Published in final edited form as:

Eur J Neurol. 2014 October ; 21(10): 1301–1310. doi:10.1111/ene.12482.

More than Memory Impairment in Voltage-Gated Potassium Channel Complex Encephalopathy

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Abstract

Objective—Autoimmune encephalopathies (AE) are a heterogeneous group of neurological disorders that affect cognition. Although memory difficulties are commonly endorsed, few reports of AE inclusively assess all cognitive domains in detail. Our aim was to perform an unbiased cognitive evaluation of AE patients with voltage-gated potassium channel complex antibodies (VGKC_C-Abs) in order to delineate cognitive strengths and weaknesses.

Methods—We assessed serial VGKC_C-Abs AE subjects (n=12) with a comprehensive evaluation of memory, executive functions, visuospatial skills, and language. Clinical MRI (n=10/12) was evaluated. Five subjects had serial cognitive testing available, permitting descriptive analysis of change.

Results—Subjects demonstrated mild to moderate impairment in memory (mean Z=−1.9) and executive functions (mean Z=−1.5), with variable impairments in language and sparing of visuospatial skills. MRI findings showed T2 hyperintensities in medial temporal lobe (10/10) and basal ganglia (2/10). Serial cognitive examination revealed heterogeneity in cognitive function; whereas most patients improved in one or more domains, residual impairments were observed in some patients.

Conclusions—This study augments prior neuropsychological analyses in VGKC_C-Ab AE by identifying not only memory and executive function deficits, but also language impairments, with

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Dr. Gelfand has provided expert witness medical-legal consultation related to CNS inflammatory-demyelinating diseases. Dr. Irani is a coapplicant on a patent for LGI1 and CASPR2 antibody discovery and receives related royalties. Dr. Hess receives research support from General Electric. Dr. Geschwind served as a consultant for MedaCorp, The Council of Advisors, Guidepoint Global, and Neurophage.

preservation of visuospatial functioning. This study further highlights the importance of domain-specific testing to parse out the complex cognitive phenotypes of VGKC_C-Ab AE.

Keywords

autoimmune; cognitive; LGI1

Introduction

Voltage-Gated Potassium Channel antibody associated encephalopathy (VGKC_C-Ab AE) is a primary inflammatory neurological disorder characterized by cognitive dysfunction, seizures, and hyponatremia. Patients with VGKC_C-Ab display variable clinical trajectories and relapse rates, often yielding multiple diagnostic considerations with few clear predictors of clinical course(1–3). Clarifying the neuropsychological profile of VGKC_C-Ab is critically important not only to advancing our understanding of the etiology and progression of the disease, but also to establishing accurate diagnoses and optimizing cognitive outcome measures for clinical trials. Whereas several reports have described cognitive impairments in patients with VGKC_C-Ab(3–5), these prior studies have primarily focused on memory impairment, with few studies examining other cognitive domains, including executive functions or language(6,7). In addition, a paucity of attention has been paid to areas of cognitive preservation(8), which may yield important information for both differential diagnosis and cognitive rehabilitation strategies. For these reasons, a comprehensive assessment of cognitive functions across multiple domains is warranted.

The primary aim of the current study is to elucidate patterns of performance on detailed indices of memory, executive functioning, language, and visuospatial skills in VGKC_C-Ab AE. We also examined serial data for a subset of VGKC_C-Ab AE to identify neuropsychological trajectories.

Methods

Participants

We identified patients with AE referred to the UCSF Memory and Aging Center clinic, inpatient service, or rapidly progressive dementia (RPD) research program who tested positive for antibodies to VGKC_C or LGI1 and/or CASPR2¹ through clinical reference labs and/or collaborating research laboratories. Subjects were included in our sample if they were English-speaking and could participate in a one-hour cognitive evaluation. Subjects with capacity provided written informed consent; subjects without capacity at the time of evaluation were asked to assent, and written informed consent was obtained from a surrogate decision-maker through UCSF internal review board approved protocols. The study was approved by the UCSF Committee on Human Research (CHR). Case number 10 was briefly described in a prior report [case #1 in(2)].

¹No individuals tested positive for CASPR2

Measures

A comprehensive chart review was conducted for patients seen in the UCSF Memory and Aging Center neurology clinic (n=11) or the inpatient service (n=1; later tested in clinic), and reviewed in the context of our RPD research program. Antibody results were obtained from collaborating research and clinical laboratories. Available MRI scans were reviewed by MDG and JMG; discrepancies were resolved by a subspecialty-certified neuroradiologist (CPH).

