Additional Contributions: We thank Thomas Günthner-Lengsfeld, MD, Alexander März, MD, Yanyan Xiong, MD, Brigitte Bison, MD, Julian Kunz, MD, and Jörn Feick, MD (Department of Neuroradiology, Würzburg University Hospital, Germany) for their support in data acquisition and patient handling. The authors thank Susanne Hellmig (Department of Neurology, Würzburg University Hospital, Germany) for excellent technical support. No compensation from funding sources was received for these contributions.

1. Thiebaut AM, Gauberti M, Ali C, et al. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. *Lancet Neurol*. 2018;17(12):1121-1132. doi:10.1016/S1474-4422(18)30323-5

2. Campbell BC, Mitchell PJ, Churilov L, et al; EXTEND-IA TNK Investigators. Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): a multicenter, randomized, controlled study. *Int J Stroke*. 2018;13(3):328-334. doi:10.1177/1747493017733935

3. Desilles JP, Loyau S, Syvannarath V, et al. Alteplase reduces downstream microvascular thrombosis and improves the benefit of large artery recanalization in stroke. *Stroke*. 2015;46(11):3241-3248. doi:10.1161/STROKEAHA.115.010721

4. Kollikowski AM, Schuhmann MK, Nieswandt B, Müllges W, Stoll G, Pham M. Local leukocyte invasion during hyperacute human ischemic stroke. *Ann Neurol*. 2020;87(3):466-479. doi:10.1002/ana.25665

5. Hill MD, Goyal M, Menon BK, et al; ESCAPE-NA1 Investigators. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial. *Lancet*. 2020;395(10227):878-887. doi:10.1016/S0140-6736(20)30258-0

6. Goyal M, Simonsen CZ, Fisher M. Future trials on endovascular stroke treatment: the not-so-easy-to-pluck fruits. *Neuroradiology*. 2018;60(2):123-126. doi:10.1007/s00234-017-1966-0

Residual Fatigue and Cognitive Deficits in Patients After Leucine-Rich Glioma-Inactivated 1 Antibody Encephalitis

Leucine-rich glioma-inactivated 1 antibody encephalitis (LGI1-Ab-E) typically affects older men who present with prominent amnesia and frequent seizures[1-3] and often shows a marked short-term improvement with immunotherapies.[4] In particular, seizure cessation occurs within just a few weeks. However, only traditional cognitive domains have been investigated as longer-term outcomes, with improvements in cognition described as "not good enough."[5] Here, motivated by patient feedback and our clinical observations, we aimed to quantify the residual deficits observed after LGI1-Ab-E across several functional domains.

Methods | Participants were recruited to this cross-sectional study from previous cohorts,[4] author clinics, or via the Encephalitis Society and assessed by neurologist interview and a battery of tests measuring:

1. Cognition: Addenbrooke's Cognitive Examination (ACE), Mini-Mental State Examination (MMSE), and Frontal Assessment Battery (FAB)
2. Affective symptoms: Hospital Anxiety and Depression Scale (HADS)
3. Clinician-rated disability: modified Rankin Scale (mRS) and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE)
4. Fatigue: Fatigue Scale for Motor and Cognitive Function (FSMC) and Modified Fatigue Impact Scale (MFIS).

All patients gave written informed consent (Research Ethics Committee approval 16/YH/0013).

Results | Clinical data were gathered from 60 patients with LGI1-Ab-E, assessed at a median of 41 months (range, 4-179 months) after symptom onset (**Table**). From peak illness to post illness, a marked fall in disability was noted using both the CASE (median [SD] score of 6 [3.4] to 2 [1.7]) and mRS (median [SD] score of 3 [1.1] to 2 [1.1]; **Figure**, A; both $P < .001$), with 81% (n = 48 of 59) showing a "good" functional outcome (mRS ≤2). However, only 4 of 27 (15%) of those in employment at diagnosis returned to their premorbid role (Table). The median age of those medically retired or transitioning to a less demanding role was 56 years (range, 46-70 years), representing a reduction of 10 years' fully productive working life in the United Kingdom. Consistent with this vocational effect, more detailed clinical testing captured widespread deficits.

