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Can Autoimmune Encephalitis Occur with Negative Markers? A Rare Case Report

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Abstract

In our case, we present a case of a 27-year-old male who presented with progressively worsening altered mental status and seizures. Over the course of his admission to the hospital and intensive care unit, laboratory testing failed to find an offending agent to his presentation. Testing did result in the diagnosis of encephalitis, but an underlying cause was not found. After careful exclusion of bacterial, viral, and other types of encephalopathy, autoimmune encephalopathy was diagnosed despite the absence of commonly used markers of autoimmune encephalopathy. The presentation and symptoms of our patient led to a wide range of differentials, and a high index of suspicion was needed throughout his admission in order to obtain the appropriate tests. Although appropriate testing might be ordered, due to the sensitivities and specificities of all laboratory tests, these objective tests do produce false negative results at times. It is in these times that one must weigh the physical exam, clinical judgment, and the process of elimination to diagnose an underlying pathology. Autoimmune Encephalitis diagnosis can be broken down into possible, probable, and definitive diagnoses based on antibody testing results. In this case, we present a patient with probable autoimmune encephalitis that failed to yield positive autoimmune markers after extensive testing of other possible causes of encephalitis.

Keywords

Autoimmune Encephalitis, Seizures, Paraneoplastic Syndrome, Encephalitis, Autoimmune

1. Introduction

Autoimmune encephalitis (AIE) is an inflammatory disease of the brain, characterized by a broad clinical spectrum making it difficult to recognize at times. Clinically, this disease can initially present with psychosis, seizures, cognitive

deficits, changes in behavior, dysautonomia, and altered mental status but can also lead to life-threatening presentations as severe as a comatose state, encephalopathy, and status epilepticus. AIE is associated with autoantibodies that target both extracellular and intracellular neuronal components. Antibodies against extracellular neuronal components, such as cell surface antigens, can alter synaptic transmission and neuronal excitability. Antibodies on the intracellular antigens are T-cell mediated and lead to detrimental progression of the disease [1]. AIE could be a paraneoplastic syndrome and can often be diagnosed prior to the underlying malignancy. More specifically, malignancy tends to lead to AIE caused by the Intracellular antibodies and the T-cell mediated damage; nevertheless, any patient with AIE should be screened for underlying malignancy. The diagnosis of AIE is most commonly confirmed with autoantibody testing. These autoantibodies can attack cell surface antigens, synaptic transmission, and intracellular components of the neurons. Like all tests, though, no confirmatory test is accurate and precise all the time, and for that reason, false negatives are possible. In this case, a 27-year-old male presented to the emergency department with altered mental status and was later diagnosed with AIE through a protracted clinical course with the reasonable exclusion of alternative causes.

2. Case Presentation

A 27-year-old male with no known previous medical history presented to the emergency department for altered mental status. The patient's family described a grand-mal seizure activity, including shaking of all extremities, foaming at the mouth, and eye-rolling. Upon further history taking, it was noted that he had been seen five days prior at an urgent clinic for a fever and was diagnosed with an unknown viral infection and given azithromycin. The patient had a second attack of seizure in the emergency department and was given Keppra and antibiotics for possible meningitis or encephalitis. The patient had continuous rigors throughout his admission. His mental status continued to wax and wane throughout his hospital course, regardless of intervention. He later developed status epilepticus that warranted immediate airway protection and intubation. He was arousable after intubation but would develop rigors throughout his whole body when aroused.

Over the course of his admission, the patient had a lumbar puncture, electroencephalogram (EEG), magnetic resonance imaging (MRI), and other special tests that included testing for Lyme disease, mycobacterial infections, toxoplasma, and sarcoid. Lumbar puncture revealed a white blood cell count of 11 cells, protein of 26 mg/dL, and glucose of 75 mg/dL. The EEG showed non-specific encephalopathy with no evidence of seizures or epileptogenic potentials. A follow-up video EEG had comparable results. MRI of the brain revealed interval development of restricted diffusion with hyperintensity in the left hippocampus, highly suggestive of possible encephalitis (**Figure 1**). All other special tests yielded negative results. The autoimmune panel resulted in positive glutamic