Neuropsychological assessment—All patients were administered a neuropsychological protocol, consisting of measures of global cognition, memory, executive functions, language, and visuospatial skills(9). Memory measures included tests of verbal consolidation [California Verbal Learning Test (CVLT)] and visual recall [Benson Figure (Benson-D)](10,11). Executive function tests included verbal [Phonemic (D-words), Category (Animals)] and visual (Design Fluency) fluency, working memory [Digits Backward (Digit-B)], set-shifting [Modified Trail-Making (Modified Trails)], and inhibition (Stroop-Inhibition); visuospatial tests included visual localization [Visual Object Space Perception (VOSP), Number Location] and construction [Benson Figure Copy (Benson-C)]; language tests included naming [Abbreviated Boston Naming Test (BNT)](12), single-word comprehension [Peabody Picture Vocabulary Test (PPVT)], and sentence repetition (Repetition).

The following variables for each test were used in analyses: delayed recall (10' for CVLT short; 20' for long form) and delayed copy (15', Benson-D) for memory; total words (D-words;Animals), highest number of digits (Digit-B), total time (Modified Trails), number correct (Stroop-Inhibition), and total designs (Design Fluency) for executive functions; total correct (Benson-C;VOSP) for visuospatial perception/construction; and total correct (BNT; PPVT;repetition) for each language test.

Statistical Analyses

For cognitive data, we used a normative reference group based on a large San Francisco sample(9), given the epidemiology and relatively high level of education of our patients. Z-scores were calculated based on the patients' age and education for each test, and impairments were noted for individuals who scored ≥ 1.5 standard deviations below the normative mean (i.e. $Z \leq -1.5$: mild impairment; $Z \leq -2.0$: moderate impairment; $Z \leq -2.5$: severe impairment). We calculated means across subjects for each available test, and generated a composite score for all tests within a domain. The proportion of patients impaired on individual tests was also examined (i.e. number of patients with ≥ 1.5 standard deviations below normative mean, divided by number of patients with results available for that test). In addition, serial data was available for five patients, allowing for descriptive longitudinal evaluations.

Results

Clinical Characteristics

Twelve VGKCC-Ab AE patients who received formal neuropsychological testing (mean age 64.4, median 64, range 48–79 years) were identified. Eight subjects were LGI1 positive; the remaining four were not tested. Overall, patients displayed a high level of education (mean 16.8, SD 3.6, median 18, range 12–20 years) and 67% were female. The average number of days since onset was 394, SD 292 (median 296, range 152–1205).

As shown in Table 1, the majority of subjects reported cognitive difficulties as one of their primary symptoms, with recent memory difficulties representing the most frequently reported complaint (100%). General mental confusion, anxiety, altered speech output and limb jerking were also reported as primary symptoms. Eleven subjects (92%) had a history of seizures and 75% were on anti-epileptic drugs (AEDs) at the time of cognitive testing. Four subjects (33%) had facial brachial dystonic seizures (FBDS). Eleven (92%) subjects received steroids, 5 (42%) IVIg, 3 (25%) plasma exchange (PLEX), and 2 (17%) Rituximab prior to cognitive testing; further evaluation of subjects' treatment histories indicated that 6 had only received prednisone, 2 had both IVIg and prednisone, 1 had 3 agents (prednisone, IVIg, PLEX), 2 had all 4 agents, and 1 received no treatment prior to cognitive testing (Table 1).

MRI findings nearest to time of cognitive testing showed nonspecific atrophy that was probably within normal limits for age (5 of 10 available, see Table 1) and abnormal T2 medial temporal lobe (MTL) hyperintensities (10 of 10). In addition, T2 hyperintensities in the putamen and caudate were noted in two patients. Except for the bifrontal white matter hyperintensities in case 8 and confluent white matter disease in case 10, all other white matter hyperintensity findings were considered within normal limits for age.

