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Case Report

Anti-NMDAR encephalitis, a mimicker of acute infectious encephalitis and a review of the literature

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ABSTRACT

Anti-N-methyl-D-aspartate receptor encephalitis has become an increasingly recognized etiology of acute psychosis in young patients. The diverse constellation of symptoms allows for misdiagnosis as an infectious, psychological, or toxicological entity resulting in delays in treatment with increasing morbidity. We describe a case of anti-NMDAR encephalitis that was a particular challenge to diagnose. Practitioners should maintain a high index of suspicion for anti-NMDAR and related neuroautoimmune syndromes, especially in young patients that present with acute mental status decline or dyskinesia.

Case report

A 21-year-old female was admitted due to altered mental status after 2 weeks of headache. One week earlier she was evaluated in the emergency room and discharged on analgesics after a nonfocal neurologic exam and unremarkable non-contrast head CT. Over the following week her headaches increased in severity with the development of nausea, subjective fevers, and photophobia. One day prior to admission, she became emotionally labile and incoherent.

On admission, the patient's vitals were 38.6C, heart rate 111 bpm, 124/84 mm, respiratory rate 24 bpm, O_2 saturation 98% on ambient air. On exam, she had intermittent shaking of extremities and episodes of staring into space intermixed with inappropriate crying and laughing. She answered questions incoherently and did not follow commands. Cardiopulmonary, abdominal, and skin exam were unremarkable with rectal tone intact. Her laboratory studies were significant for white blood count 15.8 $\times$ 10^3 cells/μL with an 87% neutrophil predominance. Additionally, a toxicology panel, thyroid-stimulating hormone, and urinalysis were negative. The patient underwent a lumbar puncture with the following results; white blood count 298 cells/μL, 93% lymphocytes, red blood count 8 cells/μL, protein 122 mg/dL, lactate dehydrogenase 27 U/L, and glucose 47 mg/dL. The patient had no travel history and no known toxin, tuberculosis, rabies, or prion exposure.

On hospital day 3, the patient became unresponsive, hypotensive, and hypoxic requiring intubation and initiation of pressors. A repeat lumbar puncture was unchanged from admission. EEG showed focal temporal slowing and frontal-intermittent-rhythmic-delta activity consistent with diffuse cerebral dysfunction. Repeat CT and MRI scans of the brain performed on day 3 and day 7 were unremarkable. Blood cultures, fungal blood cultures, and cerebrospinal fluid (CSF) cultures were negative. Throughout this time the patient had been receiving empiric intravenous acyclovir therapy which was discontinued on hospital day 8 after three successive negative PCR tests for herpes simplex. Additional studies including HIV test, syphilis serology, anti-nuclear antibody, cryptococcal antigen, and toxoplasma serology were negative. CSF analysis for West Nile, Eastern Equine, Enterovirus, Ebstein-Barr virus, Varicella, Cytolomegalovirus, Adenovirus, and St. Louis encephalitis virus were negative. As an infectious etiology for the patient's symptoms was unable to be identified, an evaluation for neoplastic etiologies was initiated. MRI of the chest, abdomen, and pelvis was unremarkable except for a 2.2 cm simple physiologic left ovarian cyst. Antibodies reactive to N-methyl-D-aspartate receptors were detected both in CSF and in serum. Subsequently, the patient was treated for NMDAR antibody mediated autoimmune encephalitis with high dose corticosteroids and plasma exchange followed by intravenous immunoglobulin infusion.

Despite medical therapy, the patient continued to deteriorate and her hospital course was complicated by persistent 39.5C fevers, deep vein thrombosis, and while receiving anticoagulation

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development of gastrointestinal bleeding. On hospital day 30, it was determined to proceed with endocopic salpingo-oophorectomy. Histologic exam of resected tissue identified a left mature cystic teratoma. However, despite these interventions, the patient's mental status failed to recover and the patient eventually expired.

Discussion

Mental status change is a common trigger for infectious disease consultation due to the myriad of potential pathogens that can cause acute neurologic deterioration. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was described in 2007 and has since become an increasingly recognized etiology of progressive encephalitis. This syndrome can have a diverse presentation including catatonia, movement disorders, seizures, memory disturbance, and limbic encephalitis. It is especially important to consider because the disease process mimics aspects of schizophrenia and patients are initially referred for psychiatric evaluation delaying appropriate diagnosis [1]. The frequency of anti-NMDAR encephalitis may be grossly underestimated. In a retrospective analysis, NMDAR antibodies were identified in 1% of encephalitis cases of unknown origin [2]. In the California Encephalitis Project, half of children with idiopathic encephalitis and psychiatric symptoms had antibodies directed against NMDAR. The frequency was four times that of encephalitis caused by Herpes simplex, Varicella-zoster, and West Nile combined [3].