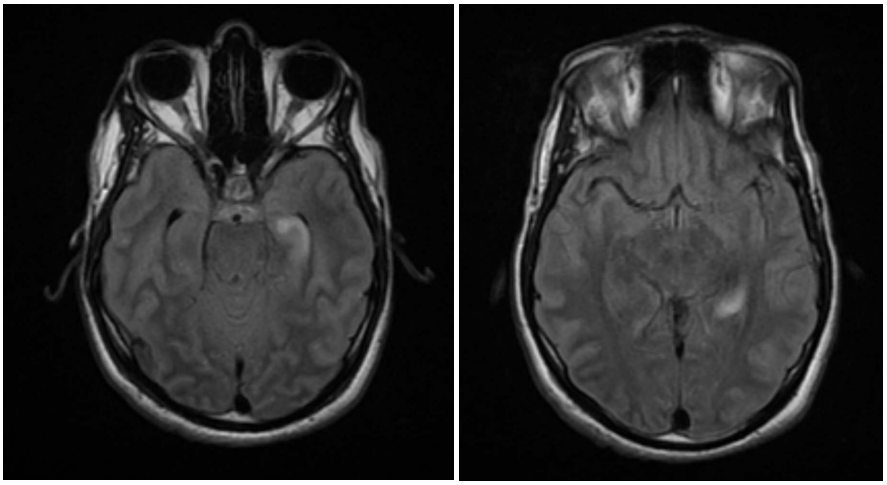

Figure 1. MRI of the brain revealing hyper-intensity in the left hippocampus, highly suggestive of possible encephalitis.

acid decarboxylase, which has low specificity to autoimmune encephalitis but was negative for N-methyl-D-aspartate (NMDA) receptor antibodies. Other autoantibodies in CSF such as AGNA-1, ANNA 1-3, CRMP-5-IgG and PCA-Tr were also all found to be negative. The patient continued to be monitored in the medical intensive care unit. When consulting with the neurologist, the patient was given dantrolene to cover the possibility of a neuroleptic malignant syndrome. The patient was also covered with wide-spectrum vancomycin, ceftriaxone, Bactrim and acyclovir, and steroids for infective causes of encephalitis. Due to a lack of clinical improvement, non-convulsive status epilepticus was highly suspected. Without an apparent cause of encephalitis, the patient was diagnosed with autoimmune encephalitis and received a five-day course of 25 g intravenous immunoglobulin (IVIG) daily and a six-day course of 1 g of methylprednisolone daily, to which he responded well. From the literature, establishing the diagnosis of AIE on antibodies results is not reliable, as first, it might take weeks for the results to come back, and secondly, negative results do not exclude AIE.

3. Discussion

Encephalitis, a state of inflammatory disorder in the brain, encompasses a wide variety of differential diagnoses. Encephalitis has been attributed mainly to infectious causes; however, over the past decade, AIE has been increasing in incidence, which is about five per hundred thousand. Research in AIE has been evolving in recent years in regard to diagnosis and treatment. The International Encephalitis Consortium 2013 diagnostic criteria for encephalitis of possible infection vs. autoimmune necessitates the presence of altered mentation lasting at least twenty-four hours with no other identifiable cause. Confirmation would occur if the patient meets at least 3 minor criteria: 1) fever in the last 3 days, 2) new onset of focal neurological deficit, 3) CSF leukocytosis, 4) acute new abnormality is seen on neuroimaging characteristic of encephalitis, or 5) EEG ab-

normalities consistent with encephalitis [2]. Those five criteria can help differentiate autoimmune causes from infectious causes in both adults and children. Certain antibodies in the circulation and the response to immunotherapy are manifested in AIE. Graus et Titulaer [3] concluded that it is not realistic to have antibody testing as a part of early diagnostic criteria for the evaluation of AIE due to many reasons. First, antibody testing can take many weeks to come back, depending on the hospital's capabilities. Second, negative antibodies result does not negate or exclude the diagnosis of AIE. Third, a positive result does not confirm the diagnosis. They also concluded that the response to immunotherapy is not practical for different reasons, for example, the lag in time between the treatment and the effect and the different responses for AIE patients to the same treatment. Graus et Titulaer developed new diagnostic criteria for AIE by identifying possible autoimmune encephalitis, which is not dependent on neuronal auto-antibody status, which resulted in the establishment of three levels of clinical evidence for AIE: possible and probable (for which auto-antibody test is not needed in most cases) and definite (for which auto-antibody test is needed).