Cross-sectional Cognitive Performance

Patients displayed mild to moderate impairment on memory (mean $Z=-1.9$; median $Z=-2.0$), particularly verbal memory (mean $Z=-2.4$, median $Z=-2.5$). Additional mild impairments were observed for executive functions (mean $Z=-1.5$; median $Z=-1.1$) and language (mean $Z=-1.5$; median $Z=-.4$). Notably, the median for language functions was in the average range, suggesting that mean scores were driven by isolated patients' impairments. No group-level impairments were noted in visuospatial functions (mean $Z=-.1$; median $Z=+.4$) (Table 2). An examination of the proportion of patients (Figure 1) impaired indicated that more than 50% of patients were impaired on measures of verbal memory (CVLT, 83%), verbal fluency (D-words and Animals, 55 and 64%, respectively), and set-shifting (Modified Trails, 67%). Few (<20%) patients displayed difficulty with measures of inhibition (Stroop inhibition, 11%), figure copy (Benson-C, 8%), or repetition (18%).

Longitudinal Cognitive Performance (Online Only Figure S1)

Case 1 is a 76-year-old woman with 12 years of education. Her initial cognitive symptomatology included short-term memory difficulties, and vague, imprecise speech

output, and her baseline testing was performed 22 months after symptom onset. Although her cognitive profile marginally improved, she still remained in the mildly impaired range on memory at follow-up, and continued to report verbal recall difficulties in everyday life.

Case 2 is a 56-year-old woman with 16 years of education. Early cognitive difficulties included poor short-term recall, misplacement of objects, poor planning, and repetitive questioning. Her baseline testing was 5 months after symptom onset; sixteen months later, she displayed variable changes in cognitive performance, although language functions represented the only cognitive domain that remained in the mildly impaired range.

Case 3 is a 66-year-old woman with 13 years of education. Initial cognitive symptoms included confusion and increased speech output, and evolved to include difficulties with planning and short-term memory. Greatest improvements in cognitive functioning occurred between her first two visits at 5 months and 51 months from symptom onset, which was also the longest duration from baseline. Her cognitive presentation remained relatively stable between her 2nd and 3rd visit, with no objective impairments.

Case 4 is a 64-year-old man with 20+ years of education. Initial cognitive symptoms included confusion and disorientation, and progressed to difficulties with memory, planning, “speech arrests”, and word finding. He did not present with impairments at his initial visit at 7 months from onset, however his scores were considered lower than expected given his level of education. His testing showed mild improvements in multiple domains over the course of his next two follow-ups, at 21 months and 32 months from onset. He continued to report feeling less cognitively ‘sharp’ at his final visit.

Case 8 is a 48-year old woman with 20+ years of education. Her initial cognitive symptoms included a sudden onset of retrograde amnesia, extending back approximately 5 years, as well as short-term memory and calculation difficulties. She displayed verbal memory difficulties on baseline testing at 9 months from symptom onset; however, her memory markedly improved over the next few months. Cognitive testing at 16 months from symptom onset revealed average performance, although she continued to report difficulties with recalling recent and long-term events.

Discussion

Patients presenting with VGKC_C-Ab AE exhibit broad cognitive deficits that extend beyond impoverished memory consolidation profiles. This study extends and expands upon prior neuropsychological studies of VGKC_C-Ab patients(7). Specifically, we delineated areas of both impairment (memory, executive function, and language) and cognitive preservation (visuospatial function), and identified individual cognitive measures with potentially strong diagnostic utility (verbal fluency; cognitive switching). We also showed that although patients improve over time, there are still residual impairments or plateaus in improvements in some patients.

Consistent with prior AE reports detailing impairment on measures of episodic memory(2,3,5,13–16), our study suggests that recall deficits are a primary source of both subjective complaints and objective clinical presentation in patients with VGKC_C-Ab.

Imaging changes in patients with VGKC_C antibodies are commonly seen in MTL structures(13), thereby corresponding with their memory-predominant profile. Indeed, the most common antigenic target of these antibodies (LGI1) is also found abundantly within the MTL but is more diffusely expressed throughout the brain(17). Prior studies have also hinted at executive dysfunction(6,7,14), but assessments have typically been limited. Results from our study suggest that executive functioning impairment is clearly evident; although we administered more tests of executive functions relative to memory, our findings highlight that assessment of this domain is critically important to understanding VGKC_C-Ab cognitive symptomology. Furthermore, we examined not only composite scores, but also individual subtests. Our patients displayed notable impairment on measures of fluency (i.e. phonemic, category) and cognitive switching (i.e. Modified Trails), suggesting that these tests may provide greater sensitivity to executive impairment. Patients were not impaired on tests that measure inhibition; further studies, however, are warranted to definitively select the most robust assessments. An additional consideration is whether the impairments stem from information processing speed deficits. Executive functions are highly influenced by processing speed, thus general slowing may have contributed to the subjects' performance; given intact performance on some timed tasks (i.e. Stroop), however, it is unlikely that results were driven *solely* by speed.

