A Case of Seronegative Limbic Encephalitis with Multiple Sclerosis: A Possible Overlapping Syndrome

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Patient: Female, 45
Final Diagnosis: Autoimmune encephalitis
Symptoms: Memory loss • altered mental status • anhedonia
Medication: Methylprednisolone • immunoglobulin
Clinical Procedure: Immunotherapy
Specialty: Neurology

Objective: Rare co-existence of disease or pathology
Background: Autoimmune encephalitis might coexist in patients with autoimmune demyelinating disorders.
Case Report: We report on a case of a 45-year-old female multiple sclerosis (MS) patient presenting with acute onset short-term memory loss, altered mental status, inflammatory cerebrospinal fluid (CSF) findings and an MRI lesion on the left temporal lobe. An extensive panel for neuronal autoantibodies proved negative. Neuropsychological symptoms gave a prompt response to immunotherapy but nevertheless control MRI showed left hippocampal atrophy.

Conclusions: Several recent reports of concurrent emergence of autoimmune encephalitis and MS suggest a common mechanism for these disorders. Since autoimmune encephalitis and MS share certain common CSF and neuroimaging findings, an increased understanding of overlapping autoimmune brain disorders is required to avoid misdiagnosis especially in antibody negative autoimmune encephalitis cases.

MeSH Keywords: Autoimmunity • Encephalitis • Multiple Sclerosis

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Background

Multiple sclerosis (MS) is a demyelinating autoimmune disorder of the central nervous system and might coexist with other autoimmune diseases such as type 1 diabetes mellitus, inflammatory bowel disease, and autoimmune thyroiditis [1]. Previously reported cases of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis co-occurring with neuromyelitis optica, optic neuritis, and MS have led to the emergence of the so-called “overlapping syndrome” [2–4]. A recent study found neuroimaging features suggesting a demyelinating disorder in approximately 3% of NMDAR encephalitis patients [3]. Moreover, NMDAR encephalitis occasionally presents with immunotherapy responsive white matter lesions [5]. However, to our knowledge, concurrent emergence of demyelinating disorders with other types of autoimmune encephalitis has not been reported.

Case Report

A 45-year-old woman (height 165 cm, weight 72 kg), diagnosed four years ago with MS according to McDonald’s criteria [6] due to three separate inflammatory demyelinating episodes (optic neuritis, diplopia, and left hemiparesis) with contrast-enhancing MS lesions (brainstem and periventricular white matter) on magnetic resonance imaging (MRI), was admitted with a 15-day history of anhedonia, involuntary crying episodes, short-term memory impairment, and time/place disorientation. She was under interferon beta-1b treatment during admission and she had no history of other neurological or psychiatric diseases. Her somatic neurological examination was normal. MRI studies showed left medial temporal hyperintensity and multiple ovoid lesions in the white matter with no gadolinium enhancement (Figure 1A, 1B). EEG revealed slow waves over the left hemisphere. Cerebrospinal fluid (CSF) analysis showed increased number of lymphocytes (17/mm³), elevated protein level (62 mg/dL) and oligoclonal bands (in CSF only, pattern 2). CSF PCR assays for viral pathogens (VZV, HSV1/2, CMV, and HHV-6) and an extensive panel for rheumatological-vasculitic disorders were negative. Serum and CSF samples were negative for antibodies against Hu, Ri, Ma2, CV2, amphiphysin, NMDAR, α-amino-hydroxy-methyl-isoxazoleproionic acid (AMPA) receptor, contactin-associated protein-like 2 (CASPR2), leucine-rich, glioma inactivated 1 (LGI1), gamma-aminobutyric acid (GABA)_A receptor, glutamic acid decarboxylase (GAD), aquaporin-4, and myelin oligodendrocyte glycoprotein. A whole body positron emission tomography (PET) scan done for a potential underlying tumor proved negative. Seronegative limbic encephalitis was considered on the basis of clinical, neuroimaging, and CSF findings. Her symptoms ceased two weeks after monthly treatments of intravenous methylprednisolone (1000 mg/day) and intravenous immunoglobulin (0.4 g/kg/day). A control cranial MRI showed normal signal intensity and atrophy in the left temporal lobe (Figure 1C). The patient was discharged three months later without neurological symptoms.

Discussion

Although our patient had the typical clinical features and MRI lesions of MS, her neuropsychiatric manifestations and left temporal lobe involvement were atypical for MS. Moreover, her clinical features and EEG-CSF findings fulfilled the recently published criteria for seronegative autoimmune encephalitis (rapid progression of short-term memory deficit, and altered mental status, temporal lobe lesion on MRI, inflammatory...
CSF findings, exclusion of alternative causes [7], thus prompting the diagnosis of limbic encephalitis overlapping with MS. Prompt response to immunotherapy and residual hippocampal atrophy occasionally seen in autoimmune encephalitis [8] further supported this diagnosis.

Concurrent emergence of MS and autoimmune encephalitis might be discussed through different perspectives. Oligodendrocytes express NMDAR and other ion channels and thus antibodies involved in autoimmune encephalitis pathogenesis might also participate in myelin dysfunction [9]. Although our patient was negative for an extensive panel of anti-neuronal antibodies, she might hypothetically have developed as yet uncharacterized antibodies leading to both an MS-like disease and limbic encephalitis. Alternatively, the activated autoimmune system and disrupted blood-brain barrier in MS patients might facilitate emergence of other autoimmune brain disorders. Also, overlapping syndrome patients might have an immunogenetic background rendering them susceptible to diverse autoimmune brain diseases. Higher levels of acute-phase proteins, such as ceruloplasmin, have been shown to occur in MS patients treated with interferon-beta [10]. Thus, immunomodulatory treatment might plausibly activate inflammation pathways and induce susceptibility to autoimmune encephalitis-related processes in the brain.

Conclusions

Our case emphasizes that concurrent autoimmune encephalitis and MS may occur in seronegative patients and the spectrum of overlapping syndrome is presumably wider than previously considered. MS and autoimmune encephalitis share similar CSF findings such as oligoclonal bands, and autoimmune encephalitis patients may frequently present with white matter lesions posing a significant diagnostic challenge especially in seronegative cases. Therefore, awareness of overlapping syndrome is important in differential diagnosis of neuroimmunological disorders of the brain.

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