Neuropsychiatric Manifestations of Autoimmune Encephalitis in a Tertiary Hospital: A Case Series and Current Perspectives

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ABSTRACT

Importance: *Autoimmune encephalitis* (AE) refers to a group of neuropsychiatric conditions associated with specific circulating autoantibodies directed against synaptic receptors, neuronal cell surface proteins, and intracellular targets. Increased recognition of these disorders is of value, as affected patients prominently display cognitive impairment, behavioral disturbances, and seizures requiring multidisciplinary teams, with early recognition often impacting prognosis.

Observations: This case series is based on a retrospective record review of adult patients diagnosed with AE between January 1, 2010– January 1, 2020. Cases 1 and 2, demonstrating anti– *N*-methyl-D-aspartate receptor (NMDAR) encephalitis with initial manifestations of neurologic and psychiatric symptoms, correlate with the literature describing a higher prevalence of this condition in young women. Case 3, despite being seronegative, exhibited classic features of anti-NMDAR encephalitis. Case 4 demonstrates a classic presentation of anti–leucine-rich glioma-inactivated 1 (LGI1) encephalitis: a middle-aged male with psychosis, altered mentation, and epilepsy. Case 5 had a more indolent neuropsychiatric presentation with mild elevation of N-type voltage-gated potassium channel (VGKC) antibody. Case 6, with glutamic acid decarboxylase 65 (GAD65) antibody, was an elderly female with speech dysfunction and altered mentation, and case 7 was an elderly male with GAD65 antibody who had stiff-person syndrome, ataxia, cognitive decline, and thymoma.

Conclusions: This retrospective case series describes the clinical details of 7 individuals with AE and overlapping neuropsychiatric symptoms. This series is limited in scope, with a small number of cases and observational findings, which prevents specific conclusions from being drawn. Despite this limitation, the present article explores the nuances of variable presentations of this disease to inform better interdisciplinary management and emphasize the gap areas that need rigorous research.

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The first case of "limbic encephalitis" was described in 1960 by Brierley et al, who described a patient with an acute inflammatory change in the limbic structures with no clear etiology.[1] Eight years later, Corsellis et al[2] reported 3 similar clinical presentations in association with malignancy, suggesting potential paraneoplastic causation. In 2004, Vincent et al[3] described a significant number of limbic encephalitis cases occurring in the absence of cancer. Ultimately, Dalmau et al[4] identified a variety of autoantibodies directed against synaptic antigens, introducing the term *autoimmune encephalitis* to describe this group of patients with more diffuse neurologic symptoms. Since then, the clinical spectrum of central nervous system autoimmune disorders has expanded considerably. Since 2005, a multitude of novel syndromes and their associated antibodies affecting synaptic transmission and neuronal plasticity have been described.

Among AE patients, psychiatric symptoms are prevalent in 60%, including nearly all cases caused by anti–*N*-methyl-D-aspartate receptor (NMDAR) antibodies.[5] In a prospective study in a specialized neurology setting, almost 31% of patients with AE were first treated for psychiatric symptoms, including psychosis, in a mental health unit. Of all anti-NMDAR encephalitis cases, 40% were first evaluated by a psychiatrist.[5] Given the significant overlap with psychiatric disorders, psychiatrists must at least consider AE among their differential when evaluating patients. The aim of this case series is to review some of the existing literature on AE in the context of the 7 patients described. By illustrating the neuropsychiatric presentation in this manner, our goal is to raise awareness among psychiatrists and neurologists and hopefully yield better management outcomes.

