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Doctors Garcia and Houtrow have reported no relationships with proprietary entities producing health care goods or services.

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Anti-N-methyl-D-aspartate Receptor Encephalitis: Diagnostic and Treatment Information for the Physiatrist

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Clinical Vignette

A previously healthy 17-year-old girl presented to the emergency department (ED) with headaches and vertigo that began four days prior to presentation. In the ED, she seized and developed choreathetoid movements. Her level of consciousness rapidly declined, and she was admitted to the pediatric ICU for management and further work-up. After being administered several anti-epileptics, including phenobarbital and levetiracetam, an electroencephalogram (EEG) demonstrated diffuse slowing and disorganization. Magnetic resonance imaging (MRI) was unremarkable. Lumbar puncture was positive for anti-N-methyl-D-aspartate-receptor antibodies, which led to the diagnosis of anti-N-methyl-D-aspartate encephalitis. The patient was treated with a five-day course of methyl-prednisone, followed by intravenous immunoglobulin (IVIG), which produced some clinical improvement. After a four-week hospitalization, she was admitted to the UPMC Rehabilitation Institute for comprehensive inpatient rehabilitation to address her motor and cognitive deficits. Her parents were very concerned about her diagnosis and prognosis for improvement. They wanted to know if their daughter would ever regain her baseline status and return to school.

Definition of Problem

Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis is a neuropsychiatric disorder that was first described in a young woman in 2005 as part of a paraneoplastic syndrome associated with teratomas.[1-4] It was further classified by Dalmau et al in 2007.[5] Recent research suggests that anti-NMDA receptor encephalitis is a member of a family of neuroautoimmune syndromes that make antibodies against synaptic proteins in response to several potential stimuli, such as neoplasms or infections.[1]

In this disease, the antibodies are made against the Glu-NR1 subunit of the N-methyl-D-aspartate receptors, which are located in the hippocampus, amygdala, and cortex of the brain[3,5,6,7] (see Figure 1). As a whole, synaptic NMDA receptors play a role in synaptic plasticity, and act as the cellular substrate for learning and memory.[5,8]

Several retrospective analyses, including the California Encephalitis Project,[2] have found a significant incidence of anti-NMDA receptor-caused encephalitis. In particular, the California Encephalitis Project found that half of the children with idiopathic encephalitis and psychiatric symptoms were found to have anti-NMDA receptor antibodies. The frequency of anti-NMDA receptor encephalitis was four times the frequency of encephalitis caused by various viruses, including herpes simplex encephalitis, varicella-zoster, and West Nile.[2] One group found more than 400 cases of anti-NMDA receptor encephalitis in a three-year period. Many of these cases were initially misdiagnosed with either a seizure disorder or psychiatric illness.[3]

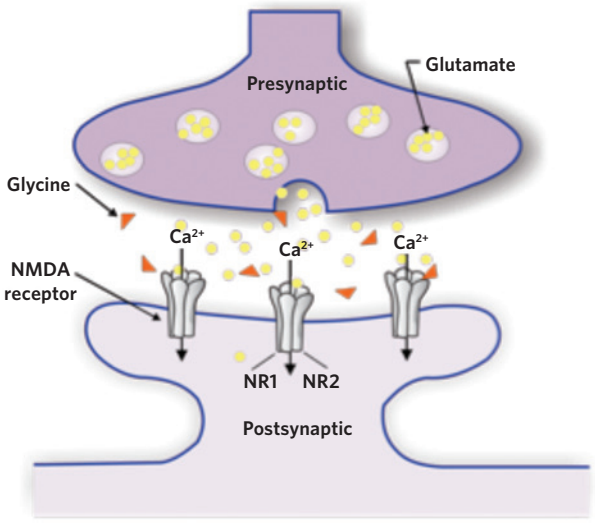

FIGURE 1: **Structure of the NMDA receptor, which is located in the amygdala, hippocampus, and cortex of the brain.**

A recent case series in the *American Journal of Physical Medicine and Rehabilitation* describes six cases of anti-NMDA receptor encephalitis in children and their recovery from a rehabilitation standpoint.[9] The true incidence is unknown because many centers do not send cerebrospinal fluid (CSF) for assay and are frequently misdiagnosing this treatable condition. While much of the research literature focuses on adults, there is a growing body of literature that focuses on the diagnosis in children.

