Anti-N-methyl-d-aspartate receptor encephalitis: mimicker of lupus and multiple sclerosis

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SUMMARY

Anti-N-methyl-d-aspartate receptor encephalitis (NMDARE) is a B-cell-mediated autoimmune encephalitis with wide non-specific symptoms like acute-onset psychiatric or neurological ones mimicking various other conditions. A careful history and appropriate workup, including cerebrospinal fluid analysis for anti-NMDAR antibodies, imaging, and electroencephalogram, should be conducted, considering all differential diagnoses that can mimic its presentation. Combination therapy with high-dose steroids, plasma exchange, or immunoglobulin therapy has been shown to be more efficacious. In patients who fail first-line therapy, rituximab or cyclophosphamide should be considered. It is essential to rule out ovarian teratoma or other occult malignancies that can cause NMDARE, as removal of the tumor itself resolves this condition. Timely diagnosis and early intervention are necessary to avoid an untoward outcome.

Key words: *Encephalitis, autoimmune, delirium, optic neuritis, lupus, neuromyelitis optica, multiple sclerosis.*

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INTRODUCTION

Anti-N-Methyl-D-Aspartate receptor encephalitis (NMDARE) is a B-cell-mediated autoimmune encephalitis with wide non-specific symptoms like acute-onset psychiatric or neurological ones mimicking various other conditions (1). It is a rare disease that is commonly underdiagnosed or misdiagnosed due to variability in presentation. It can present with flu-like symptoms such as upper respiratory symptoms, headaches, or fever (1, 2). Sometimes, it presents with hallucinations, catatonia, and emotional lability, which can be confused with acute psychiatric episodes. Neurological deterioration can occur in the following 1-3 weeks, followed by autonomic dysfunction (1). The diagnosis is confirmed by observing immunoglobulin G (IgG) antibodies against the *GluN1* subunit of the NMDA receptor in cerebrospinal fluid (CSF) (3). While it can be confused with encephalitis due to infectious causes, autoimmune diseases like Sjögren's syndrome and lupus also need to be ruled out. Multiple sclerosis is another diagnosis that should be in the differential as it presents with optic neuritis and oligoclonal bands in the CSF. Therefore, a positive test does not conclude a definitive diagnosis; hence, differentials should be broad, and a thorough history with complete investigations should be carried out for an accurate diagnosis. All females diagnosed with NMDARE should undergo a workup to rule out ovarian teratoma (1). In a multi-institutional study, 36% of patients with NMDARE had neoplasms, and 94% of all tumors were ovarian teratomas (4). This case report emphasizes the importance of timely diagnosis of this rare condition while ruling out other mimickers.

CASE REPORT

A 19-year-old girl presented with sudden onset of severe headache and worsening altered mental status associated with delirium

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and visual hallucinations for 5 days. The initial differential diagnosis was meningitis: she was empirically treated with intravenous vancomycin (15 mg/kg every 12 hours), ceftriaxone (2 g every 12 hours), and acyclovir (15 mg/kg every 8 hours) for a few days at the outside hospital, until the lumbar puncture culture results were reported as negative. She was then started on antipsychotics due to worsening delirium, high-dose steroids, and intravenous immunoglobulins before being referred to our center for further management. She had no history of a similar episode in the past, no recent history of weakness, tingling or numbness, upper respiratory tract illness, trauma, insect bite, recent travel, oral or nasal ulceration, photosensitivity, dry eyes, or dry mouth. Her past medical history was significant, with an episode of optic neuritis at the age of 15 years, which resolved with oral steroids and thyroid disorder in her maternal aunt. On index examination, the vital signs were stable, and the physical examination was normal, except she was extremely lethargic to participate in the interview.

Previous hospital records showed an elevated white blood cell (WBC) count of 18 k/μL (normal range 5 to 10 K/μL) and an erythrocyte sedimentation rate (ESR) of 70 mm/hr (normal range 0 to 20 mm/hr). CSF analysis revealed glucose 50 mmol/L (normal: >60 mmol/L), protein 132 mg/dL (normal 15-45 mg/dL), WBC 195 (<5), neutrophil 26%, lymphocyte 68%, monocyte 6%, and negative culture for virus, bacteria, and fungi. The electroencephalogram (EEG) showed generalized background slow activity.