METHOD

This case series is based on a retrospective record review summarizing data on adult patients diagnosed with AE between January 1, 2010, to January 1, 2020, at an academic institution with an associated general hospital. Institutional review board (University of Missouri-Columbia) approval was sought and obtained with informed consent waiver and HIPAA exemption due to the retrospective nature of the study. Cases were located using billing codes rather than *ICD* codes in the electronic medical record (PowerChart, Cerner Corporation) due to billing codes proving more sensitive at locating possible candidate cases. Codes corresponding to autoimmune encephalitis (67789838), limbic encephalitis (710011), paraneoplastic anti-*N*-methyl-D-aspartate (NMDA)

Clinical Points

- The diversity in neuropsychiatric manifestations of autoimmune encephalitis (AE) in adults, as seen in this case series, underscores the need to maintain a high index of suspicion of AE when treating patients with mixed neuropsychiatric symptoms.
- The importance of both collaborating with other services to coordinate the workup and managing patients' symptoms to improve their overall prognosis is also emphasized.

receptor encephalitis (58053785), anti-NMDA receptor encephalitis (809127), and limbic encephalitis associated with anti–leucine-rich glioma-inactivated 1 (LGI1) antibody (1493564415), voltage-gated potassium channel (VGKC) antibody (15493868), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibody (56163562), contactin-associated protein-like 2 antibodies (1493564429), and NMDA receptor antibodies (77219524) were used. After the query, each incidence was manually reviewed to verify compliance with diagnostic criteria as established by Graus et al.[6] A total of 7 cases meeting these criteria were found, with the details of hospitalization, diagnosis, and treatment summarized in Table 1. A literature review was conducted using the search terms "autoimmune encephalitis," "anti-NMDA receptor encephalitis," "limbic encephalitis," and "paraneoplastic encephalitis" in PubMed covering relevant articles from January 1, 2005, to May 1, 2021, to allow the authors a more encompassing understanding of the patients discussed herein. The search was performed by 2 authors and was reconciled in discussion.

CASE VIGNETTES

Case 1: Definite Anti-NMDAR Encephalitis

A 21-year-old female with no known past psychiatric history presented to the emergency department (ED) with episodic slurring of speech, "locking up of jaw," and involuntary blinking. The first onset of symptoms was 6 weeks prior. Admission records detailed auditory hallucinations, paranoia, irritability, insomnia, anorexia, mood lability, and unprompted profanity. A few days before this presentation, she had been started on citalopram for mood changes by her primary care physician. Her interview featured pressured speech, agitation, and disorganized thoughts. At one point, the patient stripped herself, believing she was in labor and was at the hospital to give birth. The patient was placed on an involuntary commitment.

Initial cerebrospinal fluid (CSF) analysis, brain magnetic resonance imaging (MRI), electroencephalography (EEG), and computed tomography (CT) of the chest/abdomen/pelvis were all interpreted as negative for any pathology. While the results of a CSF autoimmune panel were awaited, she was transferred to the psychiatric unit, where she was started on lithium and olanzapine for acute mania. On day 13, the patient's autoimmune panel returned positive for NMDAR antibodies. Olanzapine and lithium were tapered off, and with the diagnosis of definite anti-NMDAR encephalitis, she was transferred to inpatient neurology to be started on intravenous (IV) methylprednisolone and intravenous immunoglobulin (IVIg). With appropriate treatment, her symptoms quickly improved, and the patient was discharged on day 18 in stable medical condition.

Case 2: Definite Anti-NMDAR Encephalitis

A 20-year-old female was admitted by the neurology service for intractable seizures. Six months prior, she had been diagnosed with right temporoparietal seizures generalizing to tonic-clonic seizures. Despite treatment with lacosamide, valproate, and levetiracetam, she experienced frequent staring spells that were felt to be a manifestation of breakthrough seizures. Personality changes developed, with depression, irritability, mood lability, decreased social interactions, and increased use of foul language. Cognitive impairment, weight loss, and fixation about dying, as well as auditory-visual hallucinations, arose over the preceding 2 months. Citalopram was initiated for major depressive disorder a month before admission.

Psychiatry was consulted for an alternative assessment of what was initially thought to be postictal mentation changes. The physical examination was remarkable for nystagmus, ankle clonus, and poor attention and registration on the mental examination. Ultrasound of the pelvis, brain MRI, head CT, and chest/abdomen/pelvis CT were all negative for occult tumors. Initial CSF analysis showed no specific abnormalities but was then sent for paraneoplastic and autoimmune panels. On day 5, the patient's agitation led to her punching her mother, and, for the safety of both patient and staff, she was administered quetiapine. Video EEG identified epileptic spikes in posterior leads, prompting valproate and levetiracetam to be exchanged for topiramate and phenytoin. On day 6, a lumbar puncture was repeated, showing a white blood cell count of 9/mm^3 and positive oligoclonal bands. Ultimately, CSF testing returned positive for NMDAR antibodies at a titer of 1:320, allowing diagnosis of definite anti-NMDAR encephalitis. Treatment with IVIg and methylprednisolone led to improvement, allowing discharge to a rehabilitation center by day 9 in a stable medical condition.

