LGI1 antibody encephalitis: acute treatment comparisons and outcome

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ABSTRACT

Objective To compare acute treatment responses and long-term outcome in leucine-rich-glioma-inactivated 1 (LGI1) antibody encephalitis.

Methods Retrospective case series of 118 patients with LGI1 antibody encephalitis evaluated at Mayo Clinic across all US sites from 1 May 2008 to 31 March 2019. Patient clinical data were identified and analysed through the neuroimmunology laboratory and electronic medical record. LGI1 antibody detection was by cell-based indirect immunofluorescence assay of serum, cerebrospinal fluid or both. Clinical outcomes were faciobrachial dystonic seizure (FBDS) resolution, modified Rankin Scale (mRS) score, Kokmen Short Test of Mental Status (STMS) score (0–38 point scale) and neuropsychometric testing results.

Results Compared with intravenous immunoglobulin (IVIg) (n=21), patients treated with single-agent acute corticosteroids (intravenous, oral or both) (n=49) were more likely to experience resolution of FBDS (61% vs 7%, p=0.002) and improvements in mRS score (ΔmRS score 2 vs 0, p=0.008) and median Kokmen STMS scores (ΔKokmen STMS score 5 points vs 0 points, p=0.017). In 54 patients with long-term follow-up (≥2 years), the median mRS score was 1 (range 0–6) and the median Kokmen STMS score was 36 (range 24–38) after all combinations of immunotherapy. Neuropsychometric testing in 32 patients with long-term follow-up (≥2 years) demonstrated short-term memory impairments in 37%.

Conclusions Corticosteroids appeared more effective acutely than IVIg in improving LGI1 antibody encephalitis in this retrospective comparison of immunotherapies. While improvement with immunotherapy is typical and long-term outcome is favourable, short-term memory deficits are noted in approximately a third of the patients.

INTRODUCTION

Leucine-rich glioma-inactivated 1 (LGI1) antibody encephalitis is an autoimmune encephalitis which frequently manifests as an autoimmune limbic encephalitis. Patients may present with subacute onset of memory loss, behavioural disturbances and seizures. Peripheral manifestations, such as neuropathy or autonomic dysfunction, often coexist but may also occur without central involvement. Faciobrachial dystonic seizure (FBDS) is highly characteristic of LGI1 antibody encephalitis and is characterised by frequent (up to 40–50 per day), brief (lasting seconds) dystonic movements of the ipsilateral face and arm; it can sometimes involve the leg. In addition, autonomic and sensory seizures and paroxysmal dizziness spells without alteration of consciousness have also been described. A variety of immunotherapies have been shown to be potentially effective (eg, corticosteroids and intravenous immunoglobulins (IVIg)), although no definitive treatment guidelines are available for optimal management, and the choice of the immunosuppressive drug is generally an empirical decision of the treating physician. In late 2019, a small prospective randomised placebo-controlled trial of IVIg in 17 patients with acute symptomatic seizures associated with autoimmune encephalitis (14 with LGI1 autoantibodies) at our facility showed a higher proportion with ≥50% seizure reduction in the IVIg arm versus the placebo arm, although many patients went on to subsequently receive corticosteroids due to incomplete response. While IVIg was more effective than placebo in that study, a direct comparison with corticosteroids was not performed, and comparisons of IVIg to other treatments are generally lacking. In this study, our aims were (1) to compare acute and long-term treatment responses in LGI1 antibody encephalitis with IVIg and corticosteroids and (2) to assess overall long-term functional and cognitive outcomes in patients with LGI1 antibody encephalitis.

METHODS

The Mayo Clinic institutional review board approved this study and all patients consented to the use of their medical records for research purposes.

Patient identification

We retrospectively identified Mayo Clinic patients from 1 May 2008 to 31 March 2019 through the Advanced Cohort Explorer, an electronic retrieval system that interrogates the electronic medical record. Data were cross referenced with our prior studies on LGI1 antibody encephalitis. Inclusion criteria were (1) LGI1 antibody positivity in serum (101 patients), cerebrospinal fluid (5 patients) or both (12 patients); (2) encephalitis; and (3) clinical information available. We excluded patients...
without encephalitis (eg, isolated peripheral nervous system disease) or without available clinical details. Ninety-three patients were included in prior studies. Of the patients with mouse composite brain tissue results available, immunostaining in a pattern consistent with LGI1 antibodies was identified in 26 of 99 (26%) in serum and 24 of 52 (46%) in cerebrospinal fluid, respectively. Three patients had coexisting contactin-associated protein-like 2 (CASPR2) antibodies.

