

Case Report

New Onset Epilepsia Partialis Continua Presenting as Complex Visual Hallucinations associated with Voltage-Gated Potassium Channel Antibody

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A 54-year old female with past medical history significant for rheumatoid arthritis on immunosuppressant therapy presented with episodes of left-sided shaking and left gaze deviation with decreased level of consciousness. A preceding one-month history of complex visual hallucinations was subsequently elicited. Brain Computed Tomography (CT) perfusion and Magnetic Resonance Imaging (MRI) showed changes in the right parieto-occipital lobe that were consistent with possible seizure activity. Electroencephalogram (EEG) subsequently confirmed electrographic seizures originating from the right occipital region during active hallucinations. Patient's right occipital lobe epilepsy partialis continua was refractory to as many as 5 concomitantly administered antiepileptic medications. Patient was subsequently treated for presumed autoimmune encephalitis, but demonstrated no response to IV steroids, and showed only marginal improvement to IVIG infusion. Serum testing ultimately showed a high titer of voltage-gated potassium channel (VGKC) antibodies; and after a 5-day course of plasma exchange the patient finally achieved better control of her partial seizures, requiring long-term therapy with multiple antiepileptic medications for seizure control.

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BACKGROUND

Autoimmune-mediated encephalopathies have significant variability in clinical phenotype on presentation. Limbic encephalitis (LE) associated with voltage-gated potassium channel (VGKC) antibodies was fairly recently described and identified to be as one of the reversible forms of LE.¹ Subsequently VGKC antibody-associated LE has been more frequently described with typical characteristics of seizures (frequently complex partial seizures), memory impairment, behavioral changes, and sleep disturbances, rarely in association with tumors.² The VGKC antibodies specifically against the leucine-rich, glioma inactivated 1 protein (LGI1) of the VGKC complex are associated with LE. Presentations of this type of LE tend to be highly variable. LE associated with VGKC antibodies has been described as a cause of adult onset mesial temporal lobe epilepsy (MTLE),³ refractory partial complex seizures,^{4,5} and auditory hallucinations with ictal EEG correlate.⁶ Clinical criteria for LE include focal seizures, psychiatric features, and confusion, but presentations

are highly variable. In VGKC-associated LE, MRI changes most often include T2 signal changes in one or both temporal lobes or hippocampi and frontal lobes^{3,4,6,7} and are sometimes associated with hyponatremia,⁵ presumably from thalamic involvement. To date, no complex visual hallucinations with EEG correlate have been described in these patients. Complex visual hallucinations related to seizure activity are usually described as brief, stereotyped and fragmentary, although sometimes prolonged with partial status epilepticus⁸, associated with seeing people's faces or animals⁹ and sometimes localized to a part of a visual field. The previously described auditory complex hallucinations in association with VGKC antibodies were thought to be related to the LGI1 glycoprotein with the hypothesis that this protein may be integral to the development of the lateral neocortex, with mutations associated with autosomal dominant lateral temporal epilepsy. We present here a unique case of VGKC antibody-associated new onset epilepsia partialis continua originating from the right occipital lobe, resulting in intricate complex visual hallucinations, refractory to multiple antiepileptic medications ultimately with some improvement and better seizure control after a course of IV steroids, multiple courses of IVIG and 5 sessions of plasma exchange.

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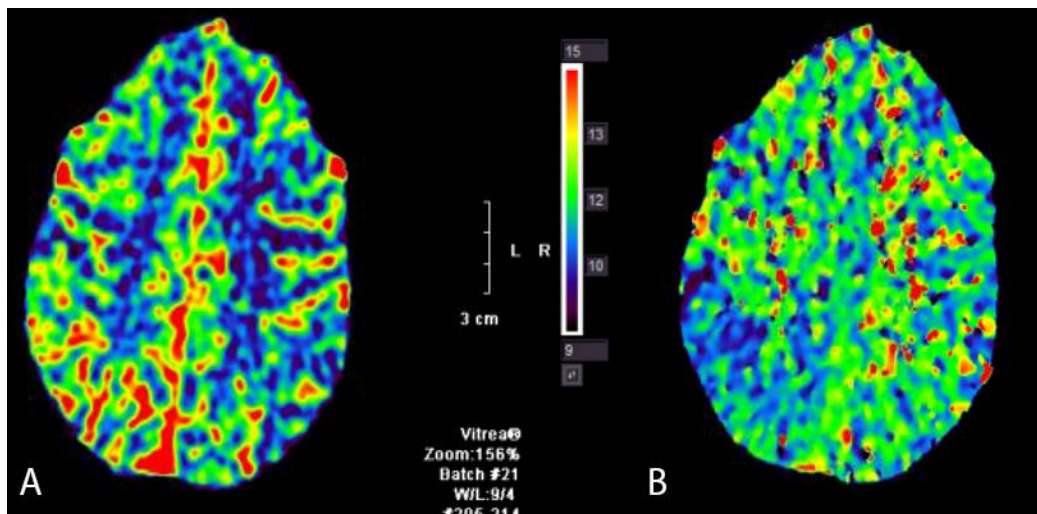