Unfortunately, within 6 days the patient was readmitted on account of agitation and violent actions. Citalopram and quetiapine were increased in dose. She was continued on phenytoin with the addition of phenobarbital, while lacosamide and topiramate were discontinued. After the second round of IVIg and methylprednisolone, her cognition and emotional outbursts again improved, allowing discharge to rehabilitation on day 15. She was followed up in the clinic, where her anti-NMDAR titers were < 1:10 while only on maintenance with levetiracetam.

Case 3: Probable Anti-NMDAR Encephalitis

A 37-year-old female with a history of bipolar disorder presented for fluctuating mental status and recurring

Table 1. Summary of Autoimmune Encephalitis Cases in the Case Series

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age, sex	21, Female	20, Female	37, Female	47, Male	72, Female	67, Female	74, Male
Clinical features	Seizures, dystonia, dysarthria, auditory hallucinations, paranoia, insomnia, mania, agitation	Seizures, personality changes, depression, weight loss, auditory-visual hallucinations, agitation	Seizures, catatonia, auditory-visual hallucinations, paranoia, agitation	Altered mental status breakthrough seizures, memory impairment, psychosis	Cognitive decline, anomia, agitation, paranoia	Altered mental status, short term memory loss, transcortical motor aphasia, anomia, mood lability, knee clonus	Altered mental status, slurring of speech, ataxia, rigidity, agitation
Initial diagnosis	Bipolar disorder type I, mania with psychotic features	Acute metabolic encephalopathy, major depressive disorder, possible autoimmune encephalitis	Acute metabolic encephalopathy, bipolar disorder type I, mania with psychotic features, possible autoimmune encephalitis	Acute metabolic encephalopathy, conversion disorder, possible autoimmune encephalitis	Prion disease, major neurocognitive disorder	Acute metabolic encephalopathy, paraneoplastic vs autoimmune encephalitis	Acute metabolic encephalopathy, seizure disorder
Initial treatment	Olanzapine, lithium, quetiapine	Quetiapine, valproic acid, levetiracetam, phenytoin, topiramate, citalopram	Lacosamide, oxcarbazepine, IV valproic acid, IV haloperidol PRN	Valproic acid	Risperidone, donepezil, memantine	Levetiracetam	Levetiracetam
Antibody in CSF	Anti-NMDAR IgG	Anti-NMDAR IgG	None	LGI1 and VGKC complex	N type VGKC	GAD-65	GAD-65
Interval until antibody detection	Day 13	Day 6	None	Day 13	Diagnosed as outpatient	Day 30	Negative initially, repeat panel was positive 3 mo later
Neuroimaging, EEG, laboratory, and CSF findings	Leukocytosis on day 8 Unremarkable EEG, MRI	CSF WBC: 9/mm^3 Oligoclonal bands: 6 EEG: posterior spikes	EEG: epileptiform discharges in frontal lobe	EEG: focal dysfunction at right temporal lobe	EEG: mild generalized encephalopathy	T2 FLAIR hyperintensity in right mesial temporal lobe EEG: generalized slow activity	CSF: increased protein WBC: 12/mm^3
Tumor	None	None	None	None	None	None	Thymoma, pulmonary adenocarcinoma
Revised diagnosis	Definite anti-NMDAR encephalitis	Definite anti-NMDAR encephalitis	Probable anti-NMDAR encephalitis	Definite autoimmune encephalitis associated with LGI1-VGKC complex antibodies	Possible autoimmune encephalitis associated with N-type VGKC antibodies	Autoimmune encephalitis associated with GAD-65	Autoimmune encephalitis associated with GAD-65, thymoma associated paraneoplastic encephalitis
Immunotherapy	IVIg + methylprednisone	IVIg + methylprednisone	IVIg + methylprednisone (empiric)	IVIg + methylprednisone (empiric)	Plasmapheresis + methylprednisone	IVIg + methylprednisone (empiric)	None Resection of thymoma
Initiation of treatment	Day 13	Day 6	Day 7	Day 2	Treated as outpatient	Day 2	Month 4
Day of discharge	Day 18	Day 15	Day 14	Day 6	Treated as outpatient	Day 9	Day 37
Discharge medication	None	Levetiracetam	Valproic acid, lacosamide, oxcarbazepine	Valproic acid	None	Levetiracetam	None
Relapses	None/unknown	1	1 for catatonia	2	Never returned to premorbid functioning	1	Patient transitioned to palliative care after diagnosis of lung adenocarcinoma
Repeat treatment	None	IVIg + methylprednisone	IV lorazepam	Weekly methylprednisone Monthly IVIg	Mycophenolate followed by monthly IVIg	Monthly IVIg followed by monthly plasmapheresis + daily mycophenolate	None