By comparison with age-appropriate cutoffs derived from manuals or publications, 63% of the LGI1-Ab-E cohort (n = 38 of 60) were impaired on at least 1 of cognition, mood, and fatigue (Figure, B). Cognitive testing revealed total ACE was impaired in 32% (n = 18 of 56; score <88 of 100); 16% (n = 9 of 56)

Table. Cohort Demographics and Clinical Features of 60 Patients With Leucine-Rich Glioma-Inactivated 1-Antibodies

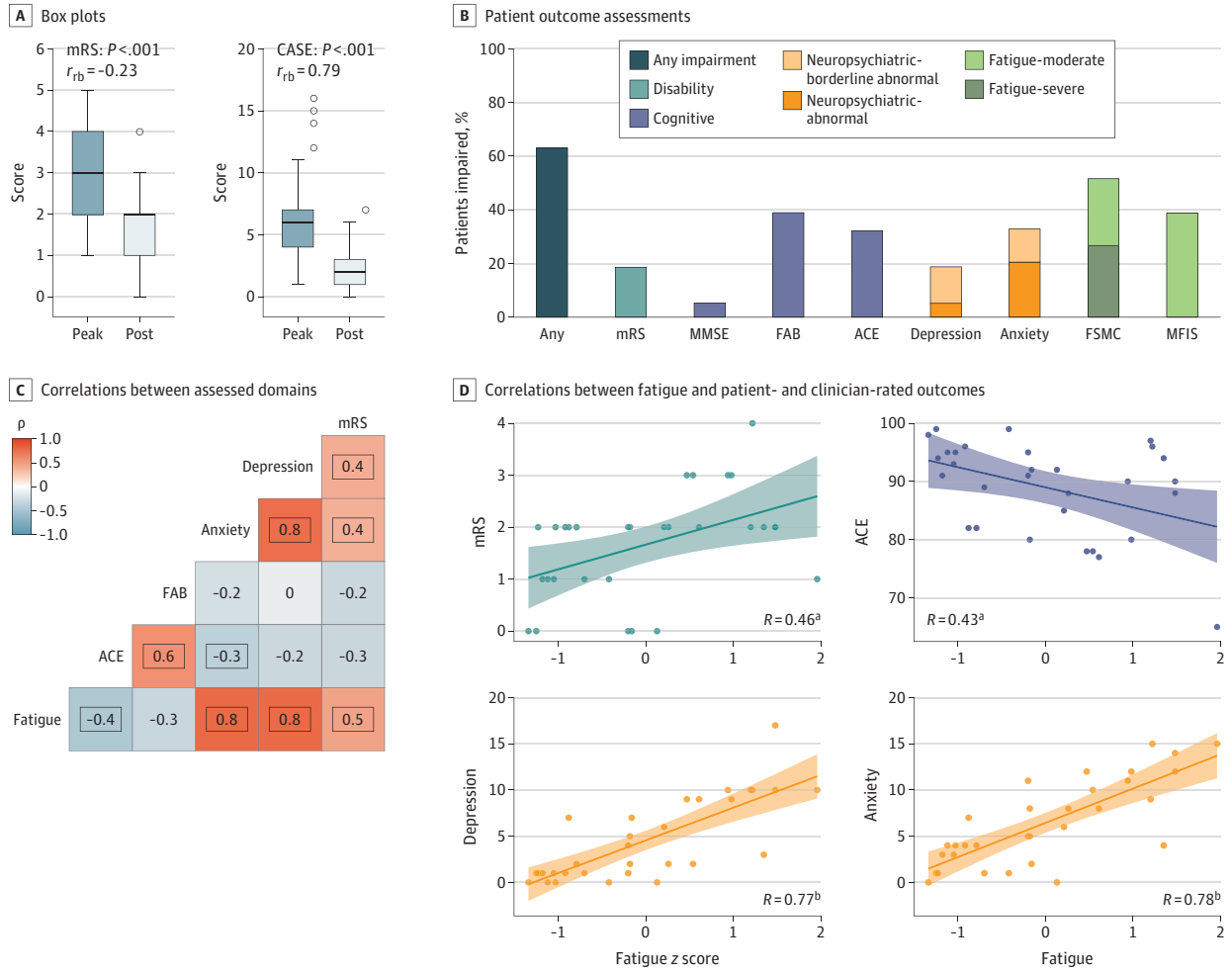
Demographics	Median (range)[a]	Patients, No./total No. (%)[b]
Age at onset, y	64 (44-86)	60 (100)
Age at assessment, y	70 (44-92)	60 (100)
Assessment post onset, mo (range)	41 (4-179)	60 (100)
Female	NA	20/60 (33)
Clinical syndrome at presentation		
Epilepsy	NA	10/60 (17)
Encephalitis	NA	48/60 (80)
Morvan syndrome	NA	1/60 (2)
Other (stroke)	NA	1/60 (2)
Clinical features at presentation		
Any seizure	NA	59/59 (100)
Faciobrachial dystonic seizures	NA	42/59 (71)
Focal onset seizures	NA	39/59 (66)
Generalized seizure	NA	17/59 (29)
Amnesia	NA	49/59 (83)
Tumor	NA	10/59 (17)
Therapeutic and medical history		
Ever had immunotherapy	NA	53/59 (90)
Steroids	NA	52/59 (88)
Intravenous immunoglobulins	NA	25/54 (46)
Plasma exchange	NA	18/55 (33)
No. of weeks to IT	16 (3-250+)	57 (NA)
Functional status		
Current mRS, mean (range)	1.6 (0-4)	59 (NA)
mRS>2	NA	11/59 (19)
Employment status when assessed		
Employed, same role	NA	4/58 (7)
Employed, reduced role	NA	12/58 (21)
Medically retired because of LGI1-Ab-E	NA	11/58 (19)
Retired at onset or other cause	NA	31/58 (52)

Abbreviations: IT, immunotherapy; LGI1, leucine-rich glioma-inactivated 1 antibody encephalits; mRS, modified Rankin Scale.