LGI1-IgG assay
LGI1 and CASPR2 autoantibodies were detected in patient serum or cerebrospinal fluid by transfected cell-based immuno-fluorescence assay (EUROIMMUN, Lubeck, Germany) and were performed in conjunction with the Mayo Neuroimmunology Laboratory’s comprehensive autoantibody evaluation, as described previously.18 19

Clinical evaluation
Two neurologists (AR and EPF) used the Mayo Clinic medical records linkage system to review the medical record for neurological manifestations and examination findings.

Corticosteroid and IVlg treatment regimens
We identified 49 patients who received corticosteroids (intravenous, oral or both) and 21 patients who received IVlg as acute first-line immunotherapy. The corticosteroid and IVlg treatments in this study were not standardised and varied by provider preference, patient choice or inclusion in the prior clinical trial of IVlg in this disease. The treatment regimens could generally be categorised into a few groups. The corticosteroid treatment group typically first underwent an acute course of 1 g of intravenous methylprednisolone once per day for 3–5 days followed by either no additional treatment, by intermittent intravenous steroid infusions (eg, 1 g of intravenous methylprednisolone once per week for 6–12 weeks with subsequent lengthening of the duration between infusions) or by prolonged daily oral prednisone (eg, 1 mg/kg/day with a slow taper over 3–12 months). For IVlg, the typical regimen comprised 0.4 g/kg once per day for 3–5 days alone or followed by intermittent infusions (eg, 0.5 g/kg on day 1 and 1 g/kg (not exceeding 80 g) on day 2 followed by 0.6 g/kg every 2 weeks for two infusions), with the latter used in the previously published clinical trial.3

Functional score
Modified Rankin Scale (mRS) was used to assess outcome. The mRS is an ordinal 7-point scoring system that measures neurological disability and has been widely applied to evaluate acute and long-term outcomes in patients with autoimmune encephalitis.20

Cognitive assessments
Long-term cognitive outcome was assessed with the Kokmen Short Test of Mental Status (STMS) and neuropsychometric testing. The Kokmen STMS is a 38-point bedside cognitive scoring system that measures orientation (8 points), attention (7 points), learning (4 points), calculation (4 points), abstraction (3 points), information (4 points), construction (4 points) and recall (4 points).21 22

Neuropsychometric testing assessed global cognitive function ( Mattis Dementia Rating Scale); learning memory (Auditory–Verbal Learning Test, delayed recall and California Verbal Learning Test Second Ed. Short Form (CVLT-2-SF)); visual learning and memory (Visual Reproduction Subtest from the Wechsler Memory Scale); language (Boston Naming Test, Controlled Oral Word Association Test and Category Fluency); visuospatial functioning (Rey-Osterrieth Complex Figure Copy Trial); auditory attention and working memory (Digit Span Subtest from the Wechsler Adult Intelligence Scale); visual attention and processing speed (Trail Making Test Part A); and executive function (Trail Making Test Part B and Stroop Color-Word Test).23–36 For the Visual Reproduction and Digit Span tests, Wechsler norms were used.26 For participants who completed the CVLT-2-SF list-learning task, internal CVLT norms were used. All other tests were converted to scaled scores using the Mayo Older Adult Normative Studies (MOANS).27 28 30 31 For participants below the MOANS age range (≥56 years), the lowest age group was used to determine their scaled score. Participants were then classified into three subgroups based on their scaled score. Scaled scores of ≥9 were considered within normal limits. Scaled scores between 6 and 8 were defined as low. Cognitive impairment was defined as a scaled score greater than 1 and a half SD below the mean, which equates to a scaled score of ≤5.

These tests were obtained during the illness course and at the last follow-up.

Other ancillary testing
Brain MRI reports were generated by a radiologist at the last follow-up and were analysed to assess for ongoing signal abnormalities or atrophy with or without prior baseline studies. Seizures were classified based on clinical records and electroencephalogram (EEG) reports, which were generated by a reading epileptologist.