Abbreviations: CSF = cerebrospinal fluid, EEG = electroencephalography, GAD-65 = glutamate decarboxylase, Ig = immunoglobulin, IV = intravenous, LGI1 = leucine-rich glioma inactivated, MRI = magnetic resonance imaging, NMDAR = *N*-methyl-D-aspartate receptor, VGKC = voltage-gated potassium channel, WBC = white blood cell count.

episodes of bilateral upper extremity movements that had developed over the preceding day. Initial laboratory findings, head CT, and chest/abdomen/pelvis CT with contrast were negative for any pathology. Lacosamide and oxcarbazepine were started after a witnessed generalized tonic-clonic seizure, requiring lorazepam on day 1. She was started on video EEG after this, with multiple seizures validated over the first 8 days. An unremarkable CSF sample was obtained and subsequently sent for autoimmune testing. Psychiatry was consulted on day 2 for concerns of polypharmacy. The patient's home medications included amitriptyline, bupropion, sumatriptan, oxycodone, milnacipran, and risperidone. Due to concerns of serotonin syndrome, all medications were held. Early in her stay, she exhibited mutism, staring episodes, mild rigidity, and verbigeration suggestive of catatonia.

During day 3, she expressed that an alien vessel had appeared, with the occupants shooting her. She affirmed, however, that a face mask allowed her to hide from further incursions from aliens. After this point, she was mistrustful of staff, reporting that a nurse attempted to administer poison and was having an affair with her husband. Due to increasing agitation, oral and IV haloperidol were administered. The patient was started on IVIg for probable anti-NMDAR encephalitis on day 7. Due to her paranoia, oral oxcarbazepine was changed to IV valproate. Ultimately, she approached her premorbid baseline with resolution of seizures, agitation, paranoia, and perceptual disturbances, allowing for discharge to a rehabilitation facility on treatment with valproate, lacosamide, and oxcarbazepine on day 14. Despite a high index of suspicion, the CSF autoimmune panel ultimately returned negative. Five months later, the patient had another admission for symptoms of catatonia that resolved with scheduled IV lorazepam.

Case 4: Definite Autoimmune Encephalitis Associated With LGI1-VGKC Complex Antibodies

A 47-year-old male with polysubstance abuse and chronic hepatitis B and C infection was transferred from an outside facility for management of breakthrough generalized tonic-clonic seizures. Around 8 months prior, he had stripped naked during a religious service, walking out of the church into the road. This occurrence was interpreted as mania, and he was hospitalized and treated with quetiapine for bipolar disorder. Soon thereafter, he began having seizures characterized by staring, eye fluttering, and grunting, for which he was started on valproate. Three months before his transfer, he had begun experiencing new tonic-clonic seizures 2 to 3 times weekly. Head CT, chest/abdomen/pelvis CT, and brain MRI findings were unremarkable. Routine EEG showed focal neurologic dysfunction localized in the right temporal lobe. By day 2, autoimmune encephalitis was suspected, and IVIg and methylprednisolone were started. Rapidly improving to near his baseline, by day 6 the patient exhibited no witnessed seizures or disorganized behavior and was allowed to return home. The autoimmune panel pending at discharge returned positive for LGI1-VGKC complex antibodies.

