CASE REPORT

Seronegative Autoimmune Limbic Encephalitis: A Case Report

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Abstract

Autoimmune encephalitis (AE) is an immune-mediated disorder of the central nervous system (CNS). Its definitive diagnosis relies on the identification of a specific antibody. Autoimmune limbic encephalitis (LE) is a subset of AE characterized by inflammation of the limbic cerebral cortex. Cognitive decline, behavioral disturbance, and seizures are its cardinal manifestations. We present the case of a 70-year-old man with subacute progressive gait imbalance, cognitive impairment, and psychiatric manifestations. Extensive serum and cerebrospinal fluid (CSF) investigations did not reveal any abnormality. Autoimmune and paraneoplastic encephalitis antibody panels were negative. Magnetic resonance imaging (MRI) and positron emission tomography (PET) brain scans suggested LE. He responded well to immunotherapy. This case illustrates that AE must be suspected in the appropriate setting, even in the absence of a specific antibody. These patients should be given the benefit of early immunotherapy.

Introduction

Acute encephalitis is frequently caused by infection. Recently, similar cases have been caused by AE, an immune-mediated CNS disorder caused by autoantibodies targeting surface, synaptic, or intracellular autoantigens. Recognition of these disorders is of utmost importance as immunotherapy often leads to favorable clinical outcomes. Although a wide array of autoantibodies cause these disorders, there remain many similar cases that respond to immunotherapy without the identification of a specific antibody.

Case Description

This 70-year-old man was admitted to a Mumbai tertiary care hospital in June 2015. His chief and only complaint was a mild imbalance while walking since about a month prior. He was not a diabetic or hypertensive imbalance with no significant past or family history. A detailed neurological examination was normal, apart from a mildly abnormal tandem walk.

All his routine blood investigations, venereal disease research laboratory, HIV, vitamins B1, B12, and E, thyroid profile, and thyroid antibodies were normal. His chest X-ray and abdominal ultrasound were normal. His systemic and paraneoplastic antibody and tumor marker profiles were also negative. The MRI and PET brain scans were normal. As his symptoms were mild and did not impact his daily activities, he was sent home and asked to review after a month. Unfortunately, he was lost to follow-up for 6 months.

He was readmitted 6 months later in January 2016 with a marked decline in short-term memory, bouts of aggressive behavior, visual hallucinations, and significant gait imbalance.

On examination, his Mini-Mental Status Examination score was 14/30 and his Frontal Assessment Battery score was only 5/18. He had significant gait ataxia, but no limb incoordination or nystagmus. The rest of the neurological examination was normal.

Once again, all laboratory investigations were normal. An AE antibody panel (anti-NMDA-R, VGKC (LGI-1, CASPR2), GABA-B, AMPA (GluR1, GluR2)) and paraneoplastic antibody workup were negative, as were the anti-GAD and antigliadin antibodies. The CSF examination was normal, including viral (including herpes simplex virus 1 and 2), bacterial, and fungal workup, and negative CSF oligoclonal bands. His electroencephalogram (EEG) showed bilateral slow waves mainly over the temporal regions. A computed tomography scan of the chest and abdomen was normal. This time, a repeat brain MRI scan showed T2/fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in the medial temporal lobes, more on the left. A fluorodeoxyglucose (FDG) brain PET scan showed hypermetabolism in the left temporal region (Figs 1A and B).

With autoimmune LE as the possible diagnosis, he was treated with intravenous methylprednisolone 1 gm daily for 5 days, followed by oral prednisolone taper over 6 weeks. He showed mild improvement within the first week of therapy, with steady recovery over the next 4 weeks. When reviewed 7 months later, he had recovered fully and he continues to remain well 4 years later.

Discussion

Autoimmune LE is a subset of AE characterized by inflammation of the limbic cerebral cortex. The significant cognitive impairment, behavioral disturbance, and hallucinations in our patient were compatible with the clinical diagnosis of LE. However, no specific antibody was found. Infectious and paraneoplastic causes were ruled out so an immune-mediated, antibody-negative syndrome was considered likely.

Seronegative autoimmune LE refers to a noninfectious subgroup of LE, in which immunological mechanisms are suspected clinically, but the targeted neural autoantigens are either unknown or uncharacterized. In an immunological survey of 163 LE patients, 12 (7%) were antibody-negative LE. Recent diagnostic criteria allow for a definite diagnosis of seronegative autoimmune LE.

Cognitive impairment was the most prominent and disabling feature in our patient, similar to the antibody-negative cohort of LE patients reported by Graus et al. Our patient did not have seizures. Seronegative LE patients have a much lesser frequency of seizures than those with antibody-positive LE. The reason for this is not clear.

The unusual feature in our patient was his initial presentation with mild gait ataxia and no other symptom. Although not a defining feature, cerebellar ataxia is known to occur in LE, as was reported by Jagtap et al. in 3 of his 16 LE patients.

The CSF examination of this patient was normal. This is also not unusual, as a noninflammatory CSF occurs in a fair proportion of patients with AE. The brain MRI and PET findings were consistent with the diagnosis of autoimmune LE. The FDG-PET

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imaging is often more sensitive than MRI in revealing an increased FDG uptake in normal-appearing temporal lobes.8

An excellent response to steroids was observed in our patient with complete remission of symptoms even after 4 years of follow-up. In a comparative study between antibody-negative and-positive cases of AE, the treatment response was similarly beneficial in both groups.9 Further evidence of immune-responsiveness in seronegative encephalitis comes from the finding that 44% of rituximab responders had AE without antibodies.10

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**References**