuroradiologists who were blinded to diagnoses reviewed the earliest available MRIs and reached consensus opinion on the following features:

- T2 and/or fluid-attenuated inversion recovery (FLAIR) hyperintensities in predefined brain regions
- Swelling or volume loss in hippocampus/amygdala
- Gadolinium contrast enhancement
- Diffusion-weighted imaging changes
- Hemorrhages
- Basal ganglia T1 hyperintensities[5]

Incidental findings unrelated to the diagnosis were excluded from analyses. Statistics were performed using SPSS version 29 (IBM) and Prism version 9.4.1 (GraphPad). χ^2 and Fisher exact tests were performed to compare proportional differences between groups (LGI1/CASPR2-Ab-E, VE, CJD) with nonparametric Mann-Whitney tests. For logistic regression analyses, potentially significant features ($P < .10$) were entered into stepwise backward models. Receiver operating characteristics curves were generated for key findings, excluding missing data.

Validation Cohort

The same analyses were performed by 3 blinded neurologists from 105 MRIs at Mayo Clinic in the US, where patients provided written consent to medical record use for research (institutional review board No. 20-005622). Discovery and validation cohorts were combined when analyzing subgroups with LGI1/CASPR2-Ab-E and VE.

Results

Among 192 participants with MRIs reviewed, 71 were female (37%), 121 were male (63%), and the median age was 66 years (range, 19-92 years). The discovery cohort included 55 participants with LGI1/CASPR2-Ab-E (42 with LGI1 antibodies, 9 with CASPR2 antibodies, 4 with LGI1 and CASPR2 antibodies), 22 participants with VE (herpes simplex virus 1, n = 18; human herpes virus 6, n = 4), and 10 participants with sporadic CJD (**Table** and eTable 1 in Supplement 1). Thirty-eight of 51 patients (75%) with LGI1/CASPR2-Ab-E had imaging within 6 weeks of commencing immunotherapy.

Regional T2 and/or FLAIR Hyperintensities

From 80% to 91% of the 3 groups showed MRI abnormalities (LGI1/CASPR2-Ab-E, 44/55 patients; VE, 20/22 patients; CJD, 9/10 patients) (**Figure 1** and **Figure 2**A). T2 and/or FLAIR hyperintensities were seen in 42 of 44 abnormal scans (95%) of patients with LGI1/CASPR2-Ab-E, 19 of 20 (95%) with VE, and 5 of 9 (56%) with CJD ($P = .005$ and $P = .02$, respectively) (Figure 2B). These hyperintensities universally involved the temporal lobes in LGI1/CASPR2-Ab-E (42/42; 100%) and in almost all VE cases (18/19; 95%). However, they were confined to the hippocampus/amygdala (hippocampus, amygdala, and/or hippocampus-amygdala junction) in all but 8 of 42 patients (19%) with LGI1/CASPR2-Ab-E; by contrast, this confinement was observed in 1 of 18 patients (6%) with VE ($P < .001$) and 1 of 4 patients (25%; $P = .04$) with CJD (Figure 2C). Extension beyond the temporal lobe (ie, insula, cingulate gyrus, frontal lobe, basal ganglia) was even rarer in LGI1/CASPR2-Ab-E (3/42 patients; 7%) vs VE (17/18 patients; 94%; $P < .001$) and CJD (3/4 patients; 75%; $P = .005$)

(Figure 2D). No differences were observed in the laterality of T2 and/or FLAIR hyperintensities (Figure 2E).

Swelling of the hippocampus/amygdala was more common in VE (13/22; 59%) than LGI1/CASPR2-Ab-E (12/55; 22%; $P = .003$) or CJD (0/10; $P = .002$) (Figure 2F), and loss of hippocampus/amygdala volume was not different across the 3 cohorts (data not shown). Hemorrhage within T2-/FLAIR-hyperintense regions occurred in 4 of 22 patients with VE (18%) compared with 0 of 54 patients with LGI1/CASPR2-Ab-E ($P = .006$) and 0 of 9 patients with CJD ($P = .07$). Neither T2, FLAIR, nor precontrast T1 hyperintensities were seen in the basal ganglia in LGI1/CASPR2-Ab-E cases; both were seen in 1 of 22 separate VE cases (5%).

Diffusion Restriction and Contrast Enhancement

Strikingly, diffusion restriction with apparent diffusion coefficient hypointensity was seen in 0 of 50 patients with LGI1/CASPR2-Ab-E but 16 of 22 patients (73%) with VE (all in the context of T2/FLAIR hyperintensities) and 8 of 10 patients (80%) with CJD (4/8 in the absence of other T2/FLAIR hyperintensities; $P < .001$) (Figure 1 and Figure 2G). Furthermore, when performed, contrast enhancement was observed in only 1 of 20 LGI1/CASPR2-Ab-E cases (5%) vs 7 of 17 VE cases (41%; $P = .01$) and 0 of 2 CJD cases ($P > .99$) (Figure 1 and Figure 2H).

Clinical Associations

In LGI1/CASPR2-Ab-E, only the occurrence of seizures was associated with T2 and/or FLAIR hyperintensities in the hippocampus and hippocampus-amygdala junction (Figure 2I and eFigure 1 in Supplement 1). Neither frequency of seizures (Mann-Whitney *U* test) nor time since symptom onset (logistic regression) was associated with any of the MRI features studied (eTable 3 in Supplement 1).

