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Auditory hallucinations as ictal phenomena in a patient with voltage-gated potassium channel antibody-associated limbic encephalitis

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ABSTRACT – Limbic encephalitis involving anti-voltage-gated potassium channel antibodies (VGKC-LE) has become increasingly recognised, with seizures and psychotic features, such as hallucinations, being typical clinical manifestations. Though the literature supports auditory hallucinations as ictal phenomena, there are no reported cases of these hallucinations correlating with electrographic seizure for this disease entity. Early recognition of auditory hallucinations as seizures could alter treatment and subsequently affect short-term outcomes in these patients. We report the case of a patient with auditory hallucinations and progressive cognitive decline, as well as serological evidence of VGKC antibodies, in whom ictal hallucinations were identified by continuous video-EEG monitoring. This case highlights the subtlety of this entity, in both clinical and electrographic detection. [*Published with video sequences*]

Key words: auditory, hallucination, seizure, voltage-gated potassium channel antibody

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Case Report

A 79-year-old, right-handed Caucasian woman presented to hospital for evaluation of recurrent auditory hallucinations. She described hearing non-descript voices accompanied by sudden fearfulness and a sense that "*someone was coming to get (her)*". These episodes lasted less than one minute, during which time her family would try to reassure her that the voices would go away. She remained cognizant of her surroundings and conversant. These episodes began 18 months prior to presentation. Initially sporadic, the hallucinations gradually increased in frequency to nearly four per hour in the week preceding her presentation. Over the same time period, the patient's daughters noted that she had progressive decline in working and recent memory, such that she

became dependent on family for reminders to perform most activities of daily living and required frequent reorientation. Due to the concurrent dementia, the hallucinations were thought to be a paranoid manifestation of an underlying dementia.

The patient's medical history was also significant for four occurrences of severe hyponatraemia in the same one-month time period, which were attributed to SIADH of unknown aetiology. She also had a right lower lobe pulmonary nodule which had been stable on serial imaging over the last year. Additionally, she had rate-controlled atrial fibrillation and required a biventricular pacemaker after several failed cardioversion attempts and a complicated AV nodal ablation. Other medical conditions included hypothyroidism, osteoporosis, and COPD. She had a history of smoking 25 packs of cigarettes a year prior to quitting over 20 years ago, and alcohol use was negligible. Family history was unrevealing. Medications included: tolvaptan, warfarin, levothyroxine, raloxifene, estradiol, furosemide, lisinopril, tiotropium, fluticasone, levalbuterol, loratadine, and a multivitamin.

General and physical neurological examination was unremarkable, save for moderate hearing impairment and described cognitive changes. Bedside cognitive assessment, a fully-oriented woman was revealed, with impaired recall at five minutes and intermittent perseveration. Aside from attention deficit, no shortfalls were documented across other cognitive modalities. Brain CT was completed upon arrival with no acute intracranial processes or structural lesions noted. Unfortunately, the patient's pacer dependence precluded the use of MRI in her evaluation. Basic and dementia-specific laboratory examinations (B12, folate, TSH, and RPR) were unremarkable except for sodium at 132 mEq/dL. Continuous electroencephalography with video was initiated, during which the patient experienced several typical events, up to 1-4 per hour, in the initial 24 hours of recording. During these events, the patient would startle, turn to her left, and verbalise "*they're coming*". She described a sensation of intense fear and hearing someone approaching from her left side (*see video sequence)*. No clear EEG correlation was noted with the initial event when reviewed in a bipolar montage. On a referential montage, the symptoms clearly correlated to a right temporal ictal pattern. These electrographic seizures lasted 30-40 seconds. Some shorter clinical events with similar symptoms occurred without any detectable change on EEG. The patient also had rare subclinical right and independent left temporal electrographic seizures without associated clinical signs. There were no interictal abnormalities.

The presence of bitemporal seizures, in combination with hyponatraemia and cognitive decline, raised suspicion of anti-VGKC limbic encephalitis. Anti-VGKC antibody titre from serum was 863 pmol/L, (normal reference range: <100 pmol/L). A review of a previous work-up at another institution one year prior revealed that voltage-gated potassium channel antibodies from CSF sample were found to be "positive", though specific titre was unavailable. By report, video-EEG from that time was unrevealing, albeit without clinical events captured, and no treatments or medications were initiated. No additional work-up was performed relative to the VGKC finding.