Anti-NMDAR encephalitis shows a female to male predominance of 4:1 and classically occurs in younger patients. In the largest study to date, of 577 cases 81% were female with median age of onset 21-years and 37% of patients younger than 18-years [4]. An underlying neoplasm was present in 38% of patients and of those with neoplastic disease 97% were female [4]. Ovarian teratomas accounted for 94% of all neoplasms, with an additional 2% extra-ovarian teratomas. Neuroblastoma, lymphoma, lung, breast, thymic, testicular, and ovarian carcinoma have also been described [2,4]. In all cases, removal of the tumor resulted in clinical improvement [3].

Patients with anti-NMDAR encephalitis have a progressive syndrome with several recognized stages. An initial prodromal phase occurs in 70% of patients consisting of headache, fever, nausea, vomiting, diarrhea, or upper respiratory symptoms. Within 14-days psychiatric symptoms develop including anxiety, insomnia, delusions, paranoia, mania, or social withdrawal. Ataxia or choreiform motions may be present. Short term memory loss is common, but underestimated due to rapid language deficits ranging from echolalia to mutism and development of akinesis [2,3]. The final stage presents with dyskinesias, extrapyramidal signs, motor automatisms such as lip-smacking, sustained jaw clenching, and autonomic instability with hyperthermia, cardiac instability, hypersalivation, hypertension or hypotension, incontinence, erectile dysfunction, and central hypoventilation [2,3]. Complex seizures develop early in the disease course. The frequency and intensity of seizures decrease with disease progression; however, they may recur at any time [2].

Initially classified as paraneoplastic, increasing evidence suggests that anti-NMDAR is a neuroautoimmune syndrome in which antibodies form in response to a number of potential stimuli [3]. Although predominantly associated with ovarian teratomas, many other tumors are described and many patients have the characteristic antibodies without evidence of neoplasm. In fact, anti-NMDAR antibodies have been found in patients with a positive mycoplasma serology, active herpes zoster infection, or following vaccinations [2]. CSF and serum from afflicted patients have a distinctive pattern of reactivity with hippocampus neurons [5]. Antibodies appear to cross-react with synaptic proteins causing reversible reduction in glutamate receptors [6]. However, the initiating event causing antibody production has not been clarified.

Diagnosis of anti-NMDAR encephalitis is dependent upon identification of circulating CSF or serum antibodies. In 250 paired CSF and serum samples, antibodies were present in 100% of CSF and only 85% of serum samples [6]. This is not surprising, as intrathecal antibody production has been identified and CSF titers appear to correlate with disease activity; neurologic improvement had an associated decrease in titers [5]. The CSF typically has a lymphocytic pleocytosis and elevated protein and oligoclonal bands may be present [6]. Brain biopsy is not diagnostic; biopsies of 15 patients had normal or nonspecific histology [2]. Approximately half of patients have irregularities on MRI. EEG is abnormal but nonspecific in over 90% of persons.

The cornerstone of treatment is immunotherapy and tumor removal. High dose corticosteroids, intravenous immunoglobulin, and plasma exchange are considered primary therapy. In addition, identification and resection of underlying tumor aids recovery. Approximately half of patients show clinical improvement within 4-weeks with primary therapy. Second line therapy includes monoclonal antibodies (Rituximab) and cyclophosphamide.

With prompt and aggressive treatment, the overall prognosis remains favorable with 75% of patients having a complete recovery or mild residual sequellae. However, the remaining 25% of patients had residual symptomatology that severely affected quality of life. Titulaer, et al. postulated a 7% mortality rate while Dalmu et al., observed a 4% mortality in their 360 case cohort with cause of death due to autonomic instability and complications of prolonged hospitalization [2–4]. Independent predictors of favorable outcome include lower initial severity of symptoms, not requiring admission to intensive care, and prompt initiation of treatment [4]. This presents the challenge of whether to perform resection, typically salpingo-oophrectomy, in young patients. In fact, in 197 cases, the median time from symptom onset to surgical resection was 1.4 months [6]. In all cases, there is a protracted recovery phase which can last up to three years [3,4]. Relapse of encephalitis occurs in 20–25% of patients from 3-months to 9 years [2,3].

Anti-NMDAR encephalitis is a syndrome which is increasingly recognized as a cause of acute psychosis in young people. It has been misdiagnosed as viral encephalitis, rabies, schizophrenia or psychosis, neuroleptic malignant syndrome, dissociative neuroleptic use, or seizure disorder. Early diagnosis is critical and improves outcomes, but remains a particular challenge, as our patient had an ovarian teratoma that resembled a simple cyst on imaging. Ultimately, anti-NMDAR disease should be suspected in any individual younger than 50, especially a child or teenager, that develops rapid psychosis or movement disorder. Identification of NMDAR antibodies confirms the diagnosis and should prompt early intervention with immunotherapy and neoplastic workup.

Conflict of interest

No disclosures or conflicts of interest to report.

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