CLINICAL VIGNETTE

Olfactory Hallucination in a Young Woman

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Introduction

Limbic encephalitis is a rare but serious neurological disorder. We present a case of limbic encephalitis that demonstrated symptomatic improvement with immunomodulatory drugs.

Case

A 35-year-old female with history of idiopathic pulmonary arterial hypertension was admitted with 2-week history of olfactory hallucination "chemical smell", short-term memory deficits, emotional lability, and disorientation. She also reported intermittent numbness involving her left face and the left side of the body including arms and legs. She had no skin rash, oral ulceration, alopecia, arthritis, Raynaud's phenomenon, muscle weakness, previous thromboembolism, or miscarriage. Electroencephalograph (EEG) showed left temporal seizures. MRI brain showed with edema and abnormal enhancement in L temporal lobe, predominantly in hippocampal formation. Lumbar puncture revealed positive glutamic acid carboxylase (GAD)-65 antibodies with very high titers and elevated serum GAD antibodies. CSF tests for infections were negative. Computed tomography (CT) chest, abdomen and pelvis and full body PET scan did not reveal any underlying malignancies. N-methyl-D-aspartate (NMDA) receptor antibodies, and paraneoplastic panel was negative. Subsequent autoimmune studies were remarkable for positive ANA, nucleolar 1:320 titers. Other serologies including dsDNA, Sm, RNP, SSA, SSB, centromere, Scl-70, RF, CCP, ANCA and anti-phospholipid syndrome panel were negative.

The patient was diagnosed with GAD-65 positive autoimmune limbic encephalitis and received high dose pulse steroid (1 gram of Methylprednisone for 3 days followed by 60 mg of prednisone) and IVIG, with an excellent response evidenced by reduction in olfactory hallucination, significant improvement in disorientation and memory deficit within a week. She was subsequently treated with Rituximab every 6 months, IVIG once a month and oral Mycophenolate (1500 mg twice a day). Repeat MRI showed near resolution of associated enhancement in L hippocampus and amygdala. After 3 months of treatment, she was able to return to work with complete recovery of disorientation, memory deficits and the numbness. She continues to have infrequent episodes of transient olfactory hallucinations.

Discussion

Limbic encephalitis was described initially in case reports from the 1950s where patients with acute and subacute onset encephalopathies were found to have inflammatory pathology in the temporal regions of the brain without inclusion bodies consistent with viral encephalopathies.[1]

Limbic encephalitis is an inflammatory process affecting structures of the limbic system (eg, hippocampus, amygdala, hypothalamus, cingulate gyrus, limbic cortex). Although the disorder is considered a classic paraneoplastic syndrome, it also can be autoimmune encephalitis. Main manifestations are acute or sub-acute mood and behavioral changes, short-term memory problems, focal seizures with impaired awareness (complex partial seizures), and cognitive dysfunction.[2,3] The most frequent neoplasms associated with paraneoplastic limbic encephalitis are lung cancer, testicular tumors, thymoma, breast cancer, and Hodgkin's lymphoma.[2]

GAD antibody is high in paraneoplastic stiff person syndrome, but typically GAD antibodies are non-paraneoplastic in nature.[4] In a systematic literature review in 2016, 48% of 58 cases of GAD-65 positive limbic encephalitis were associated with autoimmune diseases, with type 1 diabetes as the most common.[4] Other autoimmune conditions found in patients with GAD-65 include autoimmune thyroiditis, psoriasis, and common variable immune deficiency.[5,6] Voltage gated potassium channel antibodies encephalitis and N-methyl-D-aspartate (NMDA) receptor antibodies associated encephalities are other autoimmune, non-paraneoplastic encephalitis that present with complex neuropsychiatric syndrome like GAD-65 positive limbic encephalitis.[2]

In the absence of prospective and randomized data, treatment decisions should be individualized and with consideration age, symptom severity, presence of co-existing medical conditions, and presence of underlying malignancies. Based on observational studies, patient cohorts with autoimmune limbic encephalitis have shown high response rates to immunotherapy with most common regimens involving corticosteroids, IVIG, and plasma exchange.[7,8] Patients with poor response to those treatments have shown clinical improvement with second line therapies such as cyclophosphamide, rituximab, or basilximab.[7] Given the rapidly progressive symptoms in patients with

autoimmune limbic encephalitis, the literature supports empiric treatment with steroids and immunotherapy after infectious etiologies have been ruled out.[7,8]

The overall prognosis in patients with autoimmune encephalitis is highly variable ranging from a complete recovery to death or having permanent neurologic sequelae of varying severity including gait disability, incontinence, and cognitive deficits.[9] Delay in diagnosis and treatment can be associated with a worse prognosis and increased recurrence.[9]

Our case illustrates symptomatic improvement of GAD-65 limbic encephalitis treated with rituximab, IVIG, and mycophenolate. Since autoimmune encephalitis is potentially treatable encephalitis, the disorder should be considered on the differential diagnosis of patients presenting with encephalopathy.

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