An unexpected finding was the variable language difficulties in a few subjects, primarily in confrontation naming. Our subjects also showed deficits in category fluency, which relies both on executive and language functions. Whereas isolated studies have suggested that word finding impairments may represent a central feature of AE(3,15,18), other studies have excluded language functions from their assessment or even found relative language preservation(8). Word finding difficulty is a heterogeneous cognitive symptom that may connote language impairment (i.e. phonological/lexical access) or executive dysfunction (i.e. retrieval), rendering it difficult to determine the origin of these difficulties. Additional studies examining language functions in a larger sample may be beneficial in parsing out the etiology of their presentation.

Our subjects displayed relative preservation of visuospatial skills. Given that cognitive patterns of strength and weakness may be helpful in differential diagnosis (i.e. ruling out a more posterior degenerative process, such as Alzheimer's disease) and in monitoring these patients in future studies, isolating visuospatial skills as a cognitive strength in patients with VGKC_C-Ab may yield greater diagnostic clarity.

Finally, a global cognitive measure (MMSE) was administered to all subjects, and only 4/12 patients displayed striking impairment. Several individuals who performed within normal range on the MMSE displayed memory deficits on more comprehensive testing. In addition, the MMSE did not identify the executive dysfunction present in many subjects. Although global measures such as the MMSE can be useful, our results highlight that further testing of individual cognitive domains is warranted.

An important consideration in evaluating the cognitive presentation is whether the phenotype corresponds to the proposed neuroanatomy. The noted memory deficits are consistent with the predilection of AE's to target limbic structures and are congruent with

this study's MRI findings of MTL abnormalities. The executive dysfunction and mild language deficits extend beyond the anatomy denoted by the classic terminology of limbic encephalopathy and suggest a contribution of lateral frontal, basal ganglia, or white matter by the inflammatory disease process. Although only two individuals displayed T2 hyperintensities in basal ganglia structures, this does not negate the possibility of subtle changes in fronto-subcortical connections or decrements in network connectivity. Given the susceptibility of white matter to chronic immune processes(19), it may also be that white matter involvement with associated alterations in white matter signal and/or diffusion metrics account for variations in cognitive presentations.

We also evaluated longitudinal data available for five cases. Appraisal of these cases revealed variability in course, although no dramatic declines in any domain were noted. Importantly, two of five patients remained in the impaired range on one domain (i.e. language, memory) at follow-up, and all patients continued to report subtle cognitive difficulties. Each patient varied in terms of immune treatment; overall, however, this suggests that although cognitive symptomology may improve over time (or at least rise above mild impairment), some patients continue to experience lingering subjective difficulties that are not fully abated by treatment. This is consistent with a recent report by Butler and colleagues(20) that reported while most VGKC_C-Ab subjects' cognition improved with immunotherapy, residual memory deficits were still evident. Although the sample size of our study remains small, recovery is clearly incomplete for these subjects and may include lasting deficits in memory and other cognitive domains (e.g. language).

The current study offers numerous strengths, including a comprehensive assessment of major neuropsychological domains with a focus on elucidating strengths and weaknesses. In addition, patients included in the study were referred from the entire department of neurology rather than subspecialties (e.g. epilepsy centers), thereby minimizing the likelihood of sample selection bias. It is also important to comment on limitations and confines of interpretation. First, sample sizes remain small and only descriptive statistical analyses were provided; thus caution is warranted in making overarching generalizations. In addition, given that many AE patients present to multiple physicians before receiving an accurate diagnosis, our center was often not their first stop in the assessment process. As is the case with other rapidly progressive dementias, AE subjects are often difficult to diagnose, and thus are seen at tertiary care centers at different stages of their disease(21). As such, our sample represents an amalgamation of patients with varying degrees and types of immunotherapy, rendering an investigation of pre- versus post-treatment cognitive profiles difficult; nevertheless, as limited literature exists on longitudinal progression in VGKC_C-Ab, such descriptive analyses remain important. Finally, although some cognitive deficits could conceivably be due to seizure activity associated with the encephalitis, none of our patients were felt to have ongoing seizures.