Figure 1. CT perfusion study showing slightly increased cerebral blood volume (A) and increased time to peak (B) in the right parietal lobe.

CASE PRESENTATION

A 54-year old right-handed Caucasian female with past medical history of insulin dependent diabetes mellitus with diabetic neuropathy, hypothyroidism, rheumatoid arthritis, and depression, presented with epilepsia partialis continua with 4-5 episodes of left upper and lower extremity shaking lasting 2-5 minutes each time over about 1 hour, without returning to baseline in between the episodes. On presentation to the emergency room patient was lethargic, unable to follow commands, and responded to questions with severely slurred speech. She had slightly increased tone in left upper and lower extremities with left facial droop and left forced gaze deviation.

The patient was taken emergently for a brain CT angiogram

and perfusion for evaluation of possible acute stroke, and was found to have slightly decreased time to peak with a slight increase in cerebral blood volume in the right parieto-occipital region and on the perfusion study. (**Figure 1**). MRI brain with and without contrast was read as unremarkable initially; but upon careful review, it revealed some T2 hyperintensity in the cortex of the right temporal and occipital lobes. (**Figure 2**).

Given the history and initial workup, the patient was treated with Lorazepam 2mg IV, as well as a loading dose of Phenytoin of 20 mg/kg for status epilepticus. Patient's mental status improved somewhat following the treatment. She started following some simple commands.

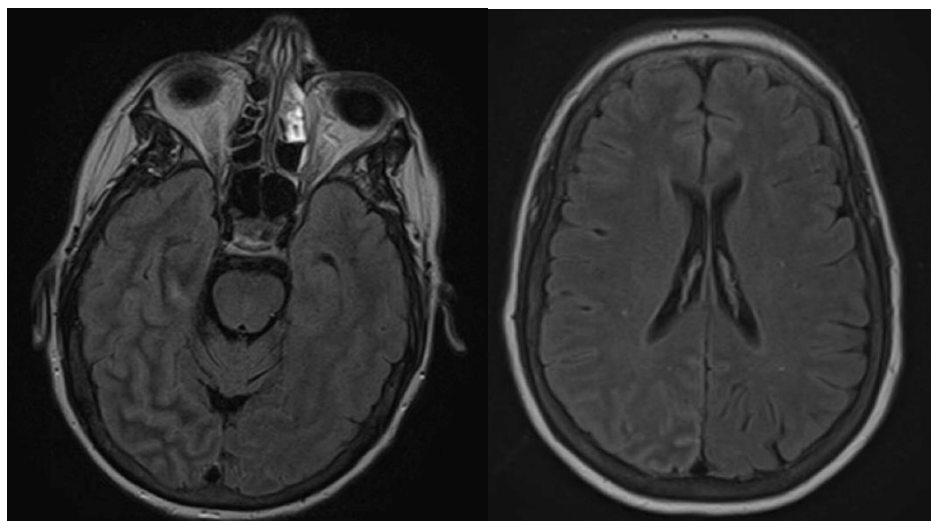


Figure 2. T2 FLAIR MRI sequences showing subtle signal hyperintensity in the right temporoparietal and occipital cortices on initial presentation.

