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Anti-N-Methyl-D-Aspartate Receptor Encephalitis: diagnosis obscured by concomitant recreational drug use

Paige Lester[1], Adam M. Franks[1], William Rollyson[1], Jenna K. Barbour[1], Matthew B. Curry[1]

ABSTRACT

Anti-NMDA receptor encephalitis (ANMDARE) is a relatively newly discovered autoimmune and inflammatory disorder affecting the limbic system. It has a clinical course that includes prodromal, psychiatric, unresponsive, and hyperkinetic stages. These stages are often confused with mental health issues in the medical literature, but they also share symptoms of various drug intoxication and withdrawal states. Implicit bias in physicians regarding substance use disorder and patient demographics can impair delivery of care and outcomes in patients with ANMDARE, especially in a setting with a high prevalence of recreational drug use. When clinical presentation aligns, this diagnosis should be investigated as soon as possible, even in the case of atypical presentations or in those with past or current substance use disorder. Early identification and treatment are essential to good outcomes and minimal sequalae at two years. Therefore, it is essential to consider ANMDARE with the symptom profile regardless of patient age, sex, race, or clinical disorder. Below, the difficulty in diagnosing ANMDARE is detailed in a 32-year-old white male with a history of methamphetamine, opioid, benzodiazepine, and marijuana use.

KEYWORDS

NMDA receptors, Autoimmune encephalitis, Drug use, Physician bias

Author affiliations are listed at the end of this article.

Corresponding Author:
Adam Franks, MD
Marshall University
Joan C. Edwards
School of Medicine
franks1@marshall.edu

INTRODUCTION

Anti-NMDA receptor encephalitis (ANMDARE) is a recently discovered autoimmune and inflammatory neurologic disorder first identified in a cohort of four women with ovarian teratomas,[1,2] but officially described two years later by Dalmau in 2007.[3,4] Predominantly seen in non-Caucasian1,3,5 females (4:1)[1,3-8] in their third decade of life,[3] it can also be seen in other mammal species.[9] Presentation normally ranges between 19 to 45 years of age[4] with a median of 21 years.10 ANMDARE has been highly associated with underlying tumors, especially those containing neural tissue,1 98% of these being ovarian teratomas.2-6,11-14 Testicular teratomas and small cell lung cancer can be seen, especially in males.[2,3]

ANMDARE often presents with four stages of characteristic symptoms (Table 1). A prodromal stage is first to present with constitutional symptoms.[1,3,5,7,9,11,12,15] This period is often missed, and clinical presentation usually occurs with the hallmark psychiatric stage.[1,2,4-8,10,11,13-16] The third stage is an unresponsive stage with catatonia, athetosis, and orofacial dyskinesia.[1,3,5,8,9,11-13] Seizures can occur,[2-6,8-16] but tend to be partial rather than generalized1 and rarely advance to status epilepticus.[1,2,5] Finally, the hyperkinetic stage occurs with autonomic instability, arrhythmias, hypotension or hypertension, central hypoventilation, hyperthermia, and urinary incontinence.[1-5,7-14,16]

Due to the psychiatric symptoms, ANMDARE is often confused with mental health conditions in the current literature. Despite the unresponsiveness,

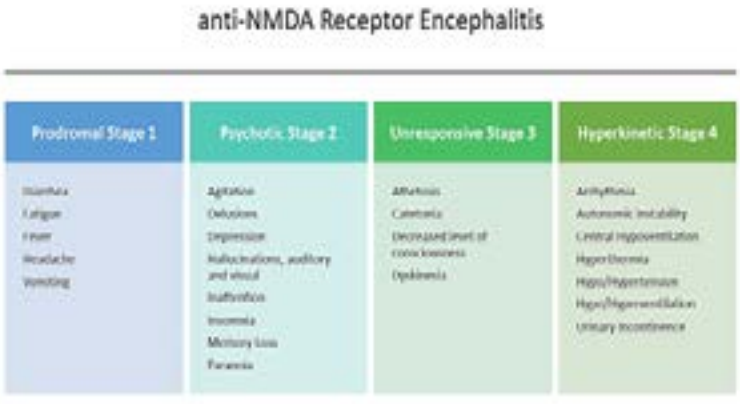

TABLE 1. Four stages of characteristic symptons of ANMDARE.

seizures, and autonomic dysfunction, little is mentioned about confusion with substance use disorders. With the potential for implicit bias of healthcare workers towards patients with substance use disorders, patient care can be deleteriously affected.[17] Below, the effect of biases is explored in this case of ANMDARE in the setting of an area with a high prevalence of recreational substance use.

