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Case Report

Psychosis in the ED: A case of NMDA receptor antibody encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate antibody receptor (NMDAR) encephalitis is a newly recognized disease increasing in diagnostic frequency. A 27-year-old female presented with symptoms of oral dyskinesia, tachycardia, and altered mental status following a three-month history of depression, lethargy, catatonia, and auditory hallucinations. We utilized our facilities neurology and psychiatry consult services, performed a lumbar puncture (LP), and requested NMDAR antibody titers. Following admission the Anti-NMDAR antibody titer was elevated warranting treatment with intravenous immunoglobulin (IVIG), corticosteroids, and later rituximab. Organic causes of psychosis are often overlooked in the emergency department, particularly in patients with a history of psychiatric illness. An understanding and awareness of NMDAR encephalitis allows for timely diagnosis, prompting quicker treatment. Emergency physicians should maintain an index of clinical suspicion for NMDAR encephalitis when encountering patients with progressive symptoms of catatonia and psychosis of unclear etiology.

1. Introduction

NMDAR encephalitis is an autoimmune encephalopathy that was first described in 2005 [1] and acknowledged as a medical diagnosis in 2007 [1-3]. Despite increasing cases, epidemiological statistics are largely undetermined [3]. The disease is often associated with a paraneoplastic syndrome in young adult females with ovarian teratomas. However it can be seen in either sex, in patients of all ages, and does not require the presence of a tumor [1,3,4]. NMDAR encephalitis presents with a range of clinical symptoms including but not limited to facial dyskinesia, catatonia, and depression [5,6]. In this report we present a prolonged case of NMDAR encephalitis that was initially diagnosed and managed as acute psychosis in a psychiatric institution. The patient was institutionalized for nearly 3 months before presenting to our institution for reevaluation. Workup was initiated based on a high index of suspicion leading to the appropriate diagnosis and treatment.

2. Case report

A 27 year-old female with bipolar depression presented as a direct transfer from a local inpatient psychiatric facility following a three-month history of progressive depression, catatonic behavior, lethargy, and auditory hallucinations of a "baby screaming in the walls." She had recently developed a mild fever, hypoxia, tachycardia, and worsening mentation and was transferred primarily for workup of meningitis. The patient had a history of bipolar depression but otherwise, prior to this disease, had no psychiatric history. She had been gainfully employed, a spouse, and a mother. Her current "psychiatric state" appeared unusually acute and extreme. There was no history of causality that would contribute to her "psychotic break." Upon arrival to our emergency department the patient was slightly tachycardic, but otherwise her vitals were within reference limits. Her exam was notable for extreme catatonia. She remained non-verbal and unresponsive to questioning during interview. She was neither cooperative nor resistant during the physical exam but appeared to be indifferent. During the exam she demonstrated no meningeal signs, no discomfort, no response to external physical stimulation. At times she was noted to lip smack. Neurologic evaluation was limited by her apathetic, uncooperative state. She was initially rigid in her extremities, but became flexible in the back and lower extremities during the lumbar puncture (LP).

Imaging and laboratory results from the facility where the patient had previously been evaluated were obtained and reviewed. Head CT was unremarkable for any intracranial pathology and it was not repeated at our facility. Initial blood work and cerebrospinal fluid (CSF) analysis results demonstrated no acute abnormalities, leading to the diagnosis of acute psychosis and subsequent institutionalization. We repeated much of this work up in our ED. Her CMP was remarkable for a mild transaminitis with an elevated AST of 62 and ALT of 101. CK was elevated at 752, and a reflex CKMB returned within reference range. CBC, TSH, and urinalysis were unremarkable and within reference ranges. The initial CSF analysis was non-concerning for meningitis or acute intracranial hemorrhage with normal ranges of protein, nucleated cells, and red blood cells.

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The patient's presentation did not fit the typical “psychotic break”. Lying before us was a once productive employee, a supportive wife, and a nurturing mother. There was no history of psychosis, no causative agents, no historical events, that would cause her to suddenly lose her ability to interact with reality. Given this unusual presentation we elected to send CSF for additional analysis, including a NMDAR antibody titer.