Validation Cohort

To validate and assess the relevance of these radiological findings, 3 neurologists independently reviewed 105 additional MRIs blinded to diagnoses of LGI1/CASPR2-Ab-E (n = 59), VE (n = 10), and sporadic CJD (n = 36) (Table). Trends were similar overall (eFigure 2 in Supplement 1), although by comparison with the discovery cohort, patients with LGI1/CASPR2-Ab-E showed fewer overall MRI abnormalities and T2/FLAIR hyperintensities (discovery vs validation: 44/55 [80%] vs 27/59 [46%] and 42/44 [95%] vs 16/27 [59%], respectively; both $P < .001$), which more often extended outside of the hippocampus/amygdala (discovery vs validation: 8/42 [19%] vs 12/15 [80%]; $P < .001$). Yet in LGI1/CASPR2-Ab-E, extratemporal extension was again rare compared with VE (1/15 [7%] vs 6/6 with VE [100%]; $P < .001$), diffusion restriction was observed in 0 of 57 patients with LGI1/CASPR2-Ab-E (vs 3/9 [33%] with VE; $P = .002$; and 25/36 [69%] with CJD; $P < .001$), and contrast enhancement in just 1 of 40 patients (3%) with LGI1/CASPR2-Ab-E (compared with 4/9 [44%] with VE; $P = .003$, and 0/26 patients with CJD; $P > .99$).

History of seizures (excluding faciobrachial dystonic seizures) trended toward a correlation with T2 and/or FLAIR hyperintensities in the amygdala (odds ratio, 0.17; 95% CI, 0.03-1.15; $P = .07$), but there were no other significant associations between clinical features and distribution of T2/FLAIR hyperintensities (eFigure 3 in Supplement 1).

Median time from onset was 7 weeks in the LGI1/CASPR2-Ab-E validation cohort (compared with 15 weeks in the discovery cohort), but time since onset was again found not to

Table. Demographic Characteristics and MRI Timing in the Discovery and Validation Cohorts

Characteristic[a]	Discovery	Validation
LGI1/CASPR2-antibody encephalitis		
No. of patients	55	59
Disease subtype, No. (%)		
LGI1 antibody	42 (76)	41 (69)
CASPR2 antibody	9 (16)	17 (29)
LGI1 and CASPR2 antibody	4 (7)	1 (2)
Sex, No. (%)[b]		
Male	43 (78)	42 (71)
Female	12 (22)	17 (29)
Age at time of MRI, median (range), y	65 (25-92)	68 (19-87)
Episode type, No. (%)		
First episode	52 (95)	42 (100)
Relapse	3 (5)	0
Time from symptom onset to MRI, median (range), wk	15.0 (0.0-554.0)[c]	7.6 (0.0-104.6)
Viral encephalitis		
No. of patients	22	10
Disease subtype, No. (%)		
HSV1	18 (82)	5 (50)
HHV6	4 (18)	0
HSV2	0	2 (20)
VZV	0	2 (20)
WNV	0	1 (10)
Sex, No. (%)		
Male	10 (45)	3 (30)
Female	12 (55)	7 (70)
Age at time of MRI, median (range), y	60 (31-83)	59 (33-91)
Creutzfeldt-Jakob disease		
No. of patients	10	36
Sex, No. (%)		
Male	8 (80)	15 (42)
Female	2 (20)	21 (58)
Age at time of MRI, median (range), y	62 (33-80)	67 (32-84)