CASE PRESENTATION

A 32-year-old Caucasian male with a past medical history of substance use disorder, anxiety, and bacterial meningitis presented to an outside hospital for seizure-like activity. Urine drug screen was positive for methadone, marijuana, and benzodiazepines. The patient declined further neurologic workup due to fear of needles and confined spaces and was treated with levetiracetam (Keppra) empirically.

After discharge, the patient's family noted him making random odd comments. He also experienced auditory hallucination followed by several minutes of tonic-clonic seizure activity, despite compliance with levetiracetam. This was followed by a post-ictal state. In the emergency department, the patient was alert, oriented to person, and able to follow simple commands. Neurologic and musculoskeletal examination were unremarkable. Laboratory assessment revealed a leukocytosis (13 k/mL), low thyroid stimulation hormone (0.323 mIU/L) with normal free t3/t4 (2.86 pg/dL and 1.01 µg/dL), normal creatine phosphokinase (144 U/L), normal metabolic profile, and a drug screen positive for methadone and marijuana. Neurology placed him on long-term video monitoring (LTVM) and changed his levetiracetam to valproic acid (Depakene). Workup for infectious etiologies was initiated, and he was monitored for benzodiazepine withdrawal.
During hospital day 2, the patient was described as "looking scared... holding stomach... and…spitting" on LTVM. Electroencephalogram during the event showed left temporal sharply contoured theta epileptic activity. His valproic acid was increased, and

Differential Diagnosis

Central Nervous System		
Demyelinating Disorders	Acute Disseminated Encephalomyelitis, Neuromyelitis Optica	
Encephalitis	Autoimmune	GABA, AMPA, LGI1 receptors
	Autoimmune Synaptic Recep	PANDAS, Sydenham Chorea, Hashimoto's, Rasmussen, Encephalitis Lethargica
	Limbic	
Meningitis	Bacterial	
	Viral	
Vasculitis, CNS		
Drug/Medication Related		
Drug Abuse		
Drug Withdrawal		
MAOI Neurotransmitter Disorder		
Neuroleptic Malignant Syndrome		
Psychiatric		
Childhood Disintegrative Disorder		
Kleine-Levin Syndrome		
Psychosis		
Other		
Inborn Errors of Metabolism		

TABLE 2. Different Diagnosis for anti-NMDA receptor encephalitis. (GABA = Gamma Aminobutyric Acid, AMPA = alpha-Amino-3-Hydroxy-5-Methyl-Isoxazoleproionic Acid, LDI1 = Leucine-Rich Glioma-Inactivated 1, PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) Citations 1, 2, 5

anti-NMDA Receptor Encephalitis	Alcohol		Amphetamines		Benzodiazepines		Cannabinoids		Cocaine		Hallucinogens		Opioids	
	Use	W/D	Use	W/D	Use	W/D	Use	W/D	Use	W/D	Use	W/D *	Use	W/D
Prodromal Stage														
Diarrhea			X	X										X
Fatigue										X			X	
Fever		X						X						X
Headache		X		X		X		X	X				X	
Vomiting	X	X	X				X				X		X	X
Psychotic Stage														
Agitation		X	X	X			X		X		X			X
Delusions			X				X		X		X			
Depression	X			X				X		X			X	
Hallucinations - auditory &		X	X			X	X		X		X			
Inattention	X			X		X				X	X		X	
Insomnia	X	X	X	X		X		X						X
Memory loss		X		X	X								X	X
Anxiety or paranoia	X	X	X			X	X	X	X	X	X		X	X
Unresponsive Stage														
Amnesia							X	?	?					
Catatonia										X	X			
Decreased level of	X				X								X	
Seizures		X	X			X	X	X	X				X	
Hyperkinetic Stage														
Arrhythmia			X					X	X				X	
Autonomic instability		X	X		X		X	X			X			
Central hypoventilation	X				X		X						X	
Hyperthermia			X						X		X			X
Hypo/hypertension	X	X	X				X	X	X		X		X	X
Hypo/hyperventilation					X		X		X		X		X	
Urinary incontinence	X													

TABLE 3. Comparison of stages of anti-NMDA receptor encephalitis with symptoms of different substance use and withdrawal disorders.

he underwent MRI, which showed patchy meningeal signal enhancement in cerebral cortices concerning for chronic meningitis. Lumbar puncture (LP) was performed showing pattern concerning for viral meningitis. He was started on Acyclovir while the PCR was pending.