In summary, this study demonstrates disproportionate impairment of memory and executive functions in VGKC_C-Ab AE, with variable impairments in language and relative sparing of visuospatial skills. Findings gleaned from the study underscore the importance of evaluating detailed performance across multiple cognitive domains, and suggest that focal memory assessments fail to capture the breadth of neuropsychological dysfunction in VGKC_C-Ab

AE. Delineating the relative strengths and weaknesses for AE remains important for differential diagnosis, and has significant implications for the development of focused cognitive therapies and compensatory rehabilitation techniques. Furthermore, identification of sensitive cognitive measures in VGKC_C-Ab will facilitate optimization of disease-specific cognitive outcome measures for clinical trials and yield greater understanding of the long-term benefits of immunotherapies for VGKC_C-Ab AE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank the laboratories of Angela Vincent and Josep Dalmau for determining antibody levels/titers for several of our subjects, and Kendra Bechtel for coordinating research visits for these patients; we would also like to thank our patients and their families for their participation and collaboration.

Funding:

The study was supported by grant numbers ADRC:P50AG023501, NIH/NCRR UCSF-CTSI (UL1RR024131), and NIH/NINDS Contract (N01-NS-0-2328). BMB was supported by NIH/NIA K23AG042492-01, Alzheimer's Association (NIRP-12-259223), and UCSF Resource Allocation Program. MDG was supported by NIH/NIA K23AG021989, R01AG031189, P01AG021601, and the Michael J. Homer Family Fund. JMG was supported by the National Center for Advancing Translational Sciences of the NIH (KL2TR000143).

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Figure 1. Proportion (%) of VGKc-Ab patients impaired on neuropsychological tests, grouped by cognitive domain

Displays the proportion of patients whose individual tests were greater than 1.5 standard deviations below the normative sample. Verbal memory and executive function tests were the most commonly affected. Language tests were variably impaired, and visuospatial domains were less commonly affected.

Table 1

Clinical Characteristics of VGKC Limbic Encephalitis

Case	Demographics Age, Sex, Educ	Primary Symptoms Seizures: Yes/No Primary symptoms	Antibody Status Days Since Onset (DSO) Days Relative to Testing (DRT) VGKC Results LGII Results	Treatment Days Since Onset (DSO) for 1 st Immunosuppressive Tx Prior to Cognitive Testing At 1 st Cognitive Testing Seizure Medication: Yes/No	MRI: Days Since Onset(DSO) Days Relative to Testing (DRT) Results	Cognitive Testing Days Since Onset (DSO) Results
1	76, F, 12	Seizures: Yes Symptoms: Anxiety; STM difficulties; hallucinations; FBDS; disinhibition	DSO: 699 Days Post DRT: 39 Days Post VGKC: 190 pM (ref <20) ^A LGII: Not tested	DSO: N/A Prior: None 1st Cog: None Seizure Medication: phenytoin	DSO: 660 Days Post DRT: Same Day T1: No significant atrophy Flair: Hyperintense L MTL T2: Punctate subcortical WM hyperintensities; capping of anterior horns of lateral ventricles; 2 punctate L OFC hyperintensities	DSO: 660 Days Post Results: Moderate impairment on verbal memory; isolated difficulties on category fluency, visual localization, and single-word comprehension.
2	56, F, 16	Seizures: Yes Symptoms: Bradycardia; panic attacks; muscle twitches; delusions; STM difficulties	DSO: 151 Days Post DRT: 1 Day Prior VGKC: Positive ^B LGII: Positive	DSO: 140 Days Post Prior: IV methylprednisolone 1st Cog: Prednisone Seizure Medication: phenobarbital	DSO: 138 Days Post DRT: 14 Days Prior T1: No significant atrophy Flair: Bilateral L>R hyperintense insula, MTL T2: Non-specific WMD; Bilateral, hyperintense insula; subtle MTL hyperintensities	DSO: 152 Days Post Results: Mild-moderate verbal memory impairment; moderate- severe impairment on isolated executive measures; severe naming impairment; preservation of visuospatial
3	66, F, 13	Seizures: Yes Symptoms: Confusion; increased speech output; STM difficulties; FBDS	DSO: 154 Days Post DRT: 1 Day Prior VGKC: 869 pM (ref <450) ^C LGII: Positive ^D	DSO: 154 Days Post Prior: Prednisone 1st Cog: Prednisone Seizure Medication: levetiracetam; valproic Acid	DSO: 140 Days Post DRT: 15 Days Prior T1: No significant atrophy Flair: L Hyperintense MTL T2: Non-specific WMD	DSO: 155 Days Post Results: Severe verbal memory impairment; moderate-severe impairment on isolated executive measures; preservation of visuospatial, language
4	64, M, 20	Seizures: Yes Symptoms: Confusion; STM difficulties; disorientation	DSO: 29 Days Post DRT: 182 Days Prior VGKC: 1240 pM (ref<20.0) ^A LGII: Not tested	DSO: 103 Days Post Prior: IVIG 1st Cog: Prednisone Seizure Medication: levetiracetam	DSO: 3 Days Post DRT: 208 Days Prior T1: No significant atrophy T2/Flair: L>R hyperintense hippocampi, uncus	DSO: 211 Days Post Results: Mild verbal memory and category fluency impairment; preservation of visuospatial, language
5	62, F, 20	Seizures: Yes Symptoms: spatial and memory difficulties; poor planning/ organization	DSO: 245 Days Post DRT: 223 Days Prior VGKC: 520 pM (ref <20.0) ^E LGII: Positive ^D	DSO: 273 Days Post Prior: IVIG; Prednisone 1st Cog: Prednisone Seizure Medication: levetiracetam; phenytoin	DSO: 256 Days Post DRT: 212 Days Prior T1: Biparietal atrophy T2/Flair: Left hyperintense MTL	DSO: 468 Days Post Results: Severe verbal and visual memory impairment; mild-severe executive dysfunction; preservation of visuospatial, language
6	58, F, 12	Seizures: Yes Symptoms: STM difficulties; anxiety; confusion; inappropriate laughter	DSO: 91 Days Post DRT: 176 Days Prior VGKC: Positive ^A LGII: Not tested	DSO: 89 Days Post Prior: IV methylprednisolone; IVIG; Prednisone; PLEX 1st Cog: Prednisone Seizure Medication: topiramate	DSO: 306 Days Post DRT: 39 Days Post T1: Bilateral hippocampal atrophy; Bilateral hyperintense MTL	DSO: 267 Days Post Results: Severe verbal and visual memory impairment; moderate- severe executive dysfunction; preservation of visuospatial