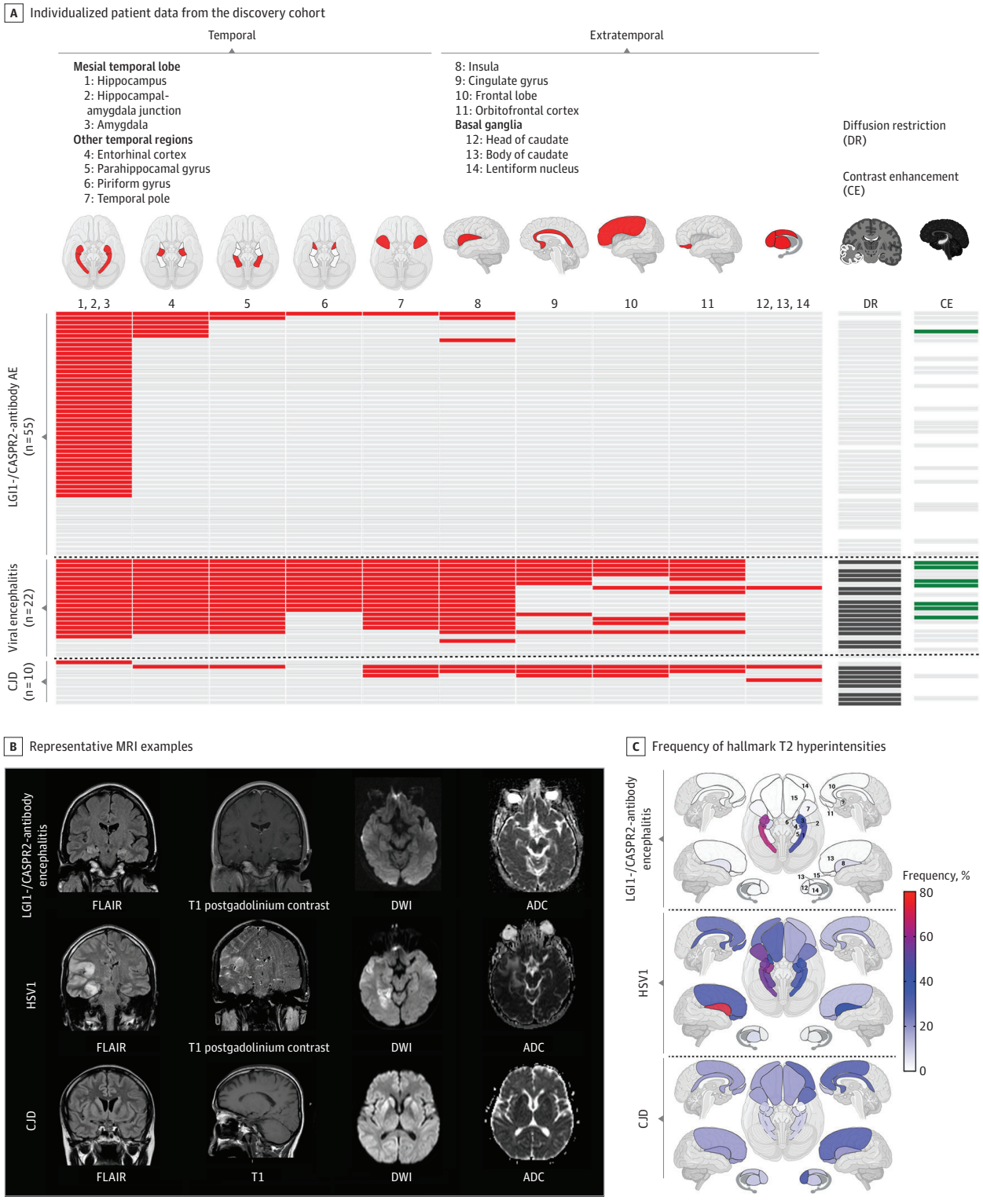
Abbreviations: CASPR2, contactin-associated protein-like 2; HSV, herpes simplex virus; HHV6, human herpes virus 6; LGI1, leucine-rich glioma inactivated 1; LGI1/CASPR2-Ab-E, LGI1- and CASPR2-antibody encephalitis; MRI, magnetic resonance imaging; VZV, varicella zoster virus; WNV, West Nile virus.

[a] All details were available for LGI1/CASPR2-Ab-E cases and basic demographic data for patients with viral encephalitis and Creutzfeldt-Jakob disease. Groups were age matched.

[b] A gender skew to males was present in the LGI1/CASPR2-Ab-E groups ($P = .02$ in discovery cohort, $P = .002$ in validation cohort, Fisher test).

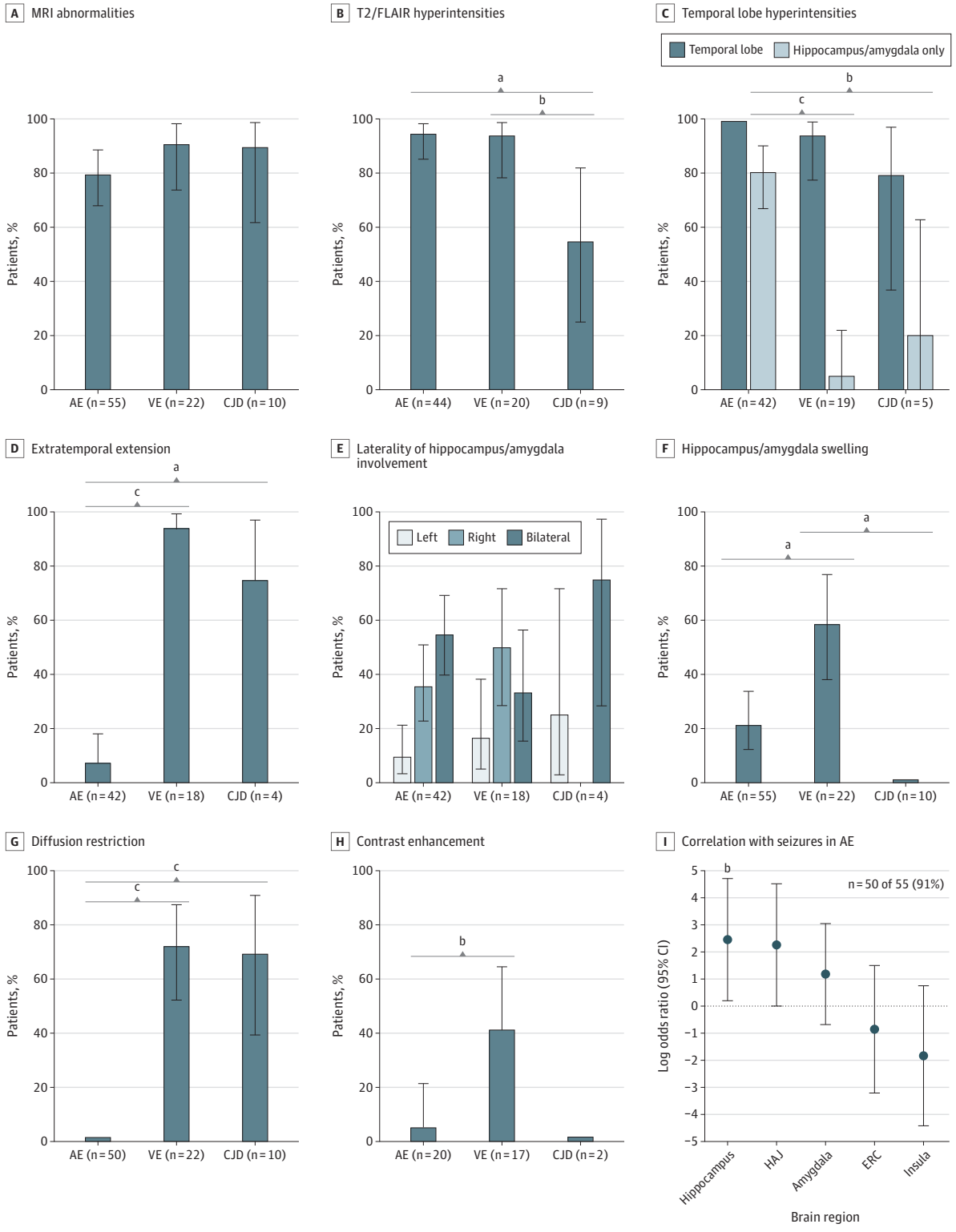
[c] The discovery cohort had a longer median time from symptom onset to MRI ($P = .003$, Mann-Whitney *U* test). There were no other significant differences between cohorts.