AIE can mimic infectious encephalitis in neurological and psychiatric symptoms; however, fever and CSF changes may be absent. Severe brain injury in AIE is usually acute (less than six weeks) and results from the uncontrolled production of anti-neuronal antibodies against cell surface (CSAab), synaptic (SyAab), or intraneuronal (INAab) antigens [1]. The CSAab (anti-N-methyl-D-aspartate receptors) disrupts neurotransmission and may result in cell death [4]. Like many autoimmune diseases, the progression of the disease can vary from one patient to another, but early detection and treatment can lead to a greater prognosis. Clinical presentations include seizures, motor weakness, behavioral changes, and abnormal movements [5]. AIE can present with variable symptoms and signs and does not always include all available presentations. However, seizures are the most common symptom [5] [6]. For instance, refractory status epilepticus is more strongly associated with Anti-NMDA (ovarian and testis teratoma), Anti-AMPA (thymoma, lung, and breast cancer in 65%), and anti-GABA (in thymoma). Although associated with some cancers, AIE can also afflict patients without cancer predisposition [1]. Sleep disturbance is very common and can get severe. Even with appropriate treatment, it can persist later and leave a negative impact on the quality of life in AIE patients [7]. It is usually significant in patients with positive anti-IgLON5 and anti-NMDA receptor encephalitis. Where primary schizophreniform psychosis arises due to genetic interaction with the environment, secondary schizophreniform psychosis occurs due to organic insult, and it includes autoimmune psychosis, which presents with acute onset of polymorphic psychotic symptoms, including (hallucination, catatonic reactions, paranoid, personality disorders, etc) commonly associated with other neurological signs (fever, seizure, movement disorder, etc.); however, can be isolated in both acute or relapse stages of AIE. In children, it's more complicated to diagnose AIE because children present with different symptoms, especially

behavioral manifestations, which are very complex and evolving at this time, which reflects in late diagnosis with worse outcomes. Regardless, all patients with AIE should be screened for tumors while considering the clinical presentation [8].

AIE is commonly treated with immunosuppressive therapy, and the prognosis depends on the response to the therapy. Regardless, early immunotherapy treatment is recommended for a better prognosis [8]. In refractory conditions, where standard steroids fail, intravenous immunoglobulin, plasma exchange (PLEX), and immune-modulating (including Rituximab and cyclophosphamide [9] [10] [11] can help. MRI and imaging studies can help in treatment as well; for example, in paraneoplastic autoimmune limbic encephalitis, tumor resection can manage the encephalitis. Recovery in AIE usually takes prolonged time, and relapses are common to occur, despite the effectiveness of many immunosuppressive therapies. Therefore, specific immunotherapy coupled with supportive target-specific therapy can help control the symptoms and shorten the disease course. The approach can also maintain long-lasting disease stability and decrease the incidence of relapses. Targeted immuno-suppressive receptor blockers, which can cross the blood-brain barrier, have shown great results. For example, daratumumab has shown clinical significance in the depletion of autoreactive plasma cells (receptor targets) in AIE [12]. Treating neurological and psychiatric symptoms has been proven to decrease morbidity and mortality. Antipsychotics and electro-convulsive therapy have succeeded in treating different psychiatric presentations of AIE. Intensive care unit management may be existential in treating life-threatening conditions like status epilepticus.

4. Conclusion

Clinicians today rely heavily on their clinical knowledge, judgment, and intuition alongside tests to guide patient care. At times, this becomes difficult as no objective tests exist with sensitivities and specificities of 100%. When objective tests fail to aid in the diagnosis, a clinician can diagnose by ruling out other causes while waiting for other time-consuming special tests. In this patient's case, standard tests failed to confirm autoimmune encephalitis. Without a clear etiology of the encephalitis based on routine testing, one should rely on clinical and distinct MRI features to diagnose autoimmune encephalitis while waiting for special test results and confirmation. Prompt recognition of characteristic presentations of these autoimmune encephalitides can lead to earlier treatment and prevent further irreversible brain degeneration [13].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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