With recurring changes in his mentation and personality and increased seizures, he was readmitted 2 months later. IVIg was started for exacerbation of AE. Lacosamide was given in place of valproate for concerns regarding his chronic liver disease. Repeat brain MRI and routine EEG showed no abnormal findings. Again, he quickly improved back to his baseline and was discharged home on day 5. Due to the relapse, he was started on weekly IV methylprednisolone and monthly IVIg coordinated through his outpatient neurologist.

Case 5: Possible Autoimmune Encephalitis Associated With VGKC Complex Antibodies

A 72-year-old female was evaluated in the clinic regarding a 1-year period of anomia, apraxia, amnesia, agitation, and paranoia. The patient had also experienced cognitive decline over the preceding 3 years. The deterioration had recently become increasingly rapid, warranting initiation of risperidone, memantine, and donepezil, which ultimately stabilized her behavioral symptoms. As she was also having unintended weight loss, a chest/abdomen/pelvis CT was conducted, showing a uterine mass. Histopathology later revealed this mass to be benign. A CSF paraneoplastic panel showed a mild elevation of N-type VGKC antibody. EEG showed mild generalized slowing consistent with a nonspecific encephalopathy, while brain MRI findings were unremarkable. With the patient not meeting definite criteria for AE, but with concern for it, plasmapheresis was performed, yielding significant improvement of her cognitive and behavioral symptoms. Treatment returned her capacity to engage in several activities of daily living, further lending credence to the argument that at least a portion of her issues were due to AE. Psychotropic doses were reduced shortly after discharge.

Case 6: Autoimmune Encephalitis Associated With GAD65 Antibodies

A 67-year-old female was brought to the ED with altered mental status, headache, and word salad a few hours in duration. Head CT, brain MRI, and transthoracic echocardiogram findings were unremarkable, although CT head perfusion showed decreased flow to her left frontal region, raising concern for ischemic stroke. EEG showed focal neurologic dysfunction in the left frontotemporal region. She was treated medically for potential ischemic stroke, but a tissue plasminogen activator was not given due to the therapeutic window having elapsed.

After a month, she was readmitted for persistent speech dysfunction and onset of altered mentation. Her husband revealed only later that she had experienced these symptoms for approximately a month before her presentation that had been interpreted as stroke. For the preceding day, she had exhibited paraphasia and transcortical motor aphasia. Brain MRI showed minimal T2 FLAIR hyperintensity in the right mesial temporal lobe and multifocal areas of enhancement in the bilateral temporal lobes, with prominent enhancement in the right subinsular region and right mesial temporal lobe. Video EEG revealed generalized slow activity.

Chest/abdomen/pelvis CT identified no features suggesting occult tumors. CSF leukocyte count was elevated at 20/mm^3. Due to the suspicion of AE, the patient was treated with IVIg and methylprednisolone starting on day 2. Though having only mild improvement in her symptoms, she was felt to be stable enough for discharge and was moved to a rehabilitation center by day 9 with a pending CSF autoimmune panel.

Three weeks later, the patient was readmitted with altered mentation, perceptual disturbances, and agitation. In the interim, her CSF autoimmune panel had returned, showing glutamic acid decarboxylase 65 (GAD65) antibodies. Levetiracetam was started due to concern of seizures. Brain MRI showed innumerable nonspecific enhancing foci within her supratentorial deep white matter, subcortical region, and meningeal tissues. Digital subtraction angiography showed no evidence of vasculitis. EEG was positive for mild-moderate diffuse encephalopathy. Positron emission tomography (PET) scan findings were unremarkable. An antinuclear antibody panel was positive for anti–Sjögren's syndrome A (SSA)/Ro60 antibodies. Dramatic improvement occurred after another treatment with IVIg, although the patient later needed monthly IVIg for a period to aid continued recovery given the severity of her condition. In the setting of yet again relapsing symptoms, her treatment plan was eventually set to be monthly plasmapheresis treatments and daily mycophenolate mofetil.