Figure 1. Regional T2 Magnetic Resonance Imaging (MRI) Hyperintensities, Diffusion Restriction, and Contrast Uptake



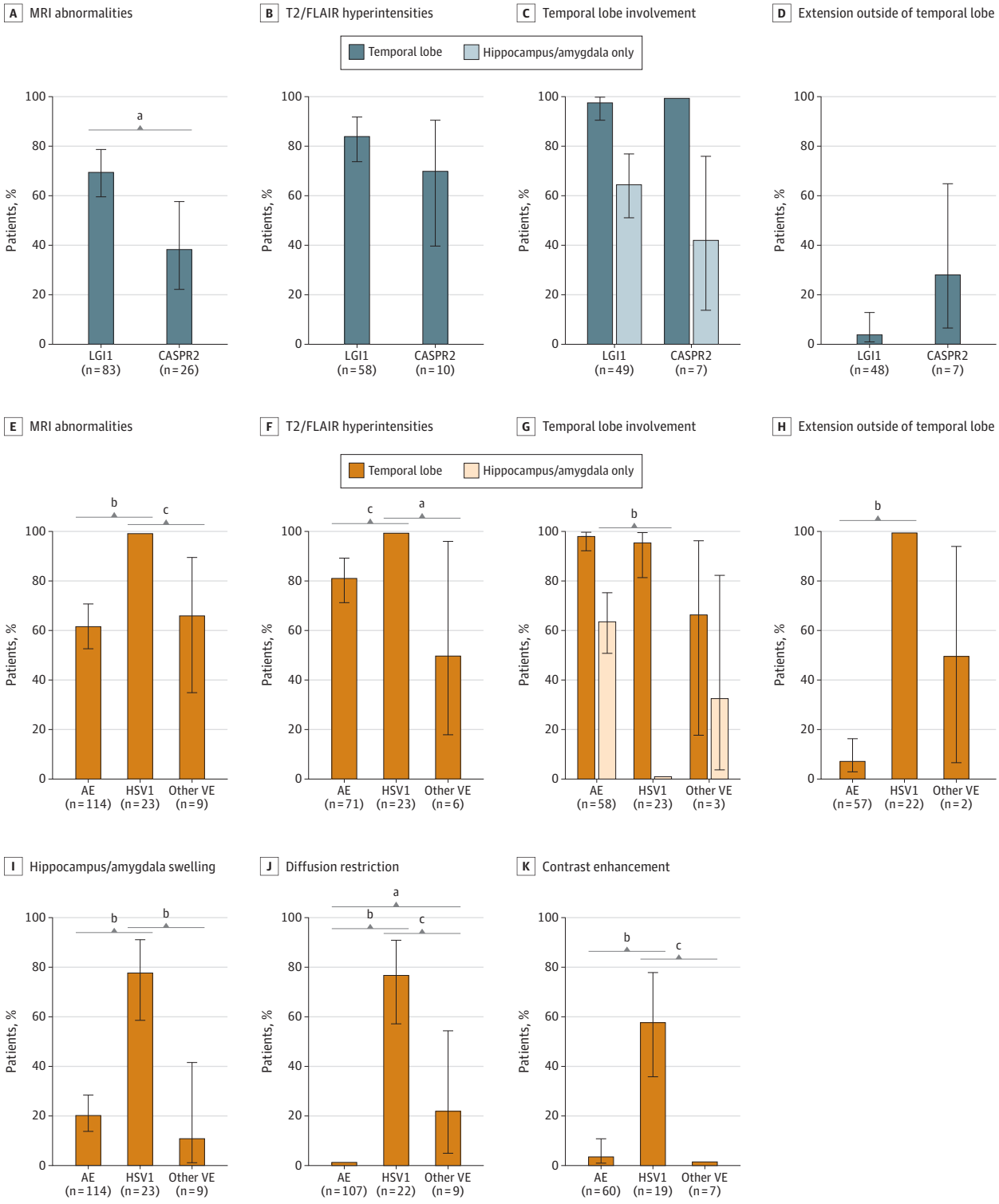
A, T2 hyperintensities across brain regions (red), the presence of diffusion restriction (dark gray), and contrast enhancement (green) in LGI1/CASPR2-antibody encephalitis (LGI1/CASPR2-Ab-E, n = 55), viral encephalitis (VE, n = 22), and Creutzfeldt-Jakob disease (CJD, n = 10). Light gray indicates absence; white indicates not performed. C, Raw data for frequencies are available in eTable 2 in Supplement 1. ADC indicates apparent diffusion coefficient; AE, autoimmune encephalitis; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; HSV1, herpes simplex virus 1.