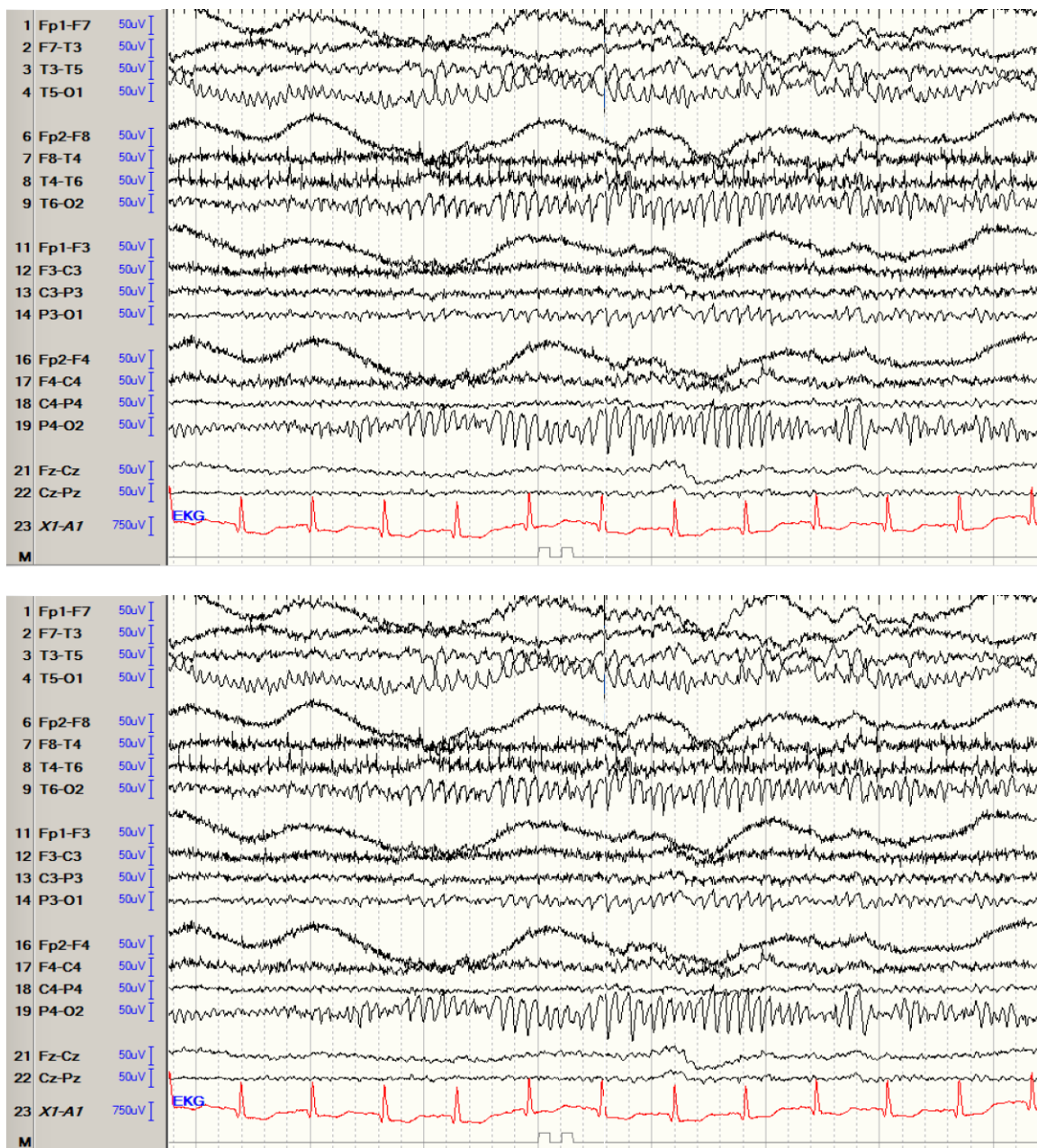


Figure 3. EEG showing the start of seizure activity in the right occipital lobe (A) and evolution of further electrographic seizure activity with additional involvement of the left occipital lobe (B).

A routine EEG done on the following day captured 3 electrographic seizures originating from the right occipital lobe as demonstrated in **Figure 3**. The patient reported having episodes of visual hallucinations in the left visual field correlated with the captured electrographic seizures. The patient was then started on Levetiracetam 1000mg BID in addition to Phenytoin 100mg TID for further seizure management. Patient described intermittently seeing a complex scene with multiple people at a fundraising auction walking around tables and looking at different baskets on those tables to bid on. Some of those people were known to patient, and the fundraiser was for someone whom she knew in the past

who needed a lung transplant. Patient also reported intermittently seeing flashing lights, mostly green in color primarily in her left visual field. She additionally complained of significantly decreased visual acuity in between the episodes.