Outcome assessments and definitions
- Favourable reduction in seizure frequency was defined as a >50% reduction.
- Outcomes were considered favourable with an mRS score of 0–2.
- Relapses were defined as the development of recurrent symptoms at 6 months or longer after an initial clinical improvement.
- Early recurrence was defined as recurrent symptoms during the first 6 months after an initial improvement with treatment.
- Clinical improvement in cognition or seizures was determined by the treating physician.
- Improvements in cognition were objectively analysed in patients who underwent serial cognitive assessments.

Statistical analysis
Continuous and categorical variables were reported as median (range) and number (percentage), respectively. Comparisons across >2 groups were performed with the Kruskal-Wallis test (continuous variables) and the Fisher exact test (categorical variables); pairwise comparisons were performed using the Wilcoxon rank-sum test (continuous variables) and the Fisher exact test (categorical variables). P values of <0.05 were considered statistically significant. We also used regression analyses to assess the potential effects of age, time from onset to treatment and duration from treatment to first follow-up on our inferences about outcomes (mRS score, Kokmen STMS score and FBDS resolution) at first follow-up. For mRS score and Kokmen STMS score, we used linear regression, and for FBDS resolution, we used logistic regression. Analyses were performed with JMP V.14.1 and the R statistical programming language V.4.0.3 software.

RESULTS
One hundred eighteen patients with LGI1 antibody encephalitis were included; the median age at symptom onset was 66 years (range

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Acute immunotherapies

After disease presentation, patients were treated with a single acute immunotherapy (n=70; corticosteroids (intravenous, oral or both) 49, IVIg 21) (online supplemental table 6) and multiple acute immunotherapies (n=36), or received no acute treatment (n=12). The baseline characteristics of patients stratified by type of acute immunotherapy were not significantly different) (online supplemental table 7).

Table 1  Clinical characteristics and treatments used in 118 patients with LGI1 antibody encephalitis

| Characteristics                        | Value*                                                                 |
|----------------------------------------|------------------------------------------------------------------------|
| Age-at-symptom onset (years), median (range) | 66 (17–87)                                                           |
| Male sex                               | 78 (66)                                                               |
| Length of follow-up (months), median (range) | 20 (0–184)                                                          |
| Time to treatment (months), median (range) | 5 (0–53)                                                            |
| Symptoms at presentation               |                                                                        |
| Memory loss                            | 103 (87)                                                              |
| Seizures (any type)                    | 104 (88)                                                              |
| Faciobrachial dystonic seizures        | 62 (53)                                                               |
| Pilomotor seizures                     | 13 (11)                                                               |
| mRS score, median (range)              | 3 (0–5)                                                               |
| Acquiring malignancy†                  | 7 (6)                                                                 |
| Kokmen STMS scale score, median (range) | 32 (18–38)                                                          |
| Immunosuppressive treatments           |                                                                        |
| First-line acute treatment             |                                                                        |
| Intravenous steroids alone (with or without an oral steroid taper) | 49 (42)                                                              |
| IVIg only                              | 21 (18)                                                               |
| Intravenous steroids and maintenance immunotherapy | 18 (15)                                                             |
| No treatment                           | 12 (10)                                                               |
| Other combination§                     | 18 (15)                                                               |
| Overall treatment at any time point    |                                                                        |
| Intravenous steroids                   | 93 (79)                                                               |
| IVIg                                    | 47 (40)                                                               |
| Oral steroids                          | 41 (35)                                                               |
| Mycophenolate mofetil                  | 38 (32)                                                               |
| Plasma exchange                        | 14 (12)                                                               |
| Azathioprine                           | 12 (10)                                                               |
| Rituximab                              | 11 (9)                                                                |
| Antiseizure medication use             | 109 (92)                                                              |

*Represented as n (%) unless otherwise specified.
†Available in 98 patients.
‡Within 1 year of diagnosis; prostate cancer (four patients), squamous cell carcinoma (two patients), thymoma (one patient) and colorectal cancer (one patient).
§See online supplemental etable 1.
IVIg, intravenous immunoglobulin; LGI1, leucine-rich glioma-inactivated 1; mRS, modified Rankin Scale; STMS, Short Test of Mental Status.

Comparison of corticosteroids versus IVIg acute monotherapy

The pretreatment characteristics and disease severity of patients treated with IVIg alone (n=21) and corticosteroids alone (n=49) as acute monotherapy were similar (table 2).