Figure 2. Magnetic Resonance Imaging (MRI) Features and Distinctions Between LGI1- and CASPR2-Antibody Autoimmune Encephalitis (AE), Viral Encephalitis (VE), and Creutzfeldt-Jakob Disease (CJD)



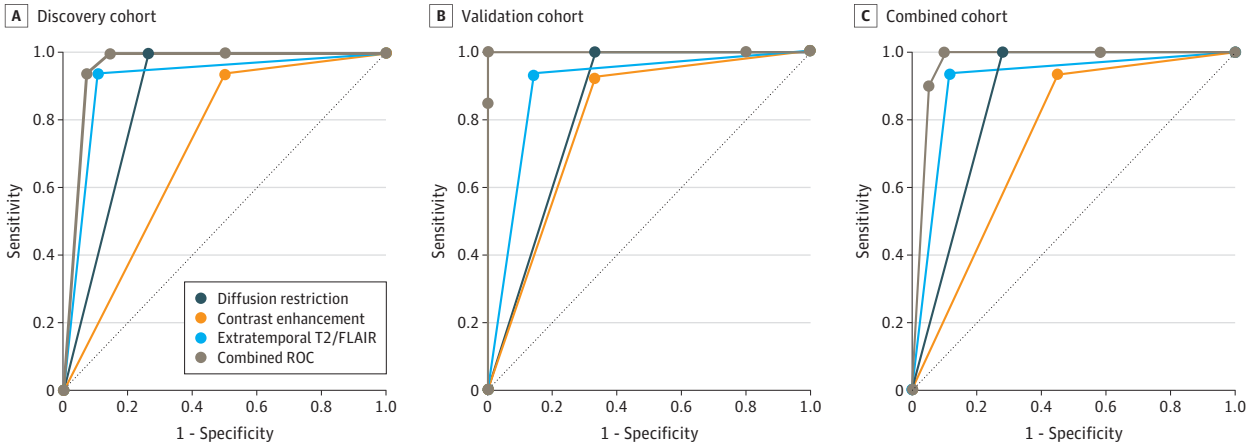
MRI abnormalities (A) included T2 hyperintensities (B) in almost all LGI1/CASPR2-antibody AE and VE cases and a smaller but high proportion of CJD cases. Fisher exact test was used for data in panels A-H. I, History of seizures was the only clinical feature associated with T2 and/or fluid-attenuated inversion recovery (FLAIR) hyperintensities in the hippocampus on multivariable regression analysis. Data expressed as log of odds ratios from univariable Fisher exact tests. Error bars indicate 95% CI. ERC indicates entorhinal cortex; HAJ, hippocampus-amygdala junction. [a] $P < .01$. [b] $P < .05$. [c] $P < .001$.

Figure 3. Subgroup Analyses in Combined Discovery and Validation Cohorts of LGI1-Antibody Encephalitis vs CASPR2-Antibody Encephalitis and LGI1/CASPR2-Antibody Autoimmune Encephalitis (AE) vs Viral Encephalitis (VE) Subtypes



LGI1-antibody AE demonstrated higher rates of abnormality than CASPR2-antibody AE but similar rates of T2/FLAIR hyperintensities, temporal lobe involvement, hippocampus/amygdala confinement, and extratemporal extension. Compared with HSV1 VE, other forms of VE demonstrated fewer abnormalities, T2/FLAIR hyperintensities, hippocampus/amygdala swelling, diffusion restriction, and contrast enhancement. Error bars indicate 95% CI. FLAIR indicates fluid-attenuated inversion recovery; HSV1, herpes simplex virus 1. [a]$P < .01$. [b]$P < .001$. [c]$P < .05$.

Figure 4. Receiver Operating Characteristic (ROC) Curves Reporting the Predictive Value of Diffusion Restriction, Contrast Enhancement, and Extratemporal T2 and/or Fluid-Attenuated Inversion Recovery (FLAIR) Hyperintensity