After fluid resuscitation the patient's tachycardia resolved and she remained hemodynamically stable throughout her ED course. Neurology and psychiatry were consulted, and workup of NMDAR encephalitis was discussed. The patient was eventually admitted to the psychiatric service for management of her presentation. On day 2 of admission NMDAR IgG antibody titers returned 1:20 confirming our suspicion of NMDAR encephalitis. A repeat LP was performed for therapy guidance and the NMDAR titer remained elevated at 1:320. CT and MRI of the abdomen and pelvis were performed to evaluate for mass or tumor and were unremarkable for either. Repeat CT of the head and MRI of the brain were also performed, which were unremarkable for intracranial abnormalities or evidence of encephalitis. The patient's care was transferred to the neurology service and IVIG and corticosteroids treatment was initiated. Her mental status fluctuated following initiation of treatment, and at hospital day 26 the patient was started on Rituximab therapy. She was discharged to from the hospital on day 41. Over the ensuing 9 months the patient continued to show signs of improvement. She is now 13 months post diagnosis. While her mental status has improved considerably, she suffers from chronic daily headaches, fatigue, and continues to show mild impairment to both recent and remote memory.

3. Discussion

Anti NMDAR encephalitis is gaining attention due to the increasing number of documented case. A multicenter report from the United Kingdom found the disease to be responsible for 4% of encephalopathies, making it potentially the most common cause of antibody mediated encephalitis [7]. There is growing evidence linking it to cases of schizophrenia; Steiner et al. identified positive antibody titers at a rate of 9.9% in a study examining 121 patients with schizophrenia [8,9]. Roughly 80% of reported cases are women, while awareness is leading to increasing rates of diagnosis among children and adolescents [7].

Antibodies to NMDAR glutamate subunit cause cellular uptake of the NMDA receptor and reversible loss. The loss of this receptor eliminates NMDAR-mediated synaptic function causing impairments in learning, memory, and behavior [10]. The initial symptoms of anti-NMDAR encephalitis are often nonspecific and are often preceded by a flu like illness [7]. Within a few weeks patients may develop psychiatric manifestations of agitation, delusions, hallucinations, and bizarre behavior. This initial presentation often goes misdiagnosed as a non-organic psychosis. If left untreated symptoms may progress towards catatonic behavior, autonomic instability, seizures, muscle rigidity, facial dyskinesia's, and hypoventilation [7].

Diagnosis requires a high clinical suspicion and is confirmed by the detection of IgG antibodies to the GluN1 subunit of the NMDAR in serum or CSF [11]. Positive CSF titers are found to be abnormal in 80% of patients. Due to the association with ovarian teratoma a diagnostic workup for ovarian teratomas is highly recommended in females presenting with this condition [3,7]. Brain MRI is capable of detecting subtle changes suggestive of encephalitis and can aid in a non-organic cause for diagnosis, but unfortunately it is estimated to be normal in as many as 70% of patients with NMDAR encephalitis [7,9].

Treatment typically starts with IVIG and methylprednisolone. If there is no significant clinical improvement after 10 days then a second line agent is initiated, typically rituximab combined with cyclophosphamide. Treatment is usually effective and one study demonstrated a good outcome, defined by modified Rankin score of 0–2, in 81% of patients treated [1]. However response to treatment may take up to 18 months. Unfortunately delayed treatment correlates with higher rates of lasting cognitive deficits [12]. Those left untreated may progress to autonomic instability, respiratory distress, and death [13].

3.1. Why is this important to emergency medicine?

Our case describes a patient presenting with symptoms that were initially thought to be purely psychiatric and later found to be of a treatable organic etiology. The patient's presentation was unusual given her limited psychiatric history, lack of inciting events for psychosis, and previously functional state. When treated early in the disease process, patients with NMDAR autoimmune encephalitis have a favorable outcome. Though once considered rare, NMDAR encephalitis has been identified as an increasingly common cause of encephalitis. This case is an unfortunate example of a patient whose workup failed to identify a treatable disease. The unfortunate result led to a prolonged course of encephalitis, residual cognitive impairments, and immeasurable consequences for the patient's immediate family.

As emergency medicine physicians we are entrusted with the great responsibility to “medically clear” potential psychiatry patients before a psychiatric evaluations. While well-grounded in most aspects of psychiatry, the Psychiatrist depends on us to ensure organic causes of psychosis have been fully evaluated. It thus becomes imperative that we, as emergency medicine physician, maintain a high index of suspicion for disease pathologies, such as NMDAR encephalitis, when unusual cases of psychosis present.

Conflict of interest

None.

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