At first follow-up (median 1.4 months, range 0–20 months), patients treated with corticosteroids versus IVIg had more favourable median mRS score (1 vs 3, p=0.004), Seizures (any type) 45/49 (92%) 19/21 (91%) >0.99

FBDS 23/49 (47%) 15/21 (71%) 0.07

Antiseizure medications 46/49 (94%) 19/21 (91%) 0.63

First follow-up

mRS score 1 (0–5) 3 (0–3) 0.004

Improvement in ΔmRS score 2 (0–4) 0 (0–3) 0.008

Kokmen STMS scale score, median (range) 36 (31–38) 31 (10–37) 0.01

FBDS resolution 14/23 (61%) 4/7 (57%) 0.009

FBDS >50% resolution 18/23 (78%) 4/7 (57%) 0.003

Seizure (any type) resolution 33/44 (75%)# 4/19 (21%) <0.001

Months after first treatment, median (range) 2 (0–18) 1 (0–20) 0.66

Adverse effects 23/49 (47%) 5/21 (24%) 0.11

Subsequent therapies 23/49 (47%) 14/21 (67%) 0.19

Corticosteroids 22/23 (96%) 13/14 (93%) >0.99

IVIg 9/23 (39%) 2/14 (14%) 0.15

PLEX 3/23 (13%) 3/14 (21%) 0.65

Maintenance immunotherapy† 14/23 (61%) 6/14 (43%) 0.33

Long-term follow-up after >24 months (n=23) (n=7)

mRS score 1 (0–6) 1 (0–3) 0.45

Improvement in ΔmRS score 5 (0–3) 1 (0–3) >0.99

Kokmen STMS scale score, median (range) 37 (28–38) 33.5 (30–36) 0.35

FBDS resolution 8/9 (89%) 4/4 (100%) >0.99

FBDS >50% resolution 8/9 (89%) 4/4 (100%) >0.99

Seizure (any type) resolution 20/23 (87%) 7/7 (100%) >0.99

Patients who relapsed 5/23 (22%) 0/7 (0%) 0.30

Patients with early recurrence 3/23 (13%) 1/7 (14%) >0.99

Development of hippocampal atrophy‡ MTS 9/23 (39%) 3/6 (50%) 0.67

Disease duration, median (range) 21 (2–80) 14 (6–68) 0.45

*Details not available about seizure resolution in one patient
†Azathioprine, mycophenolate mofetil or rituximab.
‡Months from symptom onset to maximal resolution.
§See online supplemental etable 1.
IVIg, intravenous immunoglobulin; LGI1, leucine-rich glioma-inactivated 1; mRS, modified Rankin Scale; STMS, Short Test of Mental Status.

17–87), and 78 (66%) patients were male. Patients were treated with one or more immunotherapies over time. Their baseline demographics, clinical characteristics and details on immunotherapies received are summarised in table 1.
greater overall improvement in mRS score (ΔmRS score 2 vs 0, p=0.008), more frequent seizure resolution (33/44 (75%) vs 4/19 (21%), p=<0.001), more frequent FBDS resolution (14/23 (61%) vs 1/15 (7%), p=0.002) and greater improvement in Kokmen STMS score (ΔKokmen STMS score 5 points vs 0 points, p=0.01) (table 2). Of the 19 patients with details available on the speed of FBDS or other seizure resolution, 12 patients treated with corticosteroids and 2 patients treated with IVIg reported complete resolution within the first 7 days from treatment onset. Four patients treated with corticosteroids and one patient treated with IVIg reported symptom resolution within 2 weeks. The age and time from onset to treatment were variable but did not differ between groups (table 2 and online supplemental efigure). A regression analysis showed that when adjusted for time to treatment and time from treatment to first follow-up, corticosteroids when compared with IVIg still led to a reduction in mRS score, improvement in Kokmen STMS score and an increased odds of FBDS resolution (online supplemental table 9 and online supplemental efigure).

Twenty-three (47%) patients in the corticosteroid group and 14 (67%) patients in the IVIg group underwent additional therapies after a median of 1.4 months (range 0.3–13) (table 2). Of the patients in the treatment groups (corticosteroids 23, IVIg 7) with long-term follow-up (≥24 months), there were no significant differences in any of our outcomes (table 2). Corticosteroid adverse effects (eg, insomnia, mood disturbance and weight gain) were noted in 23 patients (47%), and IVIg adverse effects (eg, headache, rash, and fatigue) were seen in 5 patients (24%) and were not statistically significantly different (p=0.11).