	Discovery cohort	Validation cohort	Combined cohort
Diffusion restriction	n = 58; AUC, 0.87; 95% CI, 0.75-0.99; *P* <.001	n = 21; AUC, 0.83; 95% CI, 0.59-1.00; *P* = .20	n = 79; AUC, 0.86; 95% CI, 0.75-0.97; *P* <.001
Contrast enhancement	n = 31; AUC, 0.72; 95% CI, 0.53-0.91; *P* = .04	n = 19; AUC, 0.80; 95% CI, 0.55-1.00; *P* = .04	n = 50; AUC, 0.74; 95% CI, 0.59-0.89; *P* = .004
Extratemporal T2/ FLAIR hyperintensity	n = 36; AUC, 0.92; 95% CI, 0.81-1.00; *P* <.001	n = 22; AUC, 0.90; 95% CI, 0.72-1.00; *P* = .003	n = 58; AUC, 0.91; 95% CI, 0.82-1.00; *P* <.001
Combined ROC	n = 31; AUC, 0.96; 95% CI, 0.88-1.00; *P* <.001	n = 18; AUC, 1.00; 95% CI, 1.00-1.00; *P* = .001	n = 49; AUC, 0.97; 95% CI, 0.91-1.00; *P* <.001

Distinguishing LGI1/CASPR2-antibody autoimmune encephalitis (AE) from non-AE cases across both cohorts separately and combined. All cases entered into this analysis demonstrated T2 and/or FLAIR hyperintensity of the hippocampus and/or amygdala. Absence of all 3 of these features was predictive of LGI1/CASPR2-antibody AE with an area under the curve (AUC) of 0.97, sensitivity of 90%, and specificity of 95% among cases with hippocampus/amygdala T2/FLAIR hyperintensity. For similar analyses including all cases (including scans without hippocampus/amygdala changes and normal scans) and comparing LGI1/CASPR1-antibody AE against herpes simplex virus 1 cases only, see eFigure 4 in Supplement 1.

be associated with MRI features. No significant differences were found in other demographic variables (Table).

Subgroup Analyses Within AE and VE

Across the combined discovery and validation cohorts, cases with LGI1-Ab-E more commonly showed abnormal MRIs than those with CASPR2-Ab-E (58/83 [70%] vs 10/26 [39%], respectively; *P* = .005) (**Figure 3**A). However, within abnormal scans, the frequency of T2 and/or FLAIR abnormalities and of temporal lobe confinement were not significantly different (Figure 3B-D).

Of all VE cases, diagnoses included herpes simplex virus 1 (HSV1, 23/32, 72%), human herpes virus 6 (n = 4), HSV2 (n = 2), varicella zoster virus (n = 2), and West Nile virus (n = 1). By comparison with HSV1, these pooled subtypes showed fewer abnormal MRIs (23/23 [100%] vs 6/9 [67%], respectively; *P* = .02) (Figure 3E) and T2/FLAIR hyperintensities (23/23 [100%] vs 3/6 [50%], respectively; *P* = .005) (Figure 3F-H) with less hippocampus/amygdala swelling (18/23 [78%] vs 1/9 [11%], respectively; *P* < .001) (Figure 3I), less diffusion restriction (17/22 [77%] vs 2/9 [22%], respectively; *P* = .01) (Figure 3J), and no contrast enhancement (11/19 [58%] vs 0/7, respectively; *P* = .01) (Figure 3K). LGI1/CASPR2-Ab-E cases continued to demonstrate lower rates of diffusion restriction than the non-HSV1 forms of VE (0/107 vs 2/9 [22%], respectively; *P* = .005) (Figure 3J) without other significant differences in this small, heterogenous cohort (Figure 3E-K).

Combined Predictive Values

Among cases with T2/FLAIR hyperintensities of the hippocampus/amygdala, we generated receiver operating characteristic curves incorporating diffusion restriction, contrast enhancement, and extratemporal T2/FLAIR hyperintensities. These revealed an area under the curve (AUC) of 0.97 (95% CI, 0.91-1.00) across both cohorts (**Figure 4**). The absence of these 3 factors identified LGI1- and CASPR2-Ab-E with a sensitivity of 90% and specificity of 95%. A parallel analysis including all cases (including normal scans) returned an AUC of 0.89 (95% CI, 0.82-0.95), 93% sensitivity, and 81% specificity (eFigure 4A in Supplement 1). Restricting the analysis to LGI1/CASPR2-Ab-E vs HSV1 cases only further improved the AUC to 0.997 (95% CI, 0.99-1.00), returning a sensitivity of 90% and specificity of 100% (eFigure 4B in Supplement 1).

Discussion

This study identifies several simply ascertained MRI features that accurately differentiate LGI1/CASPR2-Ab-E from 2 key

differentials.[2,6] Compared with VE and CJD, T2 and/or FLAIR hyperintensities in LGI1/CASPR2-Ab-E were typically confined to the temporal lobe, without diffusion restriction and only rare contrast enhancement. These widely accessible MRI sequences, validated by 2 sets of expertise (neuroradiologists and neurologists), have clear diagnostic utility in the appropriate clinical context and can help expedite immunotherapy administration to patients with AE.

Although imaging abnormalities were our focus, 43 of 114 LGI1/CASPR2-Ab-E scans (38%) showed no abnormalities, impressing the importance of considering AE even in the context of a normal MRI. Nevertheless, our most frequently observed MRI abnormality was T2/FLAIR hyperintensities within the hippocampus/amygdala, present in 80% of abnormal LGI1/CASPR2-Ab-E images.[7-9] Importantly, extratemporal extension of T2/FLAIR hyperintensities was rare in AE but almost universal in VE, emphasizing the value of precise anatomical distributions. In addition, we identified 2 other sensitive and highly specific radiological findings in LGI1/CASPR2-Ab-E: absence of diffusion restriction and contrast enhancement. These observations offer valuable clinical tools but also fundamental biological insights, suggesting inflammation in LGI1/CASPR2-Ab-E is associated with limited cytotoxic edema or 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 may relate to frequent focal seizures,[10] the only clinical feature associated with hippocampal T2/FLAIR hyperintensities in the discovery cohort.