[a] Empty cells reflect continuous variables.

[b] Denominators indicate the number of patients with available data.

Figure. Outcomes in Patients With Leucine-Rich Glioma-Inactivated 1 Antibody Encephalitis



A. Peak illness to postillness scores in physician-rated modified Rankin Scale (mRS) and Clinical Assessment Scale in Autoimmune Encephalitis (CASE). B. Results of patient outcome assessments across multiple domains. Bar graph depicting proportion of patients with abnormal scores. Shading denotes neuropsychiatric scores from Hospital Anxiety and Depression Scale (borderline abnormal or abnormal) (CASE not depicted because no normative value for healthy controls exists). Fatigue scales were introduced during the study and completed by 31 patients: those without or with fatigue questionnaires were closely matched other than a shorter duration from illness onset in the latter group (37.7 vs 75.4 months; t(51.74) = 3.270; $P = .002$). C. Single-correlation *R* values and Pearson correlation shown across outcome measures (Bonferroni-adjusted for multiple comparisons, with outlined boxes for $P < .01$). D. Graphs show correlations between fatigue *z* score (x-axes) and mRS, Addenbrooke's Cognitive Examination (ACE), and depression/anxiety (both derived from Hospital Anxiety and Depression Scale). FAB indicates Frontal Assessment Battery; FSMC, Fatigue Scale for Motor and Cognitive Function; MFIS, Modified Fatigue Impact Scale; MMSE, Mini-Mental State Examination.

[a] $P < .01$.

[b] $P < .001$.

attained scores less than that of healthy elderly individuals in memory, fluency, and visuospatial capabilities, whereas attention (9% impaired [n = 5 of 56]) and language abilities (5% impaired [n = 3 of 56]) were relatively spared. Of affective features, both depression (HADS-D >7) and anxiety (HADS-A >7) were present in 19% (n = 11 of 58) and 33% (n = 19 of 58), respectively. However, overall fatigue was the most common long-term deficit, detected in 52% with the FSMC (n = 16 of 31), rated as severe in 56% of these patients (n = 9 of 16) (Figure, B).

The interrelationships between these deficits revealed the strongest correlations between fatigue and both anxiety and depression (ρ = 0.78 and ρ = 0.77, respectively; $P < .001$, after Holm-Bonferroni multiple comparison corrections; Figure, C and D). In addition, extent of fatigue correlated with both the greater disability (from mRS) and poorer cognition by ACE (Figure, D).

Discussion | Although mRS represents the most widely used outcome measure in studies of autoimmune encephalopathies, the data here indicate that despite a "good" mRS, several long-term residual deficits remain: across domains of cognition, mood, and fatigue, with a significant effect on employment status. Our cohort's mean mRS was comparable with other LGI1-Ab-E studies,[2-4] suggesting this traditional outcome measure captures only limited long-term morbidity in multiple studies. Fatigue was the most commonly impaired domain in our cohort, a novel finding in LGI1-Ab-E. This observation is

closely reflected by the many patients in our clinic who volunteer fatigue as a major residual symptom. Also, it parallels findings in pediatric *N*-methyl-D-aspartate receptor antibody encephalitis, where fatigue is associated with quality of life.[6]

Overall, we continue to advocate early immunotherapy to achieve optimal clinical outcomes in patients with LGI1-Ab-E. Future studies can now also ask whether this approach mitigates the appearance of fatigue, in addition to amelioration of the other expanded long-term cognitive deficits highlighted within our study.

Sophie N. M. Binks, MD
Michele Veldsman, PhD
Ava Easton, PhD
M. Isabel Leite, DPhil
David Okai, MD(Res)
Masud Husain, DPhil
Sarosh R. Irani, DPhil

Author Affiliations: Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, Oxford, England (Binks, Leite, Irani); Department of Neurology, Oxford University Hospitals NHS Foundation Trust, Oxford, England (Binks, Leite, Irani); Department of Experimental Psychology, University of Oxford, Oxford, England (Veldsman, Husain); The Encephalitis Society, Malton, North Yorkshire, England (Easton); Honorary Fellow, Depatment of Clinical Infection, Microbiology and Immunology, University of Liverpool, Liverpool, England (Easton); Department of Neuropsychiatry, Maudsley Outpatients, Denmark Hill, Maudsley Hospital, London, England (Okai); Nuffield Department of Clinical Neurosciences, Oxford, England (Husain).

