

2015

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Brian K. Day

Washington University School of Medicine in St. Louis

Lawrence Eisenman

Washington University School of Medicine in St. Louis

Joseph Black

Washington University School of Medicine in St. Louis

Luigi Maccotta

Washington University School of Medicine in St. Louis

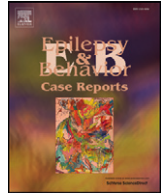
R. Edward Hogan

Washington University School of Medicine in St. Louis

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Recommended Citation

Day, Brian K.; Eisenman, Lawrence; Black, Joseph; Maccotta, Luigi; and Hogan, R. Edward, "A case study of voltage-gated potassium channel antibody-related limbic encephalitis with PET/MRI findings." *Epilepsy & Behavior Case Reports*.4, 23-26. (2015).
https://digitalcommons.wustl.edu/open_access_pubs/5809



Case Report

A case study of voltage-gated potassium channel antibody-related limbic encephalitis with PET/MRI findings



Brian K. Day ^{*}, Lawrence Eisenman, Joseph Black, Luigi Maccotta, R. Edward Hogan

Department of Neurology, Washington University in St. Louis, Campus Box 8111, 660 South Euclid Avenue, St. Louis, MO 63110, USA

ARTICLE INFO

Article history:

Received 11 December 2014

Received in revised form 27 January 2015

Accepted 4 February 2015

Available online 6 June 2015

Keywords:

Voltage-gated potassium channel

Limbic encephalitis

Autoimmune epilepsy

Positron emission tomography

Magnetic resonance imaging

PET/MRI

ABSTRACT

Preclinical and clinical studies have demonstrated the significance of inflammation and autoantibodies in epilepsy, and the use of immunotherapies in certain situations has become an established practice. Temporal lobe epilepsy can follow paraneoplastic or nonparaneoplastic limbic encephalitis associated with antibodies directed against brain antigens. Here, we focus on a patient with worsening confusion and temporal lobe seizures despite treatment with antiepileptic medications. Serial brain MRIs did not conclusively reveal structural abnormalities, so the patient underwent brain PET/MRI to simultaneously evaluate brain structure and function, revealing bitemporal abnormalities. The patient was diagnosed with voltage-gated potassium channel antibody-related limbic encephalitis based on clinical presentation, imaging findings, and antibody testing. Treatment included the addition of a second antiepileptic agent and oral steroids. His seizures and cognitive deficits improved and stabilized.

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1. Introduction

The detection of novel autoantibodies has provided etiological insight into epileptic disorders of previously unknown causes. Forerunners in this area of investigation include voltage-gated potassium channel (VGKC) antibodies, antibodies against the N-methyl-D-aspartate receptor (NMDAR), and antibodies against glutamic acid decarboxylase (GAD). Other noteworthy antibodies include those against AMPA receptors and the GABA_B receptor as well as against onconeural antigens [1,2]. Often, the diagnosis of an autoantibody-related epileptic disorder is made during the evaluation of an acute limbic encephalitis (LE), at times within the setting of drug-resistant status epilepticus. However, autoantibody testing has also returned positive results during the recovery phase of an apparent monophasic illness with acute seizures or in patients with less severe chronic epilepsy [3]. At times, the positive antibodies are not clearly directly causative for seizures but may be nonspecifically raised and serve as immune markers, implicating that there is a significant inflammatory component. The discovery of autoantibodies typically triggers a neoplastic evaluation. For example, a significant subset of patients diagnosed with anti-NMDAR encephalitis is found to have ovarian

teratomas, which are therapeutically removed [3]. But in many cases, these antibodies are nonparaneoplastic, and immunotherapy may be the only major intervention along with antiepileptic medications.

We describe a clinical case in which the use of antibody testing and PET/MRI imaging aided in the identification of voltage-gated potassium channel antibody-related limbic encephalitis (VGKC-LE). Magnetic resonance imaging findings alone did not definitively demonstrate structural abnormalities, even when repeated over time, despite clinical observations that his memory and cognition were progressively worsening. In addition to antibody testing, brain PET was obtained to evaluate for regions of hypometabolic abnormalities that might support our clinical suspicions of a limbic encephalitis. We were fortunate to have access to PET/MRI technology at our institution, which was used in this case.