Pathophysiology

Anti-NMDA-receptor encephalitis is proposed to be a member of a group of neuro-autoimmune disorders that target synaptic proteins (see Table 1). Antibodies are made against the NR1 subunit of the NMDA receptor. Other disorders that are considered to be neuro-autoimmune disorders, include myasthenia gravis, neuromyelitis optica, and systemic lupus erythematosus. Anti-NMDA-receptor encephalitis is the most well known member of a group of autoimmune encephalopathies, called autoimmune synaptic protein encephalopathy syndrome (ASPES).[1]

Anti-NMDA-receptor encephalitis and other disorders in the ASPES family have a female predominance, mainly affecting females of childbearing age. Theories as to why this occurs include the frequent association with ovarian teratomas.[3,10] Autoantibodies against the NR1 subunit of the NMDA receptor appear to be B-cell mediated, which makes it similar to myasthenia gravis (autoantibodies against acetylcholine receptors in the neuromuscular junction), neuromyelitis optica (autoantibodies against aquaporin-4 water channel in central nervous system astrocytes), and systemic lupus erythmatosus (autoantibodies against the NR2A and NR2B subunits of the NMDA receptor). The autoantibodies of anti-NMDA receptor encephalitis appear to spare neurons, while the autoantibodies of systemic lupus erythmatosus appear to cause neuronal apoptoic death.[1]

TABLE 1:

Synaptic Autoimmune Encephalitides

Target Antigen	Demographic Data	Primary Symptoms	Other Manifestations	Associated Tumor(s)
NMDA receptor	75% women 35% children + adolescents	Psychosis, seizures, autonomic instability, dyskinesia	Viral prodrome, change in speech, catatonic features, hypoventilation	Ovarian teratoma*
AMPA receptor	Predominates in women ages 50–70	Memory loss, confusion, agitation, seizures	Psychotic symptoms, affective changes	Breast or lung cancer, thymoma
GABA receptor	Either gender, middle-aged	Seizures, memory loss, confusion	Hallucinations, paranoia, odd behaviors	Small-cell lung cancer
LGI1	~2:1 male; female, middle-aged	Amnesia, seizures, confusion, disorientation	Autonomic dysfunction, apathy/ irritability, hyponatremia	Rare, thymoma
Caspr2	~4:1 male; female, middle-aged	Neuromyotonia, dysautonomia, confusion, insomnia	Amnesia, seizures, neuropathic pain, weight loss	Rare, thymoma

Clinical Presentation in Adults

Anti-NMDA receptor encephalitis presents most commonly in young females of reproductive age, but has been reported in males and females across the lifespan (ages 2 to 84).[4,5] Recent review by Perry HE et al[1] and Dalmau et al,[3] summarized the clinical presentation into four phases: a prodromal phase, the psychotic and/or seizure phase, the unresponsive phase, and the hyperkinetic phase. The psychotic/seizure phase, the unresponsive phase, and the hyperkinetic phases can vary in the sequence and severity of presentation. This sequence appears to be similar in both adults and children.

The prodromal phase can last anywhere from five to 14 days. Patients may complain of non-specific symptoms, including headache, fever, malaise, inability to concentrate, nausea, vomiting, diarrhea, and upper respiratory symptoms. Patients who present to an acute facility may be diagnosed with an upper respiratory tract infection or influenza.[1,3]

The psychotic/seizure phase consists of emotional and behavior disturbances. Patients have been described as being apathetic, fearful, depressed, anxious, and paranoid. Decreased cognitive skills and symptoms of acute psychosis, including delusions and hallucinations have been described. Disorientation is common, along with impairments in attention, difficulty in maintaining or shifting focus, and impairment in memory formation and recall. Individuals can have difficulty with maintaining normal sleep-wake cycles, resulting in insomnia. In a recent update, almost all adult patients presented with psychiatric features.[1,3,11,12]

Language and communication decrease, including a reduction of verbal output and echolalia, which can progress to mutism. Word-finding difficulties, aphasia, and dysarthria are common.[1,3] This can progress until a patient is mute and catatonic in appearance (unresponsive phase). During this phase, patients can have abnormal movements consistent with oro-lingual-facial dyskinesias, limb and trunk athetoses, oculogyric crises, dystonia, rigidity, and opisthotonic postures. They also can have echopraxia.[1,3,11,13] Physiatrists may need to utilize several medications and non-pharmcologic approaches as part of the rehabilitation program for treatment of these symptoms, as they can impact a patient's mobility and ability to perform their self-care activities of daily living.