Upon obtaining further history, it became evident that patient's symptoms began about 1 month prior to admission when patient started seeing occasional bright flashing lights in her left visual field and had a worsening of her baseline sinus headaches, with bifrontal pressure sensation. She presented initially to an outside facility, where a CT head showed sinus

opacification and patient was started on amoxicillin for treatment of sinusitis. Patient was discharged to home, but continued to see flashing lights intermittently, which progressed to visual hallucinations of seeing faces of people she knew or used to know (deceased people). She continued to take her tramadol which she had been on for about 2 years for her chronic joint pain and sinus headaches as needed, 1-2 times a day. She denied any auditory hallucinations or any episodes of extremity shaking. No significant confusion or memory changes were noted at that time either. She was also complaining of worsening visual acuity in both eyes overall and therefore presented to the outside facility again several days later with more work up performed, including a reportedly unremarkable MRI brain with and without contrast, and an ophthalmology evaluation which did not demonstrate any intraocular abnormalities, but only moderately decreased visual acuity of 20/70 in both eyes with normal intraocular pressures. Patient's visual hallucinations of people were then attributed to a potential side effect of amoxicillin. Therefore, she was switched to clindamycin with hydrocodone/acetaminophen tablets as needed for headache. Patient's headaches did not improve, and her somnolence increased with the additional opiate medications for pain control. Five days later the patient presented with epilepsy partialis continua to our hospital.

Upon admission patient had a lumbar puncture performed which showed 6 red blood cells/mm³, 1 nucleated cell/mm³, glucose of 184 mg/dl (with serum glucose at 354 mg/dl), and protein of 31 mg/dl. Cerebrospinal fluid analysis was also negative for infection including treponema pallidum, CMV, EBV, HSV 1 and 2 and HHV-6, and Lyme. A lumbar puncture was later repeated on day 9 of admission as well, again negative for infectious causes with normal protein.

On day 2 of admission bedside continued video EEG monitoring was started, which demonstrated epilepsy partialis continua with frequent seizures originating in the right occipital region. Levetiracetam was subsequently increased to 1500 mg twice a day, then to 2000 mg twice daily, and Tramadol was discontinued due to the concern of lowering seizure threshold. Given that the patient continued to have frequent episodes of visual hallucinations with EEG correlates, Oxcarbazepine was added, followed by addition of Lacosamide, Phenobarbital, and Clonazepam over the next several days. With multiple antiepileptics, the patient's visual hallucinations became less complex, the scene of the fundraiser and of people did not recur, but patient continued to have frequent and prolonged episodes of flashing green lights in her left visual field with persistently diminished visual acuity postictally. Her mental status continued to improve.

MRI brain with and without contrast repeated on day 6 of admission and showed a focal abnormality involving the visual cortex, calcarine region, as well as the more inferior occipital lobe and posterior temporal lobe on the right, with enhancement, FLAIR hyperintensity, but only minimal diffusion asymmetry.

On Day 7 of admission, given the lack of response to multiple antiepileptic drugs, negative lumbar puncture, and worsening MRI findings, the patient was started on methylprednisolone 1 gram IV x 3 days for presumed autoimmune encephalitis. Minimal improvement was observed with worsening of patient's diabetic glucose control. Therefore, a course of immunoglobulin infusion 2 mg/kg divided over 5 days was given. Some improvement was seen in the first two days of IVIG with less frequent seizures. The patient still had frequent intermittent hallucinations with red and green lights. Visual acuity severely limited at 20/200 bilaterally, worse in the left visual field.

Additional serum autoantibody testing was sent, including VGKC antibody (which later returned positive at 249 pmol/L). Anti-NMDAR antibodies, neuron specific enolase, thyroid microsomal antibody, thyroglobulin antibodies, anti-hu Western blot, anti-Ri antibody, anti-glutamic acid decarboxylase antibody were negative. Sjogrens Syndrome-A ENA was sent as well and returned positive (no titer available), thought to be an incidental finding given patient's history of rheumatoid arthritis. Unfortunately, for the subtyping for LGI-1 was not performed.

Repeat MRI brain with and without contrast on day 15 after admission did not demonstrate increase in size of previous T2 hyperintensity, but showed more conspicuous diffusion restriction of the cortical ribbon of the right occipital lobe, with less avid enhancement than before (**Figure 4**).