In vivo-dedicated brain PET/MRI is a novel multimodal technology that allows for the noninvasive simultaneous acquisition of high-resolution structural data and functional imaging within the same scanning period [4,5]. Conceptually similar to standard PET/CT, PET/MRI offers better structural imaging of most body tissues than PET/CT, especially soft tissue, and uses a much lower dose of radiation [6]. The synergistic potential of PET/MRI is its greatest strength. The ability to immediately analyze superimposed, coregistered images makes it possible to detect anatomical features and pathology that might have gone underappreciated with separately acquired single modality tests. Areas of differential metabolism or ligand specificity on PET can be examined more carefully for structural identification and analysis using MRI, and the limitations that currently exist for the

^{*} Corresponding author. Tel.: +1 314 362 7845; fax: +1 314 362 0296.

E-mail addresses: dayk@neuro.wustl.edu (B.K. Day), eisenmanl@neuro.wustl.edu (L. Eisenman), blackj@neuro.wustl.edu (J. Black), maccottal@neuro.wustl.edu (L. Maccotta), hogane@neuro.wustl.edu (R.E. Hogan).

resolution of PET images can be minimized by the much better spatial resolution afforded by immediate, precise coregistration of the MRI [5]. We present the PET/MRI images to showcase this novel technology and to present findings in a patient suffering from VGKC-LE.

2. Materials and methods

A single patient underwent an inpatient evaluation which included a comprehensive paraneoplastic panel and brain PET/MRI imaging using a Siemens Biograph mMR system. Visual analysis of the imaging was performed by neuroradiologists.

3. Case report

A 64-year-old, right-handed man presented in referral for an 11-month history of seizures. Witnessed episodes during wakefulness included behavioral arrest, staring, and confusion lasting minutes, which had progressively increased in frequency to multiple per day. He also had nocturnal episodes of arousal, moaning, repetitive hand movements, and confusion lasting seconds. The patient had no memory of these events. Despite initial treatment with levetiracetam, titrated to 2000 mg twice daily, he continued to have

worsening memory, behavioral changes, difficulty paying bills, and trouble navigating his own home. His personality changed from reserved to outgoing.

Extensive evaluation 6 months from onset, including head CT, CBC, CMP, UA, vitamin B₁₂ testing, thyroid testing, coagulation profile, creatine kinase, and CSF HSV-1 PCR, was unremarkable. A lumbar puncture showed elevated protein at 72 mg/dL, and EEG revealed left frontotemporal epileptiform abnormalities. An initial brain MRI with contrast and another repeated four months later showed possibly increased T2-weighted signal in the bilateral medial temporal lobes and insular cortex. However, the appearance of these areas did not significantly change over time despite his progressively worsening symptoms (Fig. 1).

During reevaluation on presentation to our institution, a repeat lumbar puncture again showed elevated protein at 72 mg/dL without other abnormalities. Video-EEG captured bitemporal seizures and epileptiform discharges. Brain PET/MRI revealed bitemporal and bilateral insular hypometabolism (Fig. 2). Voltage-gated potassium channel antibodies were present. Otherwise, extensive infectious, autoimmune, neoplastic, paraneoplastic, prion disease workup, CT of the chest, abdomen, and pelvis, and body MRI were unrevealing. Treatment included the addition of lamotrigine as a second antiepileptic agent and oral