Case	Demographics Age, Sex, Educ	Primary Symptoms Seizures: Yes/No Primary symptoms	Antibody Status Days Since Onset (DSO) Days Relative to Testing (DRT) VGKC Results LGII Results	Treatment Days Since Onset (DSO) for 1 st Immunosuppressive Tx Prior to Cognitive Testing At 1 st Cognitive Testing Seizure Medication: Yes/No	MRI: Days Since Onset(DSO) Days Relative to Testing (DRT) Results	Cognitive Testing Days Since Onset (DSO) Results
					T2/Flair: Bilateral(R>L), Hyperintense Bilateral(R>L), Hyperintense MTL, Punctate hyperintensities in subcortical WM GE: Multiple foci of microhemorrhages	MTL, Punctate hyperintensities in subcortical WM Punctate hyperintensities in subcortical WM
7	79, M, 20	Seizures: Yes Symptoms: STM difficulties; FBDS	DSO: 482 Days Post DRT: Same Day VGKC: 765 pM (ref <450) ^C LGII: Positive ^D	DSO: 159 Days Post Prior: Prednisone 1st Cog: Prednisone Seizure Medication: No	DSO: 298 Days Post DRT: 184 Days Prior T1: Mild, biparietal atrophy T2/Flair: Mild, bilateral hyperintense hippocampi, amygdala	DSO: 482 Days Post Results: Isolated impairment in visuoconstruction; preservation of memory, executive functions and language
8	48, F, 20	Seizures: No Symptoms: Sudden onset of retrograde amnesia, extending several years back; STM difficulties	DSO: 153 Days Post DRT: 123 Days Prior VGKC: 171pM (ref<100) ^A LGII: Positive ^D	DSO: 14 Days Post Prior: IV methylprednisolone; Prednisone; 1st Cog: Prednisone Seizure Medication: No	DSO: 321 Days Post DRT: 45 Days Post T1: Mild, superior biparietal atrophy Flair: Few, small punctate hyperintensities in subcortical WM; Hyperintense R amygdala T2: Mild hyperintensities in frontal WM	DSO: 276 Days Post Results: Severe impairment in verbal memory; preservation of executive functions, language, and visuospatial
9	70, F, 12	Seizures: Yes Symptoms: Confusion; mouth twitching; delusions; STM difficulties	DSO: 309 Days Post DRT: Same Day VGKC: 460 pM (ref<20) ^A LGII: Not tested	DSO: 149 Days Post Prior: IVIG; Prednisone; PLEX; Rituximab 1st Cog: None Seizure Medication: levetiracetam	N/A	DSO: 309 Days Post Results: Moderate-severe impairment on verbal and visual memory, executive function, language; preservation of visuospatial
10	77, F, 16	Seizures: Yes Symptoms: Personality change; STM difficulties; FBDS	DSO: 56 Days Post DRT: 1149 Days Prior VGKC: Positive ^A † LGII: Positive	DSO: 92 Days Post Prior: IV methylprednisolone; Prednisone; IVIG; mycophenolatemofetil; PLEX; Rituximab 1st Cog: None Seizure Medication: No	DSO: 192 Days Post DRT: 1013 Days Prior T1: L>R mild fronto-parietal atrophy T2/Flair: Non-specific WMD; Hyperintense L putamen and caudate, L insula and MTL	DSO: 1205 Days Post Results: Severe impairment on verbal and visual memory; isolated impairment on executive functions, visual localization and naming.
11	53, M, 20	Seizures: Yes Symptoms: Bradycardia; STM problems; Fatigue; alterations in consciousness	DSO: 334 Days Post DRT: 1 Day Prior VGKC: Positive ^B LGII: Positive ^D	DSO: 273 Days Post Prior: IV methylprednisolone; Prednisone 1st Cog: None Seizure Medication: topiramate; oxcarbazepine	N/A	DSO: 335 Days Post Results: Mild-severe impairment on executive functions; sparing of memory, language and visuospatial
12	64, M, 20	Seizures: Yes Symptoms: Bradycardia; anxiety; compulsions; STM difficulties; delusions	DSO: 175 Days Post DRT: 37 Days Prior VGKC: 110 pM (ref<20) ^A LGII: Positive ^D	DSO: 186 Days Post Prior: IV methylprednisolone 1st Cog: None Seizure Medication: valproic acid	DSO: 223 Days Post DRT: 11 Days Post T1: L Hyperintense caudate and anterior putamen T2/Flair: Bilateral, hyperintense MTL, medial cortex; Hyperintense	DSO: 212 Days Post Results: Severe impairment on verbal and visual memory; mild to moderate executive dysfunction; isolated impairment on repetition; sparing of visuospatial