The patient continued to have anxiety, paranoia, and fluctuating mental status. His symptoms were magnified during periods of invasive testing, which required general anesthesia to complete. Suspecting polysubstance dependence versus delirium, psychiatry started him on ziprasidone (Geodon). On hospital day 10, he experienced an auditory hallucination preceding a seizure despite adequate valproic acid levels. Infectious workup, including herpes PCR, returned negative, as did aerobic, anerobic, and fungal cerebrospinal fluid cultures. Carbamazepine was added. A repeat LP was performed for auto-immune encephalitis, and empiric steroids were initiated.

On hospital day 23, anti-NMDA-receptor antibodies were reported positive. IVIG was started as his steroids were tapered. Paraneoplastic workup was performed, which found no malignancy; however, a prosthetic left testicle was discovered, the etiology of which the patient could not recall. He suffered no further seizures, though he still dealt with significant anxiety. He was discharged home on hospital day 28 with family care.

DISCUSSION

Encephalitis is an inflammatory disorder of the brain[11,13] that develops rapidly[17] and has a wide differential (Table 2). It occurs in 5-10 per 100,000 people yearly, but this is likely an underestimation.[3] Encephalitis in the limbic system, which includes the medial temporal lobes, amygdala, and cingulate gyrus,[11] affects the function of the brain regarding

emotions, anesthesia induced amnesia, aversive memories, and addictive behavior.[4] ANMDARE is the most common autonomic limbic encephalitis.[12] It constitutes up to 40% of viral negative1 and idiopathic encephalitis[2] and also 1% of patients with encephalitis in the intensive care unit.[1] NMDA receptors are located in the forebrain and hippocampus,[2,3] as well as the basal ganglia, spinal cord, and cerebellum.[5] The receptors are tetramers of glutamine subunits (2 GluN1 and 2 GluN2/3)[1,3,4,7,13] that work as ligand-gated channels. Through dopamine, serotonin, and glutamate, they play a role in Schizophrenia,[2,4] Parkinson's disease,2,8 Alzheimer's disease,[2,8] and synaptic plasticity[1] the latter of which is important for memory, learning, and cognition.[1,8] Expressed symptoms depend upon affected receptor location.[5] While the exact cause has not been clarified,[6] pathophysiology follows autoimmune principles as IgG autoantibodies target the extracellular N-terminal of the GluN1 subunit.[1,8] Crosslinking causes reversible[7,8] internalization of both excitatory and inhibitory receptors,[7] which can be seen two hours after in vitro exposure.[1-5,7] Long-term exposure causes excitability of receptors upon withdrawal.[18] The high prevalence of comorbid tumors, especially those with neurogenic components like ovarian teratomas,[2-6,11-14] suggest a paraneoplastic etiology[2] and might supply the antigenic source for this disease.

The workup for autoimmune encephalitis, consisting of antibody testing, inflammatory markers, imaging changes, and immunotherapy response, is straightforward.[13] ANMDARE can be diagnosed with the triad of 1) rapid onset of classic symptoms, 2) typical electroencephalogram (EEG) findings of diffuse or local slowing[2,3,5,11,16] and extreme delta brush,[3,5,11,16] and 3) a reasonable exclusion of alternative causes.[13]

However, cerebrospinal fluid (CSF) and serum IgG anti-GLuN1 antibodies coupled with the exclusion of other diagnoses is considered reasonable certainty.[8,13] What is difficult, especially in an environment of significant substance use, is even considering the diagnosis in the first place. The onset of ANMDARE typically presents with psychiatric symptoms, confusing it with acute intoxication or recreational substance withdrawal. This requires sequential elimination of alternate options from the differential (Table 2). Psychiatric diagnoses can be ruled out by the patient's progression to the unresponsive and/or hyperkinetic stages of ANMDARE. Differentiating it from substance use disorder is more complex because of the wide range of overlapping symptoms (Table 3).