Repeat laboratory findings at our hospital showed a normal complete differential blood count and comprehensive metabolic panel, while the ESR remained elevated at 61 mm/hr and C-reactive protein was 1.4 mg/dL (normal 0.3-1 mg/dL). Antinuclear antibody (ANA) titer was 1:1280 with coarse nuclear pattern, lupus anticoagulant was positive, anti-thyroid peroxidase (anti-TPO) antibody was normal at 15.3 IU/ml, and thyroid stimulating hormone was 0.24 mIU/L (normal 0.5-5 mIU/L) with T4 of 2.84 ng/dL (normal 0.9-2.3 ng/dL). Lumbar puncture was repeated, and CSF analysis continued to remain negative for viruses [including herpes simplex virus (HSV) polymerase chain reaction], bacteria, and fungi. However, it was positive for oligoclonal bands, a high IgG index (0.81), IgG albumin ratio (0.37), and an IgG synthetase of 9.7 mg/dL. Magnetic resonance angiography of the brain revealed multifocal leptomeningitis associated with bilateral optic neuritis, right more than left.

The differential diagnosis was very broadly based on history, physical examination, and investigations. Encephalitis could be secondary to infective etiology or autoimmune etiology such as lupus, Sjögren's syndrome, or sarcoid, as the patient had a highly positive ANA and imaging showed lepto-meningeal involvement with optic neuritis. The other differential diagnoses were neuromyelitis optica-associated encephalomyelitis because of the past history of optic neuritis; multiple sclerosis as there was a history of optic neuritis and CSF analysis of high IgG index and oligoclonal bands; thyroid encephalopathy because of positive family history and anti-TPO antibodies; and NMDA antibody encephalitis.

The NMDA antibodies resulted positive at 1:160; hence, the final diagnosis was anti-NMDARE. The patient was treated with intravenous rituximab infusions of 375 mg/m^2, once a week for 4 consecutive weeks. Her mental status gradually improved, and she was able to respond verbally to all commands. She was discharged to a physical rehabilitation facility with a weekly follow-up. After 3 weeks, on the follow-up visit, she was able to carry out all the daily activities on her own. Her parents stated that she is back to her baseline with her physical and mental status.

DISCUSSION

Anti-NMDARE is an immune-mediated encephalitis with auto-antibodies against the *NR1* subunit of the NMDA receptor *GluN1*, which is a glutamate-gated ion channel (1). It is a rare disorder with limited literature. This makes the timely diagnosis and initiation of treatment for this fatal but

treatable condition difficult, because it has a broad spectrum of presentation ranging from non-specific flu-like symptoms to a wide range of psychiatric and neurological symptoms (1). The incidence is estimated to be 1.5 per million population per year, affecting children and young adults mostly between the ages of 12 and 45 years (2, 5). It affects women more than men, with a ratio of 4:1 in the younger age group, but this ratio is more balanced after the age of 45 years (6).

It is usually associated with tumors, most frequently with ovarian teratoma and viral infections, particularly HSV, but in some cases, the immunologic trigger for NMDARE is still unknown (7, 8). The NMDAR is expressed and released by the tumor cells or viruses, which are then taken by the antigen-presenting cells (APC) (6). When the APCs reach the lymph nodes, memory B cells are produced through the action of CD4+ T cells on naïve B cells. The memory B cells can cross the blood-brain barrier, undergo further stimulation, and differentiate into anti-NMDAR antibody-producing plasma cells (6). These antibodies bind to the *GluN1* subunits of synaptic and extrasynaptic NMDARs, disrupting the interaction between the ephrin type 2 receptor and NMDAR, resulting in neuronal hypoactivity (6). Sometimes these antibodies can cause abnormal NMDAR signaling, precipitating seizures (6). In this case, all the workup for ovarian teratoma or any other occult tumors was reported as negative.

The clinical manifestations are varied and depend on the phase of the disease at presentation. It has 5 phases: prodromal phase, acute psychotic phase, hypoactive phase, hyperkinetic phase, and lastly, recovery phase (7). In the prodromal phase, patients experience flu-like symptoms, while the acute psychotic phase presents as rapid-onset visual or auditory hallucinations, acute schizoaffective episodes, depression, mania, seizures (more common in adult males), and addictive or eating disorders (5). This is followed by the hypoactive phase, where mutism and catatonia are commonly seen (7). The hyperactive phase is characterized by movement disorder, which is more common in children, and dysautonomia, which is more frequent in adult patients (9). Our patient presented in this acute psychotic phase.

