CASE STUDY

Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A Case Study

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ABSTRACT

Anti-N-methyl-D-aspartate receptor encephalitis is an autoimmune syndrome that presents with personality changes, autonomic dysfunction, and neurologic deterioration. Most patients with this syndrome progress from psychosis to seizure to catatonia, often associated with abnormal movements, autonomic instability, and hypoventilation. First-line treatment constitutes resection of the associated neoplasm, corticosteroids, intravenous immunoglobulin, and plasma exchange. Second-line treatment includes rituximab and cyclophosphamide. A case of confirmed anti-N-methyl-D-aspartate receptor encephalitis is presented that illustrates the diagnostic and treatment challenges associated with this syndrome and underscores the nursing implications of medical management during immunosuppression. This case study recommends surface cooling and a pharmaceutical regimen for management of autonomic storming, which is a hallmark of this disorder.

Keywords: anti-NMDA receptor antibodies, autonomic storming, encephalitis, immunosuppressive therapy

Anti-N-methyl-D-aspartate receptor (anti-NMDAr) encephalitis is an autoimmune syndrome that presents with a variety of symptoms, including personality changes, autonomic dysfunction, and neurologic deterioration. It is commonly associated with mature ovarian teratomas. As awareness of the disorder increases, recent studies indicate that the disease is also occurring in younger teenagers and children (Brenton, Schwartz, & Madoo, 2015). Most patients with anti-NMDAr encephalitis develop a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements and hemodynamic instability, requiring ventilator and other supportive care in an intensive care unit (ICU; Day, High, Cot, & Tang-Wai, 2011). Patients treated with tumor resection and immunotherapy (corticosteroids, intravenous immunoglobulin [IVIg], or plasma exchange) respond faster to treatment and less frequently need second-line immunotherapy (cyclophosphamide or rituximab or both) than do patients without a tumor who receive similar initial immunotherapy. These patients can be quite challenging for the neurocritical care team.

Literature Review

NMDArs play crucial roles in neuroplasticity, memory formation, and learning, and their dysfunction has been associated with excitotoxicity leading to nerve cell death, schizophrenia, epilepsy, and dementia (Dalmau et al., 2007). Movement disorders are a hallmark feature of this syndrome, consisting mainly of orofacial dyskinesias, choreoathetosis, and dystonia (Jones, Benseler, & Moharir, 2013). Orofacial dyskinesias may consist of chewing, tongue thrusting, lip smacking, and facial grimacing (Tham & Kong, 2012). Patients may develop dystonia and oculogyric crises accompanied with tachycardia and hypertension, suggestive of autonomic storming (Jones et al., 2013). This autonomic nervous system dysfunction can also include hypersalivation, sweating, hypoventilation, and increased pulse, respiratory rate, blood pressure, and temperature (Brenton et al., 2015). Clinical presentation usually progresses from a prodromal phase (headache, fever, cough) to psychiatric symptoms (anxiety, insomnia, mania, delusions) to decreased responsiveness (agitation, mutism, seizures) and finally to dyskinesia and autonomic features (Ryan et al., 2013).

After the prodromal phase, patients are often misdiagnosed with psychosis. When the clinical presentation rapidly progresses to delirium, seizures, and catatonia, the diagnosis of anti-NMDAr encephalitis should be

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strongly considered. Diagnosis is supported by characteristic findings on magnetic resonance imaging (MRI) and by cerebral spinal fluid (CSF) studies (Gulyayeva, Massie, & Duhamel, 2013). Investigation of CSF can show lymphocytic pleocytosis, an increase in intrathecal protein, and oligoclonal bands; final diagnosis is based on the detection of NMDA antibodies in the serum or CSF (Wandinger, Saschenbrecker, Stoecker, & Dalmau, 2011).

Once antibodies to the NMDAr are identified, primary emphasis is placed on eradication of the associated malignancy or suppression of the immune reaction. Ovarian teratomas occur in an estimated 60% of female patients who present with this syndrome (Wandinger et al., 2011). First-line therapy for anti-NMDAr encephalitis is tumor resection (if applicable) and immunotherapy. Patients with this disorder usually require ventilatory support and intensive care for seizures and autonomic instability, which can delay tumor removal.