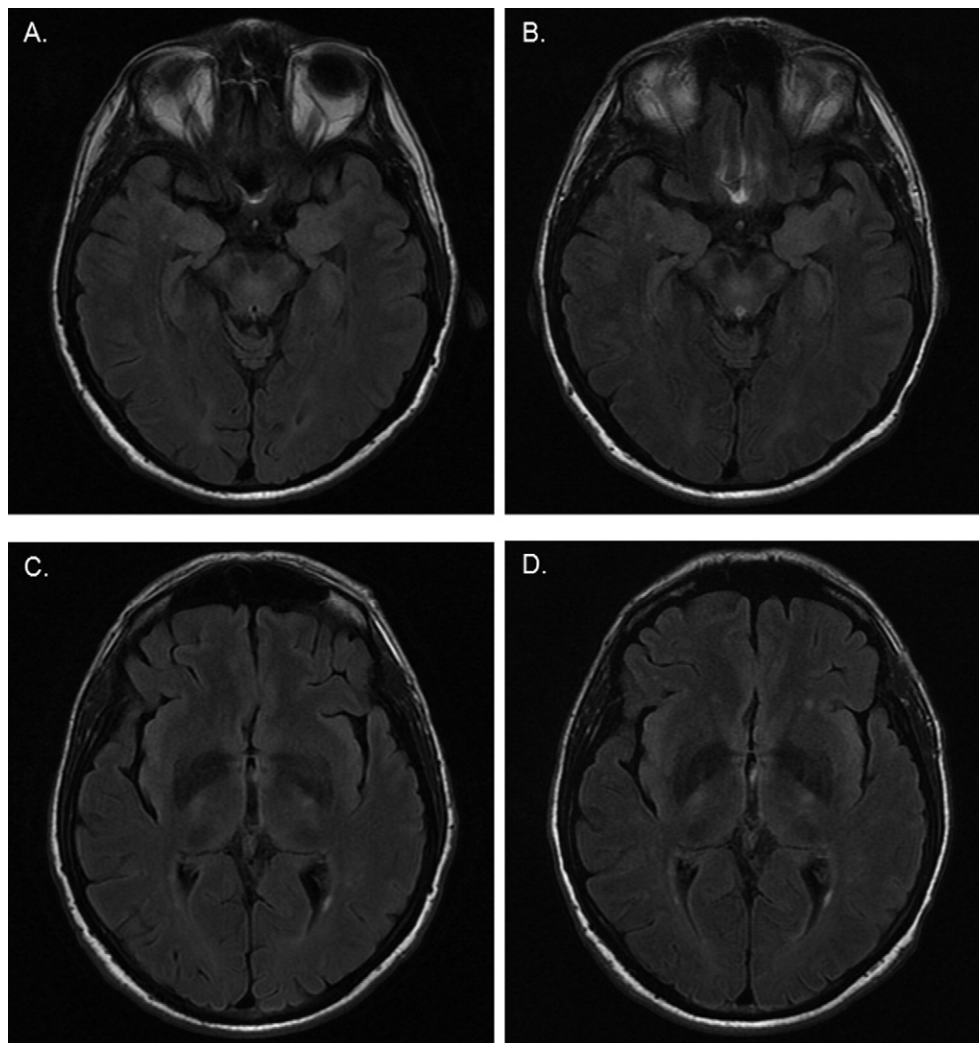


Fig. 1. Axial T2/FLAIR images obtained four months apart at the level of the temporal lobes (A. initial, B. follow-up) and insula (C. initial, D. follow-up). The somewhat increased signal bilaterally in the mesial temporal structures and insula was present, but not definitively abnormal, and did not significantly change over time.

