Chapter 10
Comorbidity and Seizures

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Case Presentation

A 21-year-old right-handed Caucasian female began to have worsening depressive symptoms, and later developed nausea and headache 2 months prior to presentation. Upon presentation to the clinic for evaluation, her family reported that she had begun to experience language difficulties, memory disturbance, and auditory hallucinations. Emergency medical personnel were notified after the patient experienced a nocturnal generalized tonic–clonic seizure. During the first several days after admission, she was agitated with stereotyped episodes of stiffening and head jerking, recognized to be seizures, and antiepileptic medication was initiated. Despite this, the patient continued to have frequent seizures during the hospitalization, which culminated in nonconvulsive status epilepticus, confirmed by EEG. The patient was intubated and placed on a continuous infusion of several antiepileptic medications. For days, different combinations of antiepileptic medications were tried, but she continued to remain in status epilepticus. An MRI of the brain, routine laboratory, and urine drug screen were normal. She was healthy otherwise without any known seizure risk factors. There was no exposure to other drugs or toxins, as well as no sign of systemic or central nervous system infection. She ultimately underwent a lumbar puncture in an effort to determine the etiology for her nonconvulsive status epilepticus. The results are shown in Table 10.1.

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Table 10.1 Cerebrospinal fluid profile obtained during nonconvulsive status epilepticus

CSF fluid analysis	Result
Appearance	Clear
Color	Colorless
Glucose	66
Protein	31
RBC	18.0 H
Nucleated cells	16.5 H
Lymph	88 % H
Mono	12 % L
Oligoclonal bands	10
IgG index	2.60 H
IgG/albumin ratio	0.65 H
Synthesis rate	24.90 H
Blastomyces antibody	Neg
Cryptococcus antigen	Neg
Histoplasma antibody	Neg
VDRL	Neg
Lyme	Neg
West nile virus IgG, IgM	Neg
Enterovirus PCR	Neg
HIV antibody eval	Neg
Varicella zoster virus PCR	Neg
Herpes simplex-1 PCR	Neg
Herpes simplex-2 PCR	Neg
CMV PCR	Neg
Parovirus B19 PCR	Neg
Angiotensin-converting enzyme	Neg
GAD65 antibody	0.00
ANNA-1	Neg
ANNA-2	Neg
ANNA-3	Neg
Amphiphysin antibody	Neg
CRMP-5	Neg
Neuronal VGKC antibody	Neg
Thyroperoxidase antibody	0.8 (nml <9.0)
Purkinje cell antibody	Neg
Anti-NMDA receptor antibody	Positive

Clinical Questions

1. What is the clinical significance of the elevated antibody titer and other CSF results?
2. What neoplasms, if any, are associated with anti-NMDA receptor antibody positivity?
3. Are there any potential alternatives to medications in prolonged status epilepticus?

4. Is there any role for immunosuppressant medications in anti-NMDA receptor antibody positivity?
5. What is the prognosis for this patient in anti-NMDA receptor antibody encephalitis?

Diagnostic Discussion

1. The presence of the anti-*N*-methyl-D-aspartate (NMDA) receptor antibody solidifies a diagnosis of autoimmune limbic encephalitis. Although multiple different autoantibodies have been implicated in refractory status epilepticus, the anti-NMDA receptor antibody was the first to be reported in 2007. This cell-surface antibody has been postulated to target epitopes on NMDA receptors located in the forebrain and hippocampus. This leads to the development of dyskinesias, autonomic instability, and seizures (often status epilepticus). Prodromal symptoms of headache, low-grade fever, and psychiatric symptoms (anxiety, agitation, hallucinations, paranoia) are often seen and should prompt clinicians to an autoimmune evaluation. The lymphocytic pleocytosis seen in this patient is often found in association with anti-NMDA receptor positivity (91 %); however, oligoclonal bands are only seen in a minority (26 %). Without the positivity of these antibodies, empiric autoimmune treatment could be tried, but aggressive immunosuppression in a critically ill patient would be empiric and risky.
2. Anti-NMDA receptor encephalitis is seen predominantly in females, although not exclusively (91 %). Tumors are seen in just over half of all patients (59 %). Almost all of them have been identified to be reproductive organ tumors (ovarian teratoma and teratoma of the testis), but small-cell lung cancer has also been reported. If a tumor is discovered, resection is the treatment of choice. This can reduce the antibody production and, in turn, the patient's symptoms. Persistence in searching for teratoma is required. It has been reported that not all ovarian teratomas are radiologically evident and exploratory laparoscopy has been required in some patients. Despite thorough investigation, no tumor was found in this patient.
3. Traditional antiepileptic medications are the mainstay for the initial treatment of status epilepticus. When status epilepticus is refractory to multiple medications, other alternatives should be considered. In this patient, the ketogenic diet was utilized with some degree of success in reducing continuous infusions of antiepileptic medications. There are a limited number of case reports describing the use of the ketogenic diet in refractory status epilepticus. In many of these limited cases, it has been shown to be beneficial. Obviously, care should be taken when altering the metabolism in a critically ill patient. In addition to the ketogenic diet, electroconvulsive therapy and vagus nerve stimulation have been described in case reports to have some benefit.
4. The potential benefit of immune-modulating therapy is to eliminate the antibodies that are operational in producing seizures and status epilepticus. Initiating treatment involves a costly evaluation and treatment for autoimmune causes. Appropriate guidelines for an evidence-based algorithm when considering

treatment of autoimmune limbic encephalitis have yet to be established. However, many centers use a similar approach. Without an identified tumor, first-line immunotherapy can consist of corticosteroids (usually high dose), intravenous immunoglobulin (IVIg), plasma exchange, or a combination. If these first-line methods are unsuccessful, then rituximab or cyclophosphamide is then considered. Currently, it is unclear whether chronic immunosuppressive agents are helpful in the prevention of relapses which can occur in 20–25 % of patients.

5. Prognosis in prolonged and refractory status epilepticus is typically poor. It has been suggested in animal models that the anti-NMDA receptor antibodies can cause neuronal dysfunction via inflammation. However, they cause less neuronal damage than other antibodies that may be found to produce autoimmune limbic encephalitis. In the original 100 patients described by Dalmau et al., 47 were noted to make a full recovery, and 28 people recovered with mild stable neurological deficits. This was despite a median length of hospitalization of 2.5 months. Early tumor identification and removal were found to be predictive of a better outcome. It should be noted that intrinsic to this series is a bias due to the ability to identify antibody positivity early so that tumor resection and/or immunomodulating treatment may be initiated.

Clinical Pearls

1. The ability to identify specific antibodies in autoimmune limbic encephalitis is relatively new in the evaluation of refractory status epilepticus.
2. When status epilepticus is refractory or superrefractory, then other treatment modalities, other than antiseizure drugs, should be considered. The ketogenic diet and other non-medication approaches show some promise.
3. Aside from antiepileptic medications, immune-modulating therapies should be considered if a case of autoimmune limbic encephalitis is identified. In many cases, success in patient outcome is a result of having a high clinical suspicion and the willingness to consider therapies other than standard antiepileptic medication.

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