The unresponsive phase can overlap with the hyperkinetic phase, which is characterized by autonomic instability that manifests as cardiac arrhythmias, hypotension, hypertension, bradycardia, tachycardia, and hypoventilation. In one patient series, 66% of adult patients required mechanical ventilation for hypoventilation. Other signs of autonomic instability include hypersalivation and urinary incontinence. Hyperthermia is a very common finding, and can lead to numerous infectious workups as part of the syndrome.

The patients usually are managed in an intensive care unit during this time. Symptoms can alternate between agitation and somnolence, and dissociative responses to stimuli may be noted.[1,3] In this setting, the rehabilitation physician may be asked to consult regarding management of dysautonomia, agitation, or difficulty with arousal.

In addition, patients can present with seizures, most likely of the generalized tonic-clonic variety. These seizures can be refractory to medical management, requiring numerous anti-epileptics and admission to a monitored floor for respiratory and cardiac support. The seizures usually decrease in severity and frequency as the disease evolves, but can reappear at any time.[1,3]

As such, part of the physiatrist role will be monitoring for the reappearance of the seizures, and treating them acutely as needed.

Clinical Presentation in Children

While the presentation in children is similar to adults, there are important differences. In children, there is not a strong female predominance. Children, especially the very young, can present with more subtle psychiatric symptoms, including an increase in temper tantrums, hyperactivity, irritability, and anxiety, which can be difficult to detect at first from normal behavior.[3] In older children, a change in personality, behavior, and mood can be detected at the time of presentation. In a recent update, children were more likely to present with non-psychiatric symptoms, including seizures, unilateral dystonia, or speech disturbances. Speech problems that can be seen in children include mutism and perseveration. Abnormal movements are more likely to be observed in children, including oral-facial dyskinesias, Children also very frequently exhibit autonomic instability during the course of their illness, but it is not as severe as what is seen in adults.[1,3,14-16]

Diagnosis

Diagnosing anti-NMDA receptor encephalitis can be a challenge. The complex presentation of the various psychiatric and neurologic symptoms and autonomic instability, over a long time period, can lead to misdiagnoses and delays in treatment.[1,3] Of note, the workup for anti-NMDA receptor encephalitis is similar in children and adults.

Magnetic resonance imaging (MRI) of the brain is unremarkable in 50% of patients. The other 50% show T2 or FLAIR hyperintensity in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and even the spinal cord. These findings can be accompanied by subtle contrast enhancement in the affected areas of the meninges.[3]

EEG are abnormal in most patients. They usually show non-specific, slow, disorganized activity with occasional electrographic seizures. In the catatonic state, slow, rhythmic activity can be seen in the delta region, which is not an electrographic seizure.[3,14] CSF analysis is abnormal in the majority of patients. Typical findings include CSF-specific oligoclonal bands, moderate lymphocytic pleocytosis, and normal or mildly increased protein concentration. Most patients have autoantibodies to the NMDA receptor. This can be detected by using a specialized, cell-based assay.[1,3,4]

Serum antibodies to the NMDA receptor also can be detected via the cell-based assay, but levels are typically lower than what is found in the CSF.[1,4]

In patients where anti-NMDA receptor encephalitis is strongly suspected or confirmed, a full imaging work-up should be completed to look for tumors, utilizing either computed tomography (CT) scan or MRI. The likelihood of a tumor being detected decreases as the age of presentation decreases. The most common tumor detected is an ovarian teratoma, as 80% of patients affected by anti-NMDA receptor encephalitis are women. Other malignancies that have been detected in adults include neuroblastoma, Hodgkin's lymphoma, and breast cancer.[1]