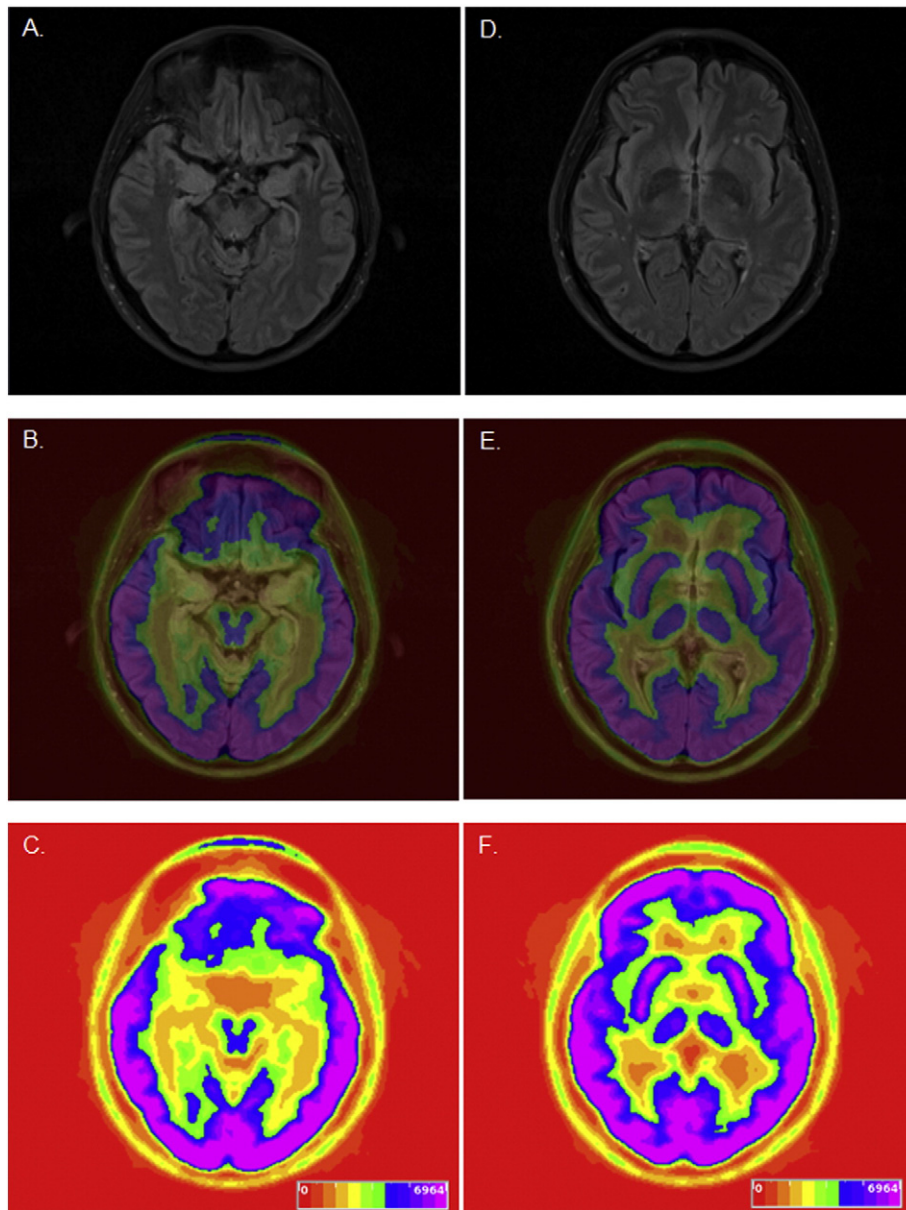


Fig. 2. A. and D. Axial T2/FLAIR MRI at the level of the temporal lobes and insula, respectively, with possible mesial temporal and insular hyperintensities; C. and F. FDG-PET images at these levels showing bilateral temporal and insular hypometabolism; B. and E. Coregistered MRI and PET at these levels, showing where the areas of hypometabolism align with the detailed neuroanatomy.

steroids (prednisone 1000 mg each weekend for 8 weeks, then every other weekend for 8 doses). His seizures and cognitive deficits improved and stabilized.

4. Discussion

This patient presented with a clinical picture of medically refractory temporal lobe epilepsy complicated by memory and cognitive problems. The majority of testing was unrevealing, and even brain MRI repeated over time did not show any definitive structural abnormalities to support an active region-specific pathological process. As the patient's behavior and thinking progressively worsened, the possibility of an ongoing limbic encephalitis was evaluated by comprehensive paraneoplastic antibody panel and advanced brain imaging. Brain PET/MRI technology, available at our institution, afforded us the opportunity to repeat the brain MRI once more while also simultaneously

assessing for functional abnormalities using PET. The PET/MRI findings proved to be key supportive evidence of bilateral temporal and insular abnormalities where serial MRI had fallen short. Although bilateral hypometabolism in these regions is not specific for limbic encephalitis and could be seen in patients with other forms of temporal lobe epilepsy, the PET/MRI results were concordant with the clinical suspicion. These results along with positive VGKC antibodies clarified the diagnosis and improved confidence in moving forward with both additional antiepileptic treatment and immunotherapy, which ultimately kept the patient seizure-free and significantly improved his cognition.

Voltage-gated potassium channel antibody-related limbic encephalitis typically includes encephalopathy, seizures, and mesial temporal lobe structural abnormalities [7–10]. Classically, regional abnormalities in the mesial temporal lobes in VGKC-LE are not seen in other VGKC antibody-related neurological disorders, namely Morvan's or Isaac's syndromes [11]. Imaging abnormalities typical of VGKC-LE have also

been reported in patients manifesting personality changes and memory deficits without evidence of seizures [12,13]. Furthermore, patients with VGKC-LE have been reported to have a normal brain MRI but bitemporal hypometabolism on brain PET [14], similar to findings in our patient.

This is the first study reporting PET/MRI findings in VGKC-LE. However, correlations of PET and MRI in VGKC-LE have previously been described. In seven patients with subacute limbic encephalitis, one with VGKC antibodies, the authors reported that the neuroimaging findings of PET and MRI did not overlap in half the patients but, when combined, revealed temporal pathology in all of them [15]. One patient with VGKC-LE had serial brain MRI and PET studies for two years, revealing a successive switch in prominence from right to left mesial temporal lobe changes. Of special relevance to the case presented, the PET findings were prominent earlier than the MRI findings during the development of left mesial temporal pathology, despite over a year of seizures prior to that time [16].

5. Conclusions

In this case report, the use of brain PET/MRI and antibody testing aided in the diagnosis of VGKC-LE. Antibody testing should be considered in cases of acute epilepsies of unknown cause, especially if they are drug-resistant or severely debilitating. Brain PET and MRI are complementary technologies for assessing regional abnormalities, and brain PET may reveal focal findings in patients with VGKC-LE missed by brain MRI alone. Simultaneous brain PET/MRI multimodal technology has synergistic potential for identifying focal abnormalities that separately-acquired single modality testing might miss.

Conflict of interest

There is no conflict of interest.

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