Long-term outcomes

Long-term outcomes were analysed in 54 patients with greater than 24 months of follow-up. Acute immunotherapies in these patients included corticosteroids in 23 patients; other combinations (corticosteroids, IVIg, maintenance immunotherapy or plasma exchange) in 24 patients; and IVIg in 7 patients. Median length of follow-up was 53 months (range 26–184). Favourable mRS score (≤2) was seen in 47 of 54 patients (87%), and median mRS score was 1 (range 0–6). The details of mRS at presentation and long-term follow up were available in 49 patients and their distribution at those time-points is shown in figure 1. Median Kokmen STMS score was 36 (range 24–38); patient scores were stable in most other categories, except for delayed recall, where residual difficulties were typical. The median score on delayed recall at the last follow-up was 3 (range 0–4) (online supplemental table 8). Early disease recurrence within 6 months was seen in seven patients (13%). Relapses beyond 6 months were noted in 12 patients (22%), of which 7 were on maintenance immunosuppression and 5 were not. Of these 12 relapses, 9 occurred after complete or near complete remission and 3 occurred in the setting of only partial remission and a fluctuating course. The median time from onset to relapse was 30 months (range 17–138). In the 12 patients who relapsed beyond 6 months, the median number of relapses was 1 (range 1–2). Sixteen patients (30%) had complete response after acute first-line treatment. Thirty-seven (69%) patients were on maintenance immunosuppression at the last follow-up. Three patients (6%) died. Of those patients who died, the median disease duration was 5.3 years (range 3.3–10.4) and the median age at expiration was 72 (range 71–72). Clinical information was available in one patient whose death was from pneumonia and heart failure while in disease remission without concurrent use of acute or maintenance immunotherapy.

Figure 1 Distribution of the modified Rankin Scale in patients with long-term follow-up.

Brain MRI obtained at a median of 29 months (range 2–183) from symptom onset demonstrated hippocampal atrophy or mesial temporal sclerosis in 17 patients (31%) and generalised atrophy in 22 patients (41%). EEG acquired in 45 patients at a median of 39 months after onset (range 4–149) included the following results: normal (24/45 patients, 53%), focal or generalised slowing (15/45 patients, 33%), epileptiform discharges (5/45 patients, 11%) or seizures (1/45 patient, 2%).

Neuropsychometric test results

Neuropsychometric testing was available for 32 patients. One patient was a non-native English speaker, and therefore these data were excluded due to lack of appropriate normative reference group. Data for the remaining 31 patients are presented in table 3.

Due to variability in cognitive tests administered, not all patients completed all measures. Overall, the greatest impairment was found on a screening measure for global cognition and measures of short-term memory/delayed recall and executive function (table 3).

DISCUSSION

This study compares acute immunotherapies and reports the long-term outcome in patients with LGI1 antibody encephalitis. Patients treated with corticosteroids (intravenous, oral or both) compared with IVIg as monotherapy had greater improvements in FBDS, other seizure types, mRS score and Kokmen STMS scores after acute treatment. However, no differences in long-term outcomes were noted between the two groups. Most patients (87%) had favourable mRS score (≤2) at follow-up after all combinations of immunotherapy, although residual memory loss, mesial temporal sclerosis and
atrophy were noted in a minority. A small proportion of patients had persistent deficits on neuropsychometric testing in global cognition, verbal memory, visual learning and executive function.

The critical importance of early effective immunotherapy in LGI1 antibody encephalitis has been highlighted in prior studies showing that early immunotherapy in FBDS may prevent limbic encephalitis and long-term cognitive deficits, and greater likelihood of a reduction in seizures. In one study of FBDSs, more than half of the patients developed cognitive impairment if FBDS was present for greater than 90 days, with return to baseline function correlated with time to initiation of immunotherapy. Thus, choosing the most efficacious treatment initially may improve long-term outcomes. While a prior clinical trial showed IVlg is efficacious in LGI1 antibody encephalitis, the effect size was small. Comparisons such as this may inform treatment approaches that may be more effective. Our findings, although retrospective, suggest that corticosteroids (typically intravenous at high dose) may be more efficacious than IVlg as acute treatment in LGI1 antibody encephalitis. These results have potential clinical implications. First, it suggests that corticosteroids should be considered as first-line treatment in LGI1 antibody encephalitis. Second, it suggests that early rescue with corticosteroid treatment should be considered in patients without complete response to IVlg by 7 days, the timeline by which 90% of patients in this study had cessation of FBDS. Third, it suggests that a corticosteroid treatment arm should be included in future randomised controlled trials in this disease.