On the basis of previous experience from Josep Dalmau and data from his review, there is no standard of care that exists. However, the preferred first-line treatment is concurrent IVIg (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) or plasma exchange (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011). In some patients, tumor removal results in noticeable neurological improvement in a matter of days or weeks. If no response is seen, then the recommendation is to start second-line therapy with rituximab (a chimeric monoclonal antibody that destroys B cells, which are found in excessive numbers in autoimmune disorders, dosage = 375 mg/m^2 every week for 4 weeks) and cyclophosphamide (a prodrug, which is converted in the liver to active forms that have chemotherapeutic effects, dosage = 750 mg/m^2 given with the first dose of rituximab), followed by monthly cycles of cyclophosphamide (Dalmau et al., 2011). This treatment is discontinued when patients have had substantial clinical recovery, which is usually accompanied by a decrease of CSF and serum antibody concentrations. Once improvement is noted, most patients continue to improve over weeks or months until full recovery, and no maintenance immunotherapy is needed. About two thirds of patients with nonneoplastic NMDAr antibody encephalitis recover with first-line immunotherapy (Dalmau et al., 2011).

Case Study

A 33-year-old woman who was in her usual state of health presented to a local emergency department with complaints of headache, fatigue, myalgias, and cough for 4 days. She was thought to have a viral illness and given a dose of Ativan for anxiety. She returned to the local emergency department the following day with confusion. Her family reports that she was "acting crazy" and did not know who people were. Per discharge summary, she was noted to be "agitated and psychotic" and was transferred to a psychiatric unit. Five days into her stay, she presented with worsening mental status, lethargy, and trismus. She was treated with IV cogentin and flumazenil with positive and immediate effect. Thirty minutes later, she experienced a generalized tonic–clonic seizure, was intubated for airway protection, and was admitted to their medical ICU.

She was initially loaded with Keppra and started on Precedex for sedation. Seizures continued despite increases in dosages of Keppra and Dilantin. Ativan pushes and Versed and propofol drips were utilized. Her seizures stopped, and she had an initial MRI of the brain, which was read as normal. Multiple, repeat electroencephalograms (EEGs) showed slowing without epileptic discharges. She was gradually weaned from Precedex and propofol, but unfortunately, her seizures reemerged. Versed and propofol drips were restarted, and seizure control was achieved. About two weeks into her admission, neurology was consulted for a second opinion. They recommended a computed tomography (CT) of the chest/abdomen/pelvis to rule out a paraneoplastic process. This revealed an ovarian mass that was resected 5 days later and confirmed to be a teratoma. She was empirically treated with IV methylprednisolone and IVIg.

A tracheostomy and percutaneous endoscopic gastrostomy tube were placed. A repeat MRI showed nonspecific edema in the bilateral medial and temporal lobes. She was maintained on propofol and Versed drips for control of arm, leg, and face twitching. At this point, 4 weeks after her initial hospital admission, she was transferred to our neuroscience ICU for further work-up and treatment for a confirmed diagnosis of anti-NMDAr encephalitis.

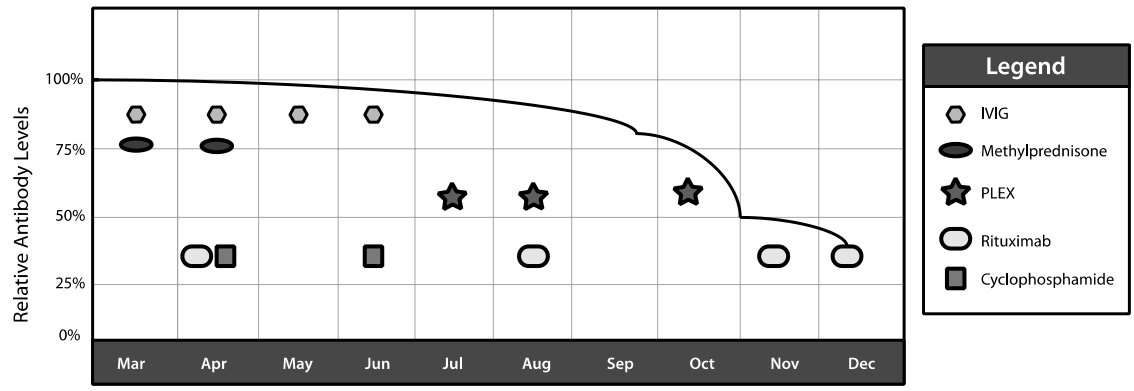
The patient's neurologic examination was significant for coma with no response to voice or noxious stimuli, intact brainstem reflexes, involuntary orofacial and upper extremity movements, and hyperreflexia with nonsustained clonus.

The standard treatment interventions for anti-NMDAr encephalitis were started. As Figure 1 shows, our patient received all five modes of immunosuppression. Of note, the initial hospital did not administer the full dose of methylprednisolone and did not administer it concurrently with the IVIg. In addition, the second ovary was removed prophylactically in the third month of therapy given her persistent comatose state.