Six days after completing the course of IVIG, the patient's hallucinations became more complex including seeing a man in a plaid shirt with a hole in the shirt, and a man in a suit with dark hair by the bed stand. Flashing lights of red and green also increased in frequency and duration. It was noted at this time that Clonazepam had been auto-discontinued for two days by Electronic Medical Record system and it was therefore restarted at this time. The patient received two additional days of IVIG (0.4 mg/kg/dose) and subsequently started plasmapheresis on Day 21 of admission with 5 courses of plasma exchange every other day. She had significant improvement in her hallucinations, which became less complex, only with some occasional patterns of wallpaper-like pattern when the patient's eyes were open, and later improved to seeing the patterns only when eyes were closed and rare occasional episodes of flashing lights. Patient completed 5 courses of plasma exchange on Day 31 of admission, with a significant decrease frequency and duration of flashing lights, lasting less than a minute one to two times per day, with significantly improved visual acuity of 20/70 bilaterally.

Her antiepileptic levels were monitored with Phenobarbital level being therapeutic most of the time. Phenytoin level was subtherapeutic early in the course of treatment and was discontinued shortly after admission. Oxcarbazepine level was also subtherapeutic. Due to a mild hyponatremia (several days of 132-133 mmol/L), the dose of oxcarbazepine was not increased.

After completion of 2 sessions of plasma exchange, MRI brain was repeated and demonstrated continued gradual improvement in restricted diffusion and FLAIR T2 hyperintensities, with trace residual enhancement of the inferior right temporal lobe. Additionally, patient was noted to have persistent paranasal sinusitis and a tooth abscess with a fractured tooth and required additional antibiotics with a balloon sinuplasty and tooth extraction performed on day 29 of admission.

Patient achieved near complete seizure control and was ultimately discharged to home on 4 antiepileptics, including Levetiracetam 2000mg BID, Phenobarbital 194.4 mg BID, Oxcarbazepine 300 mg Qam and 450mg QHS, and Clonazepam TID dosing of 0.25mg-0.25mg-0.5mg. Shortly after discharge patient's autoimmune antibody panel from day 14 of admission resulted and showed a high titer of VGCK antibody, 249 pmol/L (normal < 80pmol/L).