Corresponding Author: Sarosh R. Irani, DPhil, Oxford Autoimmune Neurology Group, Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Level 3, West Wing, Oxford, Oxfordshire OX3 9DS, England (sarosh.irani@ndcn.ox.ac.uk).

Accepted for Publication: February 5, 2021.

Published Online: March 29, 2021. doi:10.1001/jamaneurol.2021.0477

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. These authors contributed equally to the manuscript: Drs Binks and Veldsman. Joint senior authors: Drs Husain and Irani.
Concept and design: Binks, Veldsman, Easton, Okai, Irani.
Acquisition, analysis, or interpretation of data: Binks, Veldsman, Leite, Okai, Husain, Irani.
Drafting of the manuscript: Binks, Veldsman, Easton, Okai, Irani.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Binks, Veldsman, Okai, Irani.
Obtained funding: Binks, Husain, Irani.
Administrative, technical, or material support: Easton, Irani.
Supervision: Leite, Okai, Husain, Irani.

Conflict of Interest Disclosures: Dr Binks reported grants from Wellcome Trust and grants from the National Institute for Health Research during the conduct of the study; in addition, Dr Binks had a patent for PCT/GB2019/051257 pending University of Oxford. Dr Husain reported personal fees from Otsuka Consulting, Biogen, Excemed, and Lilly outside the submitted work. Dr Irani reported grants and personal fees from UCB Pharma and grants from CSL outside the submitted work; in addition, Dr Irani had a patent for LGI1/Caspr2 antibody detection with royalties paid from euroImmun AG and a patent for antibody diagnostics issued. No other disclosures were reported.

Funding/Support: Dr Irani is supported by the Wellcome Trust (104079/Z/14/Z), BMA Research Grants-Vera Down grant (2013), Margaret Temple (2017), Epilepsy Research UK (P1201), the Fulbright UK-US commission (MS Society research award), and by the NIHR Oxford Biomedical Research Centre. Dr Husain is supported by the Wellcome Trust (206330/Z/17/Z) and the National Institute for Health Research Oxford Biomedical Research Centre during the conduct of the study. Dr Binks has received salary support from the National Institute for Health Research and is currently supported by the Wellcome Trust. his research was funded in whole, or in part, by the Wellcome Trust (104079/Z/14/Z).

Role of the Funder/Sponsor: The funding sources 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 author(s) and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health).

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. Ariño H, Armangué T, Petit-Pedrol M, et al. Anti-LGI1-associated cognitive impairment: presentation and long-term outcome. *Neurology*. 2016;87(8):759-765. doi:10.1212/WNL.0000000000003009

3. 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

4. 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.

5. Day GS. Rethinking outcomes in leucine-rich, glioma-inactivated 1 protein encephalitis: 'good' isn't good enough. *JAMA Neurol*. 2017;74(1):19-21.

6. de Bruijn MAAM, Aarsen FK, van Oosterhout MP, et al; CHANCE Study Group. Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis. *Neurology*. 2018;90(22):e1997-e2005.

COMMENT & RESPONSE

Insights on Intensive vs Nonintensive Prerandomization Systolic Blood Pressure Reduction

To the Editor We have read the article titled "Outcomes of Intensive Systolic Blood Pressure Reduction in Patients With Intracerebral Hemorrhage and Excessively High Initial Systolic Blood Pressure: Post Hoc Analysis of a Randomized Clinical Trial" by Qureshi et al,[1] published online in *JAMA Neurology* on September 8, 2020. We would like to congratulate the authors for this successful analysis and make some comments and contributions.

In this interesting post hoc analysis[1] of the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH 2) trial, the authors have compared the outcome of patients with intracerebral hemorrhage and initial systolic blood pressure (SBP) levels more than 220 mm Hg with those with initial SBP levels less than 220 mm Hg. In spite of similar blood pressure (BP) at randomization and similar BP reduction over the next 2 hours, hematoma expansion was 2 times greater in the group with initial SBP less than 220 mm Hg than in those with initial SBP greater than 220 mm Hg. Adverse events (adverse kidney events, early neurological deterioration, and severe adverse events) were similar between the 2 groups. This probably is because of the intensive systolic BP reduction achieved before randomization within 4.5 hours of onset of intracerebral hemorrhage. The present post hoc analysis[1] has shown that intensive systolic BP reduction was harmful after randomization. However, the possibility of a substantial benefit of intensive blood pressure reduction before randomization cannot be ruled out. The group with intensive systolic BP reduction prerandomization and standard postrandomization SBP reduc-