CLINICAL VIGNETTE

Anti-NMDA Receptor Encephalitis Initially Diagnosed as Tuberculous Meningitis

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Case Presentation

A 22-year-old female with a past medical history of focal impaired awareness seizures presented with altered mental status. Per her family, the patient had been having two weeks of worsening occipital headaches associated with neck pain and nausea/vomiting. She denied fevers, urinary symptoms, abdominal pain or rash. That evening, the patient became acutely altered with vomiting and weakness leading to difficulty walking, and her family brought her to the emergency department.

Her past medical history included focal impaired awareness seizures, with her last known seizure 4 years prior. She had been off antiepileptics for 3 months and was previously followed by neurology.

In the emergency department, she was febrile to 38°C on rectal temperature, with normal heart rate and blood pressure, and 100% oxygen saturation on room air. On physical exam, she was obtunded, unable to answer questions or respond to commands, but responded to painful stimuli. Her neck was supple, pupils were equally responsive and reactive to light, and cardiopulmonary exam was unremarkable. No skin lesions or rashes were noted.

Given fevers and altered mental status, CT head was done with unremarkable findings prior to lumbar puncture (LP). Results included elevated opening pressure 30, low-normal glucose, and normal protein concerning for a viral process. MRI/MRV showed no acute findings. EEG was abnormal and showed diffuse slowing with left hemisphere attenuation possibly due to grey matter injury or post ictal state due to seizure disorder. CT chest/abdomen/pelvis was negative for mass or acute abnormality.

Neurology and infectious disease were consulted. The patient was empirically given IV antiepileptics and broad-spectrum antibiotics for possible bacterial meningitis, as well as IV acyclovir for possible HSV meningitis. A meningoencephalitis panel was negative. Repeat LP showed lymphocytic predominance with pleocytosis, increased WBC count of 115, leading to greater suspicion for tuberculous (TB) or fungal meningitis. Patient was empirically started on four drug therapy with rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) and dexamethasone for TB meningitis, as well as fluconazole for possible cocci meningitis and clinically improved. Her CSF later returned negative for cocci and AFB smear/culture were negative x3. The patient ended up leaving against medical advice and stopped her medications after improvement of symptoms. At her neurology follow up visit, the patient was found to have positive N-methyl-D-aspartate (NMDA) receptor Ab in CSF with concern for NMDA encephalitis.

Discussion

Anti-NMDA receptor encephalitis is associated with antibodies against the NR1 subunit of the receptor leading to a neuropsychiatric syndrome.[1] It has been described in young women and is often associated with ovarian teratoma. One study, reported 50% of female patients >12 years old with unilateral or bilateral ovarian teratomas.[2] Patients often have headache, fever, or a viral-like illness, similar to our patient's presentation.[1]

Clinical symptoms include neuropsychiatric symptoms such as seizures, anxiety, agitation, delusional/paranoid thoughts, visual or auditory hallucinations and short-term memory loss. Many patients develop decreased consciousness, leading to dyskinesias, central hypoventilation, and autonomic instability requiring ventilatory support, which can progress to death.[1]

In terms of diagnosis, CSF should be obtained and often shows lymphocytic pleocytosis[1]. It is then confirmed by IgG antibodies to the NMDA receptor found in CSF. These tests take longer to result, delaying diagnosis.[3] MRI may be normal, although characteristic findings include increased FLAIR or T2 signal in one or more cortical or subcortical regions. EEG findings are also nonspecific with infrequent epileptic activity[4] and can be attributed to many other causes of encephalopathy.[3]

First line therapy is steroids, IVIG and plasmapheresis alone or combined.[2] Our patient may have improved due to empiric steroids she received for possible tuberculous meningitis. Second line therapy includes monoclonal antibodies, such as rituximab, or cyclophosphamide. Recovery can be slow with a 10-15% recurrence rate requiring re-initiating similar therapies.[4] Patients may have persistent amnesia of what occurred during the illness, as NMDA receptors may play a role in memory and learning.[1]

Difficulty in diagnosing TB meningitis and concern for high morbidity and mortality in adults may lead to mistaken diagnoses as may be low numbers of *M. tuberculosis* in CSF and low sensitivity of current tests to rule out TB.[5] As the

natural history of TB meningitis can have insidious onset and lead to rapid deterioration, it is important for early clinical recognition of the diagnosis rather than awaiting laboratory confirmation of TB. CSF often shows lymphocytic pleocytosis with low glucose and high protein, and the diagnosis is confirmed by CSF smear/culture showing *M. tuberculosis*. Clinical symptoms can have similar presentation to NMDA encephalitis with a prodrome of malaise, fever and headache leading to a meningitis phase with vomiting and confusion, and then progressing to a paralytic phase of seizures, stupor and coma.[6]

The challenge of diagnosing anti-NMDA receptor encephalitis is the variability of clinical presentations which can lead to alternative diagnoses prior to delayed confirmation with anti-NMDA receptor Ab in CSF. In our patient, this specific CSF test needed to be sent out and took weeks to result. EEG and MRI findings can also be normal or nonspecific for this disease which can also confound clinical decision making.[4] As patients may decompensate quickly, it is necessary to initiate empiric treatment prior to obtaining all results. Clinicians should recognize this disease when evaluating patients presenting with neuropsychiatric symptoms concerning for meningitis/ encephalitis. Further studies are needed to demonstrate more definitive and timely tests for diagnosis.

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