Chest CT during admission revealed a 0.6 x 0.5-cm ground glass nodule in the right lower lobe, which was stable according to prior studies. Subsequent PET/CT showed borderline metabolic activity in a nearby pleural-based nodule, raising suspicion of metastasis. Video-assisted thoracoscopic surgery (VATS) was completed and pathology indicated adenocarcinoma. The tumour was staged as T1aN0Mx. A diagnosis of paraneoplastic syndrome was made and the patient underwent five rounds of plasmapheresis, resulting in subjective cognitive improvement. Seizures were initially treated with levetiracetam at 1,500 mg twice daily without clinical improvement, and it was not until phenytoin was initiated that hallucinations and electrographic seizures resolved. The patient established outpatient follow-up and was discharged to go home with a plan to continue outpatient IVIG treatments. Although formal cognitive testing was not pursued to qualify the reported change after initial treatment, subsequent documentation indicated that the patient's dementia steadily progressed. She was also readmitted twice in the eight weeks following discharge for intermittent confusion and worsening memory. As compared with mildly impaired recall at initial presentation, subsequent assessments were notable for significant confabulation and perseveration, and she became fully dependent for all activities of daily living. She was no longer having discrete episodes of auditory hallucinations and repeat video-EEG on both admissions was normal. Sodium level was stable at 132 mEq. She had repeat plasmapheresis (five rounds), but continued to further decline cognitively. Ultimately, her family elected to pursue palliative care. She passed away 16 weeks after presentation.

Discussion

Limbic encephalitis involving anti-voltage-gated potassium channel antibodies (VGKC-LE) is being

increasingly recognised, with memory impairment, psychotic features, seizures, and recurrent SIADH as typical clinical manifestations. Pathophysiology is attributed to lymphocytic inflammation with neuronal loss and gliosis of the mesial temporal lobes (unilateral or bilateral). Recognition of this entity is crucial as treatment with immunotherapies often results in significant clinical improvement, whereas symptoms are often refractory to isolated treatment with anticonvulsants or antipsychotics (Dalmau and Rosenfeld, 2008; Merchut, 2010).

This patient's presentation is unique with regard to "psychotic" manifestations which were actually explained by ictal auditory phenomena. Auditory hallucinations have been noted in several of the reported cases of VGKC-LE, not infrequently noting familiar verbal cues, occurring in proximity to clinical seizures, increasing with disease progression (Vincent *et al*., 2004; Parthasarathi *et al*., 2006). To date, no reported cases of auditory hallucinations in LE have directly correlated auditory hallucinations with EEG evidence of seizure. Case reports of ictal auditory hallucinations, though relatively uncommon, have been described in both mesial and neocortical temporal lobe epilepsies. These phenomena were originally qualified by Penfield and Perot as elementary (simple sounds or volumetric changes) or complex (words, speech, voices, or music/melody) (Penfield and Perot, 1963). Elementary auditory hallucinations usually localise to primary sensory cortex, namely Heschl's gyrus (Elliott *et al*., 2009). Unilateral hallucinations are presumed to originate from activation of the contralateral temporal lobe, though the ability to perceive ipsilateral hallucination has been reported (Clarke *et al*., 2003). Our patient noted hearing "(someone) coming", which has been referenced in the literature as "Hearing of a Presence (HP)", a type of paroxysmal somatognosic disorder, as originally described by Hécaen and Ajuriaguerra in 1952 (Blanke *et al*., 2004). The referenced case report details HP in a patient with left temporal lobe epilepsy in which the patient was able to consistently localise the hallucination to the contralateral extra-personal space. Our patient was unable to explicitly lateralise her hallucination, but was noted on vEEG to attend towards her left side during ictus. All of these clinical seizures corresponded to right temporal electrographic seizures.