Differential Diagnosis

The difficulty with this disorder is that it resembles different diagnoses depending on the stage of presentation. For example, many adults present in acute psychoses, leading to use of anti-psychotics for a primary psychiatric diagnosis. Many children are suspected of having behavioral problems and are placed on medications or referred for counseling. Anti-NMDA receptor encephalitis also is confused with viral encephalitis, which is suspected because of the acute neurological change and CSF pleocytosis. With this,

treatment with acyclovir for suspected herpes simplex encephalitis is routine until it is ruled out. As physiatrists, we may be consulted to determine the need for inpatient rehabilitation on a patient with an unidentified encephalitis. By recognizing the symptom pattern, which may be suggestive of anti-NMDA receptor encephalitis, we, as part of the medical team, can make recommendations to consider testing for this traditionally under-diagnosed disorder.

Medical Treatment

Medical management of anti-NMDA receptor encephalitis includes managing the systemic complications and immunosupression. Routinely, patients are first treated with acyclovir for herpes simplex encephalitis, until it has been excluded.[1,17] Once anti-NMDA receptor encephalitis is confirmed by the presence of the IgG anti-NMDA receptor antibodies in the serum or CSF, immunosuppression should be started. A treatment algorithm has been proposed by Dalmau et al.[3] First-line therapy should consist of a five-day course of high-dose intravenous corticosteroids and intravenous immunoglobin or plasma exchange. If no response is seen in 10 days, anti-inflammatory agents (cyclophosphamide), and monoclonal antibodies directed against CD-20 lymphocytes (rituximab) are initiated. Due to a relapse rate of 20% to 25% (mostly in patients without a tumor), it has been suggestive that immuno-suppressive therapy using mycophenolate mofetil or azathioprine should continue for one year.[1,3]

Prognosis

If diagnosed early, the long-term prognosis is good. Dalmau et al[3] reported that in a cohort of 360 patients, 75% had complete or near-complete recovery on the Modified Rankin Scale. The rest had sequelae that severely affected quality of life (21%) or resulted in death (4%). If the diagnosis or treatment is delayed or ineffective, mortality rate can be as high as 100%, usually secondary to autonomic instability or complications related to a prolonged hospitalization. Antibody levels in the CSF can correlate with the patient's clinical outcome.[3]

General Rehabilitation Management

Recovery from anti-NMDA receptor encephalitis happens in a multistage process that is in reverse from the order of symptom presentation, starting with awakening from coma, and ending with recovery of social behavior and executive functions. This can take several months where typical problems are identified during the inpatient rehabilitation program.

1) **Agitation:** First-line treatment should consist of non-pharmacological approaches, including placing the patient in a low-stimulation environment, frequent reorientation and reassurance by members of the treatment team; and one-on-one therapy sessions. Use of an enclosure bed can be helpful, as it can allow the patient to move freely in bed in a safe manner. Restraints should be used as a last resort, as it can increase agitation and confusion in these patients. Common medications that can be utilized for treatment of agitation include atypical antipsychotics, anti-epileptics (valproic acid), and sedatives. Use of these medications should be minimized in the rehabilitation setting if possible. Use of the Agitated Behavior Scale is recommended for monitoring and documenting response to different therapies.[18,19]

2) **Sleep-wake cycle disturbance:** Patients' sleep-wake cycles should be monitored by use of a sleep log. Useful medications for regulating the sleep-wake cycle include melatonin, which is a natural supplement; trazadone, an antidepressant that has sleepiness as a major side effect at low doses, and zolpidem, a sedative. In children, we recommend starting with melatonin as it is non-habit forming and with minimal side effects. Medications that can be used to help with wakefulness include amantadine, a dopaminergic agonist that can be safe in children and adults, and modafinil (Provigil®) in adults (mechanism unknown). Modafinil's use in children for problems with arousal has not been studied.[20,21]

3) **Inattention and impulsivity:** Impulsivity, which is the urge to act without thinking, can be part of the clinical picture for anti-NMDA receptor encephalitis. Impulsive actions can result in patient harm if not monitored closely. The mainstay of treatment for impulsivity in children and adults is behavioral management, although methylphenidate and atomoxetine can be added.