Diagnostics

MRIs of the brain performed during the first month of treatment showed T2/FLAIR signal hyperintensities within the medial temporal lobes bilaterally. EEG monitoring continued throughout therapy and consistently showed marked generalized slowing consistent with a global or multifocal cerebral dysfunction, extreme

FIGURE 1 Response to Treatment



delta brush pattern consistent with anti-NMDAr encephalitis (Schmitt et al., 2012) and abundant rhythmic delta activity suspicious for nonconvulsive seizures. EEG consistently ruled out correlation between the dyskinetic movement and seizure activity. Subsequent MRI and CT brain scans identified atrophy. In the fifth month of therapy, ictal and interictal single-photon emission CT scans were performed in an attempt to identify a potential seizure focus but were unrevealing. In the ninth month of therapy, a positron emission tomography scan of the head and body was performed to rule out a secondary neoplasm, which was also negative.

Nursing Implications

Medical management during immunosuppression therapy proved very challenging. Attempts to minimize the autonomic storming with continuous infusions of high-dose Versed and ketamine were mostly ineffective. Seizure management during these months was also challenging. Multiple antiepileptic drugs were administered and titrated to supratherapeutic levels, adjusted with recommendations from the epilepsy team.

She was never able to be weaned from the ventilator as evidenced by tachypnea and low tidal volumes during breathing trials. Oral secretions were substantial and proved a challenge when they would fall upon the subclavian central line. Many creative ideas were instituted to protect this subclavian central line. For several months, she had a Blom tracheostomy with a subglottal suctioning catheter, and between 500 and 1000 ml of secretions were collected daily. This helped quantify some of her insensible fluid loss. In addition, an Exu-Dry absorbent dressing was placed around her tracheostomy to prevent maceration of the skin around the stoma.

A rectal probe provided continuous monitoring of core temperature. The onset of an autonomic storm frequently started with a brisk rise in core temperature. She was on a cooling blanket but frequently required surface cooling to maintain normothermia, because her core temperature would quickly rise to a sustained 42°C (108°F). IV acetaminophen in addition to standing oral acetaminophen would be administered to assist with treatment of hyperthermia. During these storming episodes, the patient frequently bit her tongue or lips repeatedly, would flex her neck so significantly as to occlude her airway, and would violently flail her upper and lower extremities, often disconnecting herself from the ventilator. All vital signs would become markedly elevated, with sustained heart rate > 140, respiratory rate > 40, and systolic blood pressure > 160. A three-step pharmacological protocol was developed for autonomic storming management that consisted of 2-mg Versed IV push; then, if needed, 1-mg propofol IV push; and then, if needed, 50-mg pentobarbital IV bolus infusion. The dose of the pentobarbital bolus had to be progressively increased to 100 mg and then to 150 mg for positive effect. Physical restraints were not used.

Nursing care proved to be a challenge because of the storming, seizures, increased secretions, hyperthermia, and increased length of stay. For the entire 10 months that this patient was admitted to the neuroscience ICU, her family maintained a vigilant presence, and diligent efforts were made to provide support and include them in her daily care and rounding.

Outcomes

She showed no improvement in her symptoms after the first-line treatment (ovary removal, methylprednisolone ×5, four rounds of IVIg ×5). The second ovary was removed to rule out a secondary neoplasm, and the second-line therapy was initiated. The initial doses of rituximab and cyclophosphamide resulted in a significant neutropenia and exacerbation of colitis, which interrupted enteral feeding. She was then started on total parenteral nutrition. After her white blood cell count normalized, a second dose of cyclophosphamide was administered, again with no signs of clinical improvement. Plasma exchange therapy was begun at this time.

Serum and CSF samples were sent every 6 weeks for analysis to Dr. Josep Dalmau, credited for discovering the syndrome in 2007, who also had developed a technique for quantifying antibody titers. By the eighth month of therapy, antibody levels were seen to have reduced to 75% and then to 50% in the following month. She had been successfully weaned off Versed and ketamine and no longer presented with gross hemodynamic fluctuations. However, there was no evidence of improved level of consciousness. She remained comatose, with intermittent orofacial dyskinesias.

In the tenth month of therapy, the patient developed a hemorrhagic cystitis, most likely as a side effect to the cyclophosphamide. Her bladder ruptured into the peritoneum, and she went into cardiac arrest. She required emergent laparoscopic decompression and multiple washout surgeries and remained on vasopressors. At this point, the family elected to withdraw care, and she expired.

Conclusion

Despite aggressive first- and second-line immunotherapies, this patient's clinical presentation remained largely refractory. Medical management of the patient throughout an extended stay in an ICU became a challenge for the doctors and nurses. Efforts to stabilize the patient during episodes of autonomic storming led to the development of a protocol that included surface cooling and sedation. The diverse nature of this syndrome entailed a multidisciplinary approach. Early diagnosis will impact clinical outcomes; however, more data must be obtained to establish standards of care for this recently acknowledged syndrome.

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