Serologic testing lacks the specificity of CSF testing.[3,11,13,15] While IgG antibodies of the GluN1 subunit are useful, there is unclear significance for IgA and IgM,[7,13] as well as autoantibodies for GluN2/3.[2,7,12,13] CSF will usually show lymphocytic pleocytosis and oligoclonal bands.[1-3,5,11,13,16] EEG is abnormal in 90% of ANMDARE cases,[1,3,5,11] making it a useful tool to differentiate it from substance use disorder.[12] It most frequently shows an extreme delta brush pattern or synchronized delta wave (1-3Hz) superimposed on fast beta activity (20-30Hz)3,5,11,16 that does not vary with the circadian rhythm.[16] Imaging is largely unhelpful, as CT is usually normal and MRI is normal up to 70% of the time. When it is positive, findings tend to be transient and non-specific,[1,2,3,5] with increased signal on T2-weighted or fluid attenuated inversion recovery in hippocampus, cerebellum, frontobasal or insular cortex, basal ganglia, brain stem, and spinal cord.1 Meningeal enhancement,[1,10,11] frontotemporal atrophy,[3] and periventricular white matter demyelination[1,3,13] can also be observed. PET scans can reveal occipital lobe hypometabolism.[3] Locating an associated tumor with testicular or pelvic ultrasound may also be helpful in diagnosis.[1]

As with other autoimmune pathologies, first line treatment of ANMDARE includes decreasing autoantibodies through immunotherapies of steroids, IVIG, and plasmapheresis.[1-8,11,14,15] Resection of a tumor, if one is identified, improves success of treatment to 80% in combination with first-line immunotherapies. If those fail, second line treatment is rituximab or cyclophosphamide,[1-3,5,6,10,11,14,15] which decreases autoantibody formation by depleting memory B cells, but is limited due potential side effects.[8] Multiple forms of treatment have proven effective.[6,15] Still, long-term treatment, prolonged hospitalizations, and rehabilitation are common.[1] High levels of recovery from ANMDARE, as defined by Modified Rankin Scores, occur in approximately 80% of patients within 2 years of disease onset.[3,10,11,15] Predictors of good outcomes include lower severity

of symptoms, lower levels of antibody titers, and early detection of the disorder, thus leading to early immunotherapy and/or tumor resection.[1,3,5] In fact, not starting treatment within 4 weeks of onset strongly predicts a poor outcome at 1 year.[14]

Implicit bias in healthcare professionals presents a potential barrier to early detection of, and thus better recovery from, ANMDARE. Central Appalachia shares the nation's prevalence of substance use disorders, where up to 50% of urban emergency departments and up to 40% of inpatient admissions involve alcohol and other substance use disorders.19 Overall, physicians carry negative attitudes towards patients with substance use disorder,[17] and these attitudes deteriorate throughout training.[19] Patients are labelled as "difficult," as they are perceived to repetitively over-utilize healthcare and monopolize resources.[19] These stigmatizing attitudes can affect healthcare delivery through avoidant behaviors, poor communication, and misattributing physical symptoms.[17] Medical errors can occur from any of the 32 different identified cognitive biases, but diagnostic inaccuracies predominately are associated with overconfidence, anchoring effect, information bias, and availability bias.[20]

In this case, the patient's gender decreased the likelihood of ANMDARE. Furthermore, anchoring on his substance use disorder delayed diagnosis and treatment. Alternative diagnoses, including ANMDARE, should be considered when symptoms persist beyond the expected course of intoxication or withdrawal, or if seizures persist despite therapeutic levels of anticonvulsants. Ongoing use of recreational substances can prolong these times, but this can be reassessed with repeated drug screening.

CONCLUSION

ANMDARE is a complex medical condition that can easily be mistaken for psychiatric and substance use disorders. Physicians should consider all possible differential diagnoses, regardless of patient history and background, when presented with symptoms that resemble ANMDARE in order to get prompt treatment and increase the likelihood of full recovery.

AUTHOR AFFILIATIONS

1. Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia

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