Recent research has also found that most anti-VGKC antibodies bind isolated protein components of the VGKC complex, most notably leucine-rich glioma inactivated-1 glycoprotein (LGI1) and contactin-associated protein 2 (CASPR2). Although subunit analysis was not performed on our patient, it is probable that she had antibodies to LGI1. Investigations of autoantibodies in cases of limbic encephalitis have found a significant number of cases with LGI1 positive antibodies, ranging from 77 to 100% of cases in cohort studies of VGKC-LE. These researchers were attempting to link hyponatraemia of VGKC-LE, attributed to SIADH, to the relative increase of LGI1 expression in the hypothalamus and kidney (Lai *et al*., 2010). Interestingly, autosomal dominant partial epilepsy characterised by auditory features (ADPEAF), also known as autosomal dominant lateral temporal epilepsy (ADLTE), is often attributed to a mutation of the gene that encodes the LGI1 glycoprotein (Morante-Redolat *et al*., 2002; Di Bonaventura *et al*., 2009). The manifestation of auditory features in both VGKC-LE and ADLTE may therefore reflect activation of lateral temporal cortical neurons of primary auditory cortex (Irani *et al*., 2010). LGI1 is a glycoprotein secreted from presynaptic terminals associated with voltage-gated potassium channels. It is highly expressed in the hippocampus and neocortex, but present in varying degrees throughout the CNS. *In vitro* studies and animal models have mapped a variable pattern of expression and suggested a key migratory role of LGI1 in normal brain development, as well as regulating synaptic transmission (Nobile *et al*., 2009). One study of a family affected by ADTLE revealed lateral temporal lobe dysgenesis in 10/19 family members with a confirmed LGI1 point mutation, while another study using diffusion-tensor imaging revealed focally elevated fractional anisotropy (FA) in the left middle temporal gyrus in eight patients with LG1 mutations when compared with 24 controls (Kobayashi *et al*., 2003; Tessa *et al*., 2007). Though further research is needed, these studies, as well as the semiology of auditory hallucinations in both ADTLE and the anti-VGKC antibody syndrome, suggest that LG1 may have a specific role in the development of the lateral neocortex and possibly the increased protein expression in this region.

Our patient's clinical presentation was characteristic of VGKE-LE, a diagnosis that should be considered in patients with progressive memory impairment, psychotic features, seizures, and/or recurrent SIADH. This case suggests that seizures should be considered as a possible explanation for any paroxysmal events in LE, particularly if they are stereotyped in nature and relatively short in duration. The majority of our patient's complex auditory hallucination correlated to subtle right temporal lobe seizures on continuous video-EEG monitoring. Simple partial seizures, such as those she experienced, may not have any correlation on EEG, as was seen with shorter auras she experienced. Aforementioned research would suggest pathophysiology of LGI1 antagonism in the neocortical temporal lobe

in this patient. While we look forward to further investigation of the role of LG1 in auditory perception, this case demonstrates that the presence of paroxysmal, stereotyped auditory hallucinations should prompt consideration of an ictal aetiology and, in the correct context, the diagnosis of the anti-VGKC antibody syndrome.

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Legends for video sequences

Video-EEG captured event (with blurred face) is shown twice; first with bipolar longitudinal montage (only temporal chains depicted), with no clear EEG correlate. Patient is noted to be mildly agitated by the presence of EEG wires (Day 1 of recording) as family attends to her. She suddenly appears anxious, looks and gestures with hands towards her left and states "*they're coming in now*" (no doorway in gestured direction). Appearance of fearfulness persists, and the family attempts to calm the patient. She appears initially unable to communicate (with mouth movement and hand gesture to the family without vocalisation), and then appears confused, stating "*what*", and "*I don't know what you're saying*". Moments later, she begins a conversation, out of context, regarding showering. Event is then shown with a referential (Cz) montage (temporal chains) which demonstrates an electrographic seizure characterised by rhythmic, 4-6-Hz, 20-40-μV activity at F8/T8 that evolves to sharply contoured rhythmic 80-μV delta activity and ultimately periodic sharp waves.

Key words for video research on www.epilepticdisorders.com

Syndrome: focal non-idiopathic temporal (TLE)
Etiology: encephalitis
Phenomenology: hallucinations (auditory)
Localization: temporal lobe (bilateral)

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