The rarity of the incidence makes this condition difficult to diagnose. The diagnosis is confirmed by the presence of IgG antibodies against NMDAR in serum or CSF (10). Other CSF findings are pleocytosis, oligoclonal bands, and an elevated IgG index, but they are not specific as they can be seen in patients with multiple sclerosis (6, 11). Magnetic resonance imaging (MRI) is normal in 50% of patients and has non-specific findings during the early stages; hence, it is not very helpful (6). In some patients, MRI can show leptomeningeal enhancement, like in our patient, and T2 or fluid-attenuated inversion recovery can show hyperintensity in the hippocampi, cerebellum, frontobasal cerebral cortex, basal ganglia, and brainstem (3, 12). A unique EEG finding seen in the interictal period is the extreme δ brush (13). Some other EEG abnormalities like generalized slowing (seen in our patient), subclinical seizures, and nonconvulsive status epilepticus can be seen in NMDARE but are not as characteristic as they can be seen in encephalopathy due to other causes (7). In addition, due to its association with teratoma, routine screening for ovarian teratoma should be done for all female patients (10).

Although rare, it is important to remember that NMDARE can co-exist with neuropsychiatric systemic lupus erythematosus (NPSLE), as there have been reports of their overlap (14). NPSLE is seen in almost 50% of systemic lupus erythematosus (SLE) patients, and sometimes it can be the first manifestation. Seizures occur in 28% of NPSLE and 80% of NMDARE patients (14, 15). Laboratory analyses, especially in NPSLE, include positive anti-ribosomal-P antibodies, anti-neuronal antibodies, lupus anticoagulants, and elevated IL-6 levels (16). A study found that a positive lupus anticoagulant predicts intracranial thrombosis, while anti-ribosomal-P is related to lupus psychosis (16). While the association between NMDARE and SLE is not clearly

understood, some studies have found autoantibodies against the *NR2* subunit of NMDAR in 25-30% of SLE patients, which could be the reason for neuropsychiatric manifestations of SLE (14). Other studies have found that lupus autoantibodies might be cross-reacting with the NMDAR, initiating the apoptotic pathway and neuronal death (17). Lastly, Ogawa et al. found expression of autoantibodies against the *NR1* subunit of NMDAR in SLE and NPSLE, suggesting one of the mechanisms by which these 2 diseases could have an overlap (18). However, further studies are necessary to establish a definite etiopathogenesis.

As such, there have been no specific guidelines published so far. The treatment routinely provided is based on the results of case series and observational studies. The first-line treatment is immunotherapy, which includes high-dose steroids, iv immunoglobulins, or plasma exchange (PEX) (19). The response is fairly good, with 53-80% of patients showing improvement (19). PEX provides a rapid improvement in symptoms as it can remove antibodies quickly (20). Studies have also observed that immunoglobulin infusion after PEX has a better outcome compared to when given prior to PEX. Wang et al. observed that a combination of at least 2 of the first-line therapies has been shown to be more efficacious than a single agent (21). Our patient did not improve after the first-line combination; hence, for such a patient population, second-line options that are considered are rituximab or cyclophosphamide (19). For patients refractory to the abovementioned options, azathioprine (antimetabolite), mycophenolate mofetil (antimetabolite), tocilizumab (anti-interleukin 6 antibody), and bortezomib (proteasome inhibitor) can be considered, as there have been studies published with positive results in extremely severe cases (22, 23). Another agent that has proven effective in a case report but requires more research is alemtuzumab (anti-CD52 antibody) (24). The EXTINGUISH trial is an ongoing trial on inebilizumab, a humanized monoclonal antibody against the B-cell surface antigen CD19, which causes robust and sustained suppression of B-cell expression, in patients with NMDARE (25).

CONCLUSIONS

NMDARE is a rare, underdiagnosed, or often misdiagnosed clinical condition with heterogeneous psychiatric and neurological symptoms. A careful history and appropriate workup, including CSF analysis for anti-NMDAR antibodies, imaging, and EEG, should be conducted, considering all differential diagnoses that can mimic its presentation. It is important to remember that every positive ANA is not lupus, and every CSF high IgG index with oligoclonal bands is not multiple sclerosis. Prompt diagnosis and early initiation of therapy prevent its long-term complications. Combination therapy with high-dose steroids, PEX, or immunoglobulin therapy has been shown to be more efficacious. In patients who fail first-line therapy, rituximab or cyclophosphamide should be considered. It is essential to rule out ovarian teratoma or other occult tumors that can cause NMDARE, as the removal of the tumor itself resolves this condition. Timely diagnosis and early intervention are necessary to avoid an untoward outcome.

Contributions
Both authors made a substantial intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate
No ethical committee approval was required.

Patient consent for publication
Anonymized patient information is published in this case report.

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