Case	Demographics Age, Sex, Educ	Primary Symptoms Seizures: Yes/No Primary symptoms	Antibody Status Days Since Onset (DSO) Days Relative to Testing (DRT) VGKC Results LGII Results	Treatment Days Since Onset (DSO) for 1 st Immunosuppressive Tx Prior to Cognitive Testing At 1 st Cognitive Testing Seizure Medication: Yes/No	MRI: Days Since Onset(DSO) Days Relative to Testing (DRT) Results	Cognitive Testing Days Since Onset (DSO) Results
					caudate, anterior putamen and globus pallidus. caudate, anterior putamen and globus pallidus.	

Unless otherwise stated, diffusion/gradient echo (GE) scans were unremarkable.

Abbreviations: L=left; R=right. MTL=medial temporal lobes; OFC=orbitofrontal cortex; WM= white matter; WMD=white matter disease; PLEX=plasma exchange; FBDS: faciobrachial dystonic seizures; STM=short-term memory; Laboratory information:

- ^A Mayo Clinic, Rochester;
- ^B Research Laboratory of Josep Dalmau;
- ^C Athena Laboratory;
- ^D Research Laboratory of Angela Vincent;
- ^E Quest Laboratories;

[#] Participant also tested positive for Voltage-Gated Calcium Channel (VGCC) antibodies