Our findings help contextualize previous studies. An early report suggested diffusion restriction and contrast enhancement were common in voltage-gated potassium channel (VGKC)-antibody encephalitis,[11] likely relating to the inclusion of patients with non-LGI1/CASPR2-reactive VGKC antibodies.[12] Our data are more consistent with recent studies,[13-15] including one that identifies the combined absence of diffusion restriction, contrast enhancement, and extralimbic MRI changes, although not each in isolation, as suggestive of AE.[15]

Limitations

Limitations of this study include the use of heterogenous protocols across hospitals and variable MRI timing. While these reflect real-world practice and suggest our data may miss some early, transient findings, 75% of MRIs were performed within 6 weeks of immunotherapy commencement. In terms of their application to the individual patient, our findings were most sensitive at distinguishing between LGI1/CASPR2-Ab-E and HSV1 VE, whereas less common forms of VE appeared to have more heterogenous imaging findings. Hence, our data should be extended to other forms of VE in future studies. Similarly, we only focused on LGI1/CASPR2-Ab-E, and future studies should specifically aim to systematically translate these observations to other forms of AE, including GABAbR-antibody encephalitis and seronegative AE. Finally, our study combined MRI scans from several centers across 2 countries, implying some potential inconsistencies in imaging parameters that could be better addressed by MR parameter harmonization.

Conclusions

In this study, T2 and/or FLAIR hyperintensities confined to the temporal lobes, without diffusion restriction or contrast enhancement, robustly distinguished LGI1/CASPR2-Ab-E from key differentials. These observations should assist clinical decision-making toward expediting immunotherapy. Their generalizability to other forms of autoimmune encephalitis and VE should be examined in future studies.

ARTICLE INFORMATION

Accepted for Publication: January 12, 2024.

Published Online: March 18, 2024. doi:10.1001/jamaneurol.2024.0126

Author Affiliations: Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom (Kelly, Binks, Ramanathan, Michael, Handel, Handunnetthi, Uy, Irani); Department of Neurology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, United Kingdom (Kelly, Grant, Binks, Michael, Handel, Handunnetthi, Uy, Irani); Department of Physiology, Royal College of Surgeons in Ireland, Dublin, Ireland (Kelly); Department of Radiology, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom (Murchison, Sheerin); Translational Neuroimmunology Group, Sydney Medical School and Brain and Mind Centre, Faculty of Medicine and Health, University of Sydney, Sydney, Australia (Ramanathan); Department of Neurology, Concord Hospital, Sydney, Australia (Ramanathan); Department of Neurology, Queen Elizabeth Hospital, Birmingham, United Kingdom (Michael); Division of Neurology, Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, Canada (Uy); Department of Neurosciences, Mayo Clinic, Jacksonville, Florida (Soltys, Day, Lopez-Chiriboga, Irani); Department of Neurology, Mayo Clinic, Jacksonville, Florida (Day, Irani); Department of Neurology, Mayo Clinic, Rochester, Minnesota (Dubey, Flanagan).

Author Contributions: Dr Irani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Kelly, Grant, and Murchison contributed equally as co–first authors.
Concept and design: Kelly, Grant, Murchison, Handunnetthi, Flanagan, Sheerin, Irani.
Acquisition, analysis, or interpretation of data: Kelly, Grant, Murchison, Binks, Ramanathan, Michael, Handel, Uy, Soltys, Dubey, Day, Lopez-Chiriboga, Flanagan, Sheerin, Irani.
Drafting of the manuscript: Kelly, Grant, Murchison, Handunnetthi, Soltys, Day, Sheerin, Irani.
Critical review of the manuscript for important intellectual content: Grant, Murchison, Binks, Ramanathan, Michael, Handel, Handunnetthi, Uy, Dubey, Day, Lopez-Chiriboga, Flanagan, Sheerin, Irani.
Statistical analysis: Kelly, Grant, Michael, Irani.
Obtained funding: Irani.
Administrative, technical, or material support: Binks, Ramanathan, Irani.
Supervision: Sheerin, Irani.

Conflict of Interest Disclosures: Dr Kelly reported grants from Wellcome Trust via the Irish Clinical Academic Training (ICAT) Programme during the conduct of the study. Dr Binks reported funding from a National Institute for Health Research Clinical Lectureship during the conduct of the study; travel expenses from ECTRIMS outside the submitted work; and having had a patent for PCT/GB2019/051257 pending, "Diagnostic Strategy to improve specificity of CASPR2 antibody detection." Dr Ramanathan reported grants from the National Health and Medical Research Council, Royal Australasian College of Physicians Research Establishment Fellowship, Brain Foundation, and University of Sydney; speaker honoraria from Biogen, Novartis, Alexion, and Limbic Neurology; and consultant fees from UCB for serving on a steering committee of a phase 3 trial outside the submitted work. Dr Handel reported grants from the Medical Research Council (MRC) and UCB-Pharma during the conduct of the study. Dr Dubey reported grants and/or consulting fees from UCB, Arialys, DOD, and David J. Tomassoni ALS Research outside the submitted work and having had patents pending for LUZP4-IgG,