Our findings are consistent with prior cohort studies of LGI1 antibody encephalitis in which corticosteroids were used in at least 90% of patients with most showing improvement. By contrast, IVlg was typically used in less than one-third of patients and rarely used in isolation. FBDS cessation in prior studies on March 31, 2024 by guest. Protected by http://jnnp.bmj.com/ J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp-2021-327302 on 25 November 2021. Downloaded from http://jnnp.bmj.com/ on March 31, 2024 by guest. Protected by
that activate complement but lower efficacy with IgG4-mediated diseases that cannot activate complement.59

Most patients in this study had favourable functional outcomes after long-term follow-up and multiple immunotherapies. However, a substantial minority had persistent dysfunction in verbal memory and visual learning. These findings are consistent with prior studies in patients with LG1 antibody encephalitis.2 5 40–44 According to Finke et al, verbal and visuospatial memory deficits were persistent after disease remission.40 A telemedicine study by Sola-Valls et al demonstrated impairment in verbal fluency (53%), verbal memory (50%) and executive function impairment (31%) at long-term follow-up, which is slightly higher compared with our findings.45 Findings from Binks et al similarly showed 81% having a good outcome of mRS score of ≤2, with memory, fluency and visuospatial impairments with prominent fatigue.46 Notably, only four of 27 (15%) were able to return to their prior job positions despite the overall good mRS score highlighting a limitation in that outcome measure.47 These are further supported in this study by MRI evidence of hippocampal atrophy, mesial temporal sclerosis and generalised atrophy, all of which are integral to learning, memory and executive function. Hippocampal volume loss and generalised atrophy were common findings in prior studies and are suggestive of long-term or permanent hippocampal and global cerebral dysfunctions after disease remission.48 49 50 41 43 45

One of the limitations associated with this study is its retrospective nature. Despite this and the lack of randomisation, patients’ characteristics in both treatment arms were balanced, increasing confidence in the results. While retrospective data cannot replace prospective randomised placebo-controlled data, it is unclear whether prospective studies of corticosteroids will be undertaken in LG1 antibody encephalitis, given its low-cost, generic formulation, importance of expediency of treatment referable to outcome and relative rarity of the disease, making it less attractive for pharmaceutical companies to fund. Thus, analyses such as this are important to provide some guidance for treatment selection. Additional limitations include lack of standardised cognitive assessments, but this provides a large detailed analysis of cognitive outcomes in LG1 antibody encephalitis that are useful for prognostication. Finally, we compared steroids and IVlg treatments at first follow-up, and small numbers and variable follow-up times limited our ability to compare the steroid and IVlg outcomes at set time points. However, when controlling for time from onset to treatment and time from treatment to first follow-up, the overall findings did not change.

In summary, this retrospective study suggests that acute treatment with corticosteroids may be more effective than IVlg in improving acute outcomes in patients with LG1 antibody encephalitis. While most patients improved with immunotherapy, residual long-term memory deficits were common. These observations highlight the need to incorporate a corticosteroid treatment arm into future randomised controlled trials enrolling patients with LG1 antibody encephalitis. The presence of residual deficits despite early treatment in the majority of this cohort indicates the clinical need for identification of other treatment options in these patients in order to optimise recovery.

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Contributors AR and EPF conceived the study and were responsible for the overall content of the study. AR, EPF, CKJ and AG performed data collection. Mayo Clinic Division of Biomedical Statistics, ES and AR performed the statistical analysis. EA, MRB and SP obtained neuropsychometric testing and performed the statistical analysis. AR, ES, EA, MRB, SP and EPF designed the tables. AR and EPF drafted the manuscript. EPF, CKJ, MRB, SP, AM, JW, ASL-C, AZ, NILZ, BFB, GSD, AG, DB, MT and DD provided senior review of the manuscript. EPF is responsible for the overall content and guarantor.

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