Methylphenidate acts as an indirect catecholamine agonist that blocks the dopamine transporter and norepinephrine transporter. Atomoxetine, which is a newer drug for treating disorders of attention with impulsivity, is a selective norepinephrine transporter inhibitor that acts as a non-stimulant medication.[22]

4) **Movement disorders:** As part of anti-NMDA receptor encephalitis, patients also may develop movement disorders, including spasticity, dystonia, orofacial dyskinesias, and athetosis of the limbs and trunk.[23] Medications that can be used for spasticity and dystonia in adults include baclofen, trihexiphenidyl, tizanidine, and levadopa. In children, baclofen and trihexiphenidyl are common agents used to treat spasticity and dystonia.[24,25] Use of botulinum toxin has not been reported for this condition.

   Chorea is a rapid, uncontrolled, involuntary excessive movement that flows from one body part to another (think "dancing fingers"). Athetosis is a slow, writhing and twisting movement that can present in all body areas, including the face. Characteristic facial movements of chorea include nose wrinkling, flitting eye movement, tongue and mouth movements, which is commonly seen in anti-NMDA receptor encephalitis. Treatment of choreathetosis in children includes benzodiazapines, such as clonazepam, diazepam, or clobazam, while anti-epileptics also are effective in treatment of chorea.[26]

Special Considerations for Rehabilitation of Children

If neuro-cognitive deficits are identified, consultation with a neuropsychologist may identify strategies to utilize the child's strengths to facilitate their ability to learn and perform in the school environment. They may make suggestions to assist the child in learning, including seat placement in the classroom and identifying areas where the child may benefit from one-to-one assistance. Education strategies such as "chunking" the material, giving lectures notes, presenting the material in a novel way, or utilizing different methods to assess mastery of the material, also may be provided.

The educational specialist, who typically has some experience in special education, works with the members of the therapy team, along with the patient's family and school, to identify and plan for any accommodations and support services a child may need to assure a smooth re-entry in the school setting after their inpatient rehabilitation. They assist the school and team with making an individualized educational plan (IEP) for re-entry to school. An IEP takes into consideration the medical condition and its effect on brain functioning, and the need for accommodations based on neuropsychological testing and the clinical examination. Accommodations can be made to assist the child in the school environment, which will allow them to reach their maximal potential. Depending on the child's needs, they may qualify for physical, occupational, or speech therapies in the school setting, which will be specified in the IEP. As clinically appropriate, the educational specialist will assist the child with schoolwork while they are admitted for inpatient rehabilitation.

In pediatric patients with anti-NMDA-receptor encephalitis, length of stay in a rehabilitation facility can vary considerably, depending on the severity of deficits and medical complications. In the recent study by Houtrow et al,[9] the length of stay for pediatric patients with anti-NMDA receptor encephalitis varied from two to six weeks. Five out of six patients required ongoing cognitive and speech therapy after inpatient rehabilitation. Of note, there are no studies available describing the rehabilitation course of adults with anti-NMDA receptor encephalitis.

Clinical Vignette Summary

At the time of admission to the rehabilitation unit, the patient was dependent for all transfers, self-care, and swallowing. She had a movement disorder, agitation, receptive and expressive aphasia, and was non-ambulatory. After a four-week course of comprehensive inpatient rehabilitation, the patient's functional status had greatly improved.

Upon discharge, she required supervision for dynamic balance and ambulation; minimal assistance for self-care activities,

swallowing, and attention; and maximal assistance for memory, comprehension, and expression. She was then enrolled in an outpatient therapy program consisting of physical therapy, occupational therapy, and speech therapy. She also required an individualized educational plan (IEP) as part of her community reintegration program for persistent deficits in memory, comprehension, expression, and new learning.

Approximately one year after the onset of her symptoms, the patient had dramatically improved. Her comprehension and memory are very functional, but she is not quite back to baseline. She continues to have some difficulty with reading and writing, but has improved to grade-level work. She requires accommodations when taking tests, and some learning support with her classwork.

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Michael C. Munin, MD, discusses quantitative EMG in evidence-based medicine, and the identification of data points which support EMG diagnosis.

DISCOVERY CHANNEL PODCAST

Specialty Medical Homes for Patients with Spina Bifida

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