cavin-4-IgG, and SKOR2 IgG as markers of neurological autoimmunity and patents licensed for KLHL11 IgG. Dr Day reported grants from the National Institutes of Health (NIH/NIA) (K23AG064029) during the conduct of the study and in-kind support from Amgen Pharmaceuticals for a clinical trial in anti-NMDAR encephalitis (ExTINGUISH) and personal income related to consulting for Arialys Pharmaceuticals regarding development of a clinical trial for the treatment of autoimmune encephalitis. Dr Flanagan reported research support from UCB; serving on advisory boards for Alexion, Roche, and Horizon Therapeutics; royalties from UpToDate outside the submitted work; and having had a patent for Dach1-IgG pending (Mayo Clinic) as a marker of neurologic autoimmunity. Dr Irani reported grants from Wellcome and UK Research and Innovation/MRC during the conduct of the study; personal fees from UCB, MedImmun, Roche, Janssen, Cerebral Therapeutics, and ADC Therapeutics; grants from Brain, CSL Behring, and Ono Pharma outside the submitted work; and having had a patent for WO/2010/046716 with royalties paid from Euroimmun, a patent for WO2019211633 issued, and a patent for WO202189788A1 pending. No other disclosures were reported.

Funding/Support: This research was funded in whole or in part by a senior clinical fellowship from the Medical Research Council (MR/V007173/1), Wellcome Trust Fellowship (104079/Z/14/Z), BMA Research Grants-Vera Down grant (2013) and Margaret Temple (2017), Epilepsy Research UK (P1201), Fulbright UK-US commission (MS Society research award), Irish Clinical Academic Training Programme (Wellcome Foundation), National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC), and Oxford Health BRC.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or Department of Health.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain*. 2010;133(9):2734-2748. doi:10.1093/brain/awq213

2. Day GS. Rapidly progressive dementia. *Continuum (Minneap Minn)*. 2022;28(3):901-936.

3. Thompson J, Bi M, Murchison AG, et al; Faciobrachial Dystonic Seizures Study Group. The importance of early immunotherapy in patients with faciobrachial dystonic seizures. *Brain*. 2018;141(2):348-356. doi:10.1093/brain/awx323

4. Binks SNM, Veldsman M, Easton A, et al. Residual fatigue and cognitive deficits in patients after leucine-rich glioma-inactivated 1 antibody encephalitis. *JAMA Neurol*. 2021;78(5):617-619. doi:10.1001/jamaneurol.2021.0477

5. Flanagan EP, Kotsenas AL, Britton JW, et al. Basal ganglia T1 hyperintensity in LGI1-autoantibody faciobrachial dystonic seizures. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(6):e161. doi:10.1212/NXI.0000000000000161

6. Uy CE, Binks S, Irani SR. Autoimmune encephalitis: clinical spectrum and management. *Pract Neurol*. 2021;21(5):412-423. doi:10.1136/practneurol-2020-002567

7. Heine J, Prüss H, Bartsch T, Ploner CJ, Paul F, Finke C. Imaging of autoimmune encephalitis: relevance for clinical practice and hippocampal function. *Neuroscience*. 2015;309:68-83. doi:10.1016/j.neuroscience.2015.05.037

8. Boyko M, Au KLK, Casault C, de Robles P, Pfeffer G. Systematic review of the clinical spectrum of CASPR2 antibody syndrome. *J Neurol*. 2020;267(4):1137-1146. doi:10.1007/s00415-019-09686-2

9. Guerin J, Watson RE, Carr CM, Liebo GB, Kotsenas AL. Autoimmune epilepsy: findings on MRI and FDG-PET. *Br J Radiol*. 2019;92(1093):20170869.

10. Kim JA, Chung JI, Yoon PH, et al. Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: periictal diffusion-weighted imaging. *AJNR Am J Neuroradiol*. 2001;22(6):1149-1160.

11. Kotsenas AL, Watson RE, Pittock SJ, et al. MRI findings in autoimmune voltage-gated potassium channel complex encephalitis with seizures: one potential etiology for mesial temporal sclerosis. *AJNR Am J Neuroradiol*. 2014;35(1):84-89. doi:10.3174/ajnr.A3633

12. Lang B, Makuch M, Moloney T, et al. Intracellular and non-neuronal targets of voltage-gated potassium channel complex antibodies. *J Neurol Neurosurg Psychiatry*. 2017;88(4):353-361. doi:10.1136/jnnp-2016-314758

13. Finke C, Prüss H, Heine J, et al. Evaluation of cognitive deficits and structural hippocampal damage in encephalitis with leucine-rich, glioma-inactivated 1 antibodies. *JAMA Neurol*. 2017;74(1):50-59. doi:10.1001/jamaneurol.2016.4226

14. Shao X, Fan S, Luo H, et al. Brain magnetic resonance imaging characteristics of anti-leucine-rich glioma-inactivated 1 encephalitis and their clinical relevance: a single-center study in China. *Front Neurol*. 2021;11:618109. doi:10.3389/fneur.2020.618109

15. Van Steenhoven RW, de Vries JM, Bruijstens AL, et al. Mimics of autoimmune encephalitis: validation of the 2016 Clinical Autoimmune Encephalitis Criteria. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(6):10. doi:10.1212/NXI.0000000000200148