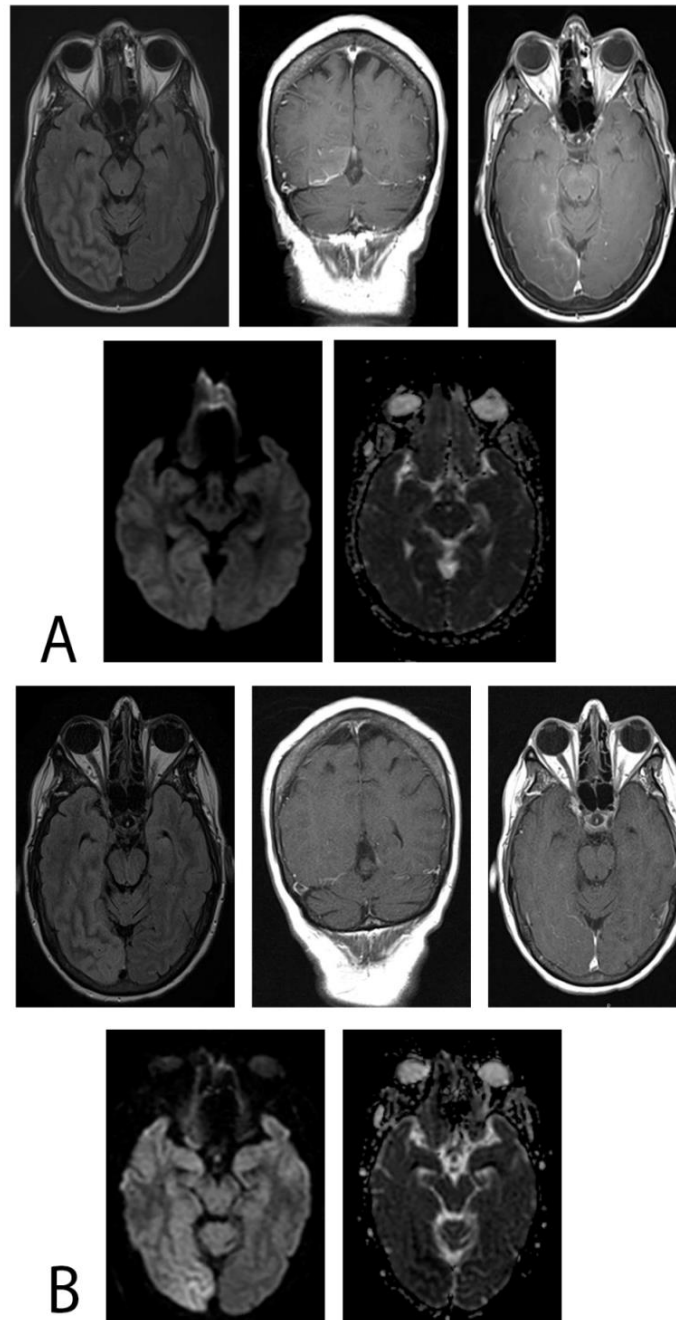


Figure 4. MRI Brain (FLAIR, coronal and axial T1 post-contrast, DWI, and ADC sequences) on day 6 (A) and day 15 (B) of admission.

DISCUSSION

New adult onset epilepsy associated with VGKC antibodies has been described before, as a cause of new onset MTLE,³ refractory partial complex seizures,^{4,5} and auditory hallucinations with ictal EEG correlate⁶ sometimes associated with hyponatremia. Here we presented a case of new onset epilepsy partialis continua with visual hallucinations.

Our patient had some of the typical MRI findings^{3,4,6,7} seen in LE, but was different as she also T-2 hyperintensity and contrast enhancement of the occipital lobe and calcarine cortex, which has not been described in the past.

Our patient also did not have a typical LE presentation as she did not have significant confusion prior to developing the motor partial complex status epilepticus. Her VGKC antibody-associated new adult onset of status epilepticus manifested as visual hallucinations and was highly refractory to treatment, and did not respond well to steroids or IVIG, ultimately requiring plasma exchange and 4 antiepileptic agents for optimal seizure control.

In a single-center chart review study by Jammoul A. et al,¹⁰ 114 patients positive for VGKC antibody were subdivided into high-level ($> 0.25\text{nmol/L}$ or 250pmol/L) and low-level ($< 0.25\text{nmol/L}$, but $> 0.02\text{nmol/L}$ or 20pmol/L) groups. Of the high-level group, 75% had definite or probable autoimmune basis, while nonautoimmune disorders were seen in 75.6% of the patients from the low-level group. Our patient's level of the VGKC antibody was 249pmol/L , just below the cutoff used in the study, which likely indicates a probable autoimmune basis for her new onset epilepsy.

This case demonstrates the importance of having high suspicion for autoimmune LE in new onset adult epilepsy when central nervous system infection is ruled out. VGKC antibody-mediated LE should be kept on the differential and patients should be tested early, with IVIG and plasma exchange used in cases which are not immediately responsive to steroids. In addition, there have also been some case reports with possible development of autoimmune demyelinating disease in patients chronically on anti-TNF-alpha agents.¹¹ It is interesting to note that our patient was also on chronic treatment of her rheumatoid arthritis with golimumab (a TNF-alpha inhibitor) for about 3 years prior to presentation. This more likely coincidental, as it is more likely that our patient had a predisposition to developing autoimmune disorders given her history of hypothyroidism, diabetes, and rheumatoid arthritis, but perhaps the relationship of TNF-alpha inhibitors and development of autoimmune diseases as a whole should be explored further. Our patient so far has not been started on any chronic immunosuppressive therapy for the presumed

autoimmune encephalitis, as she was incidentally already on a small dose of weekly methotrexate for treatment of her rheumatoid arthritis. The golimumab was not restarted. She will be followed very closely for any recurrence or increase in VGKC antibodies, and may require further plasma exchange treatments and potentially additional/stronger immune-suppressive agents if a relapse occurs.

FOLLOW UP

The patient has followed up multiple times in our outpatient neurology clinic after discharge. Her visual hallucinations resolved and she has been seizure free for over 10 months with being slowly tapered off Phenobarbital, but continued to take Levetiracetam, Clonazepam, Oxcarbazepine, and Lacosamide. The MRI brain was repeated about three months after achieving optimal seizure control with complete resolution of previous abnormal findings in the brain parenchyma. Patient's VGKC antibody was repeated one month after discharge and was negative.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose related to this publication.

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