Table 2

Neuropsychological Scores at First UCSF Evaluation

Global Raw			Memory Raw (Z-Score)		Executive Functions Raw (Z-Score)					Visuospatial Raw (Z-Score)			Language Raw (Z-Score)					
Case	Age	DSO	Tx S	MMSE	CVLT*	Benson-D	D-Words	Animals	Digit-B	Mod. Trails	Stroop-Inh	Design Flu.	Benson-C	VOSP	BNT	PPVT	Repetition	
VGKC	1	76	660	Pre	27	2/9 (-2.1)	7 (-1.2)	14 (-0.4)	8 (-2.5)	4 (-0.8)	36" (+0.3)	42 (-0.4)	14 (-1.3)	2 (-3.0)	13 (-0.9)	14 (-1.6)	5 (+0.6)	
	2	56	152	On	26	5/9 (-1.9)	14 (+0.6)	7 (-2.1)	18 (-1.0)	6 (+0.5)	120" (-8.7)	43 (-1.0)	17 (+1.4)	9 (-0.1)	9 (-6.1)	16 (+0.5)	5 (+0.4)	
	3	66	155	On	29	2/9 (-4.1)	9 (-0.9)	6 (-1.9)	12 (-1.9)	4 (-1.4)	73" (-4.5)	60 (+0.9)	15 (-0.2)	10 (+0.6)	14 (-0.4)	16 (+0.4)	4 (-1.4)	
	4	64	211	On	28	4/16 (-1.5)	10 (-0.9)	13 (-0.9)	12 (-2.8)	5 (-0.3)	N/A	41 (-1.3)	N/A	10 (+0.8)	14 (-0.5)	16 (+0.4)	4 (-1.0)	
	5	62	468	On	29	2/16 (-2.5)	6 (-2.4)	7 (-2.3)	10 (-3.3)	4 (-1.1)	46" (-1.6)	52 (-0.4)	15 (-0.5)	10 (+0.8)	15 (+0.6)	15 (-1.6)	5 (+0.4)	
	6	58	267	On	23	0/9 (-5.3)	1 (-5.0)	N/A	N/A	2 (-2.6)	120" (-8.1)	N/A	16 (+0.4)	N/A	N/A	N/A	N/A	
	7	79	482	On	28	10/16 (+1.0)	10 (0.0)	20 (+1.0)	20 (-0.1)	6 (+0.5)	N/A	54 (+0.9)	14 (-1.6)	7 (-0.9)	15 (+0.7)	16 (+0.7)	5 (+0.5)	
	8	48	276	On	30	5/16 (-2.5)	14 (+0.6)	16 (-0.2)	24 (+0.5)	5 (-0.3)	17" (+0.8)	53 (-0.3)	17 (+1.8)	10 (+0.8)	15 (+0.6)	16 (+0.4)	5 (+0.3)	
	9	70	309	Post	19	0/9 (-3.0)	6 (-1.9)	4 (-2.3)	2 (-4.0)	4 (-1.4)	120" (-9.1)	N/A	2 (-3.2)	16 (+0.5)	N/A	3 (-12.7)	8 (-19.5)	3 (-3.4)
	10	77	1205	Post	19	0/9 (-3.0)	2 (-3.0)	7 (-1.8)	19 (-0.2)	3 (-1.6)	49" (-0.3)	N/A	12 (+0.8)	16 (+0.3)	5 (-1.6)	12 (-1.8)	N/A	4 (-0.9)
	11	53	335	Post	29	8/16 (-0.5)	11 (-0.5)	7 (-2.3)	12 (-2.8)	3 (-1.9)	N/A	44 (-1.0)	N/A	16 (+0.4)	9 (-0.2)	15 (+0.6)	16 (+0.4)	4 (-1.0)
	12	64	212	Post	23	3/9 (-3.4)	4 (-3.1)	11 (-1.4)	15 (-2.2)	4 (-1.1)	69" (-3.6)	33 (-1.9)	6 (-2.0)	16 (+0.4)	8 (-1.2)	15 (+0.6)	16 (+0.4)	4 (-2.2)
Group Mean (Z-score)					-2.4	-1.5	-1.3	-1.8	-1.0	-3.9	-0.5	-0.4	0.1	-0.4	-1.8	-2.0	-0.7	

Bold Values Reflect Impairment

Abbreviations: DSO= Days since symptom onset; Tx S= Treatment Status; MMSE= Mini-Mental State Exam; CVLT= California Verbal Learning Test, Delayed Free Recall; Benson-D= Benson Figure, Delayed Recall; Digit-B= Digits Backwards; Mod. Trails= Modified Trails; Stroop-Inh=Stroop Inhibition; Design Flu.= Design Fluency; Benson-C= Benson Figure, Copy; VOSP= Visual Object Space Perception, Number Location; BNT= Boston Naming Test; PPVT= Peabody Picture Vocabulary Test.

* Note that some individuals received short form, and some individuals received the long form.