Case 7: Autoimmune Encephalitis Associated With GAD65 Antibodies

A 74-year-old male presented with acute onset altered mental status, slurring of speech, and difficulty walking for 3 days. Unremarkable brain MRI, head CT, and brain magnetic resonance angiography were obtained during a stroke evaluation along with normal EEG findings. Chest radiograph revealed a mediastinal mass, with later biopsy showing it to be a B1 thymoma. CSF analysis showed increased protein at 150 mg/dL and a mild increase in leukocytes at 12/mm^3. Acetylcholine receptor antibody test results were positive, but this was not felt to entirely explain his presentation. Findings of a CSF paraneoplastic and autoimmune panel were unremarkable. After a 2-week hospitalization and improvement in symptoms, the patient was discharged to a rehabilitation center. Chemotherapy and radiation therapy were planned to begin on an outpatient basis.

Within 4 days of discharge, he was readmitted with staring, drooling, and a stiff left upper extremity. During the assessment, he had no response to verbal or aversive stimuli and was unable to recognize his wife. Head MRI and EEG results were again normal, with no findings of stroke or seizures, respectively. Despite the normal findings, levetiracetam was started for seizure concern, with symptom improvement occurring, and he was then returned to his rehabilitation center. Although the patient was objectively improved compared to the initial assessment, his wife reported continued sundowning and mild cognitive decline.

Three months later, the patient was readmitted with altered mental status, worsening disorientation, and agitation, prompting administration of quetiapine. Video EEG was performed, yet it was again unremarkable for seizures. A CSF autoimmune panel was repeated, now returning positive for GAD65. Courses of IVIg and methylprednisolone were prescribed for suspected thymoma-associated paraneoplastic encephalitis. The stiffness improved, but altered mentation persisted. Thymectomy was performed, leading to a significant improvement in his neurologic examination results and psychiatric issues and allowing him to be discharged to a rehabilitation facility on day 37. After over a year, he yet again presented with altered mental status. Testing identified a malignant pleural effusion and multiple sites of poorly differentiated pulmonary adenocarcinoma in bilateral lungs. Given the diagnosis of stage 4 lung adenocarcinoma, his family elected to pursue hospice care.

DISCUSSION

Although cases frequently share commonalities in their workup and treatment, as illustrated here, AE occurs across a wide range of demographics with diverse neuropsychiatric presentations. The suggestion of Al-Diwani et al,[7] in their review of NMDA encephalitis, of using specific higher-level categorization to report cases is of the utmost importance for further study of all AE subtypes. We too see the value of attempting to use precise terminology and of illustrating specific examples of behavioral and psychiatric symptoms in detail for these patients, as they often defy categorization and are not easily labeled by traditional psychiatric nomenclature. Table 1 summarizes the clinical presentation, workup, and treatment outcomes of each case.

Neuropsychiatric Manifestations

In the existing literature, the most common psychiatric symptoms in AE are behavioral problems, followed by hallucinations, memory deficits, confusion, paranoia, depression, and catatonia.[5] Predominant psychiatric symptoms may lead providers to diagnose primary psychiatric disease, as was done with the bipolar diagnosis first assigned in case 1 and the major depression diagnosis first made in case 2. Though AE commonly occurs in patients without underlying psychiatric conditions, case 3 illustrates the difficulty in recognizing the condition in a patient with an existing psychiatric diagnosis.

As demonstrated by case 2, it is often difficult to fully separate neurologic and psychiatric symptoms. Although the patient's mood changes were first attributed to a postictal state considering her EEG, these issues may have been purely related to AE. Cases 5, 6, and 7 emphasize how altered mentation, varying in severity and pattern, can be a hallmark feature, although, as demonstrated, this does not always improve with immunotherapy.

AE may mimic or be confounded by psychiatric conditions (cases 1, 2, 3, and 4). Changes in patients from

an older population (cases 5, 6, and 7) are understandably often first attributed to age-related cognitive decline or age-associated medical issues such as strokes. Close attention to patient presentation and knowledge of the diagnostic criteria are needed to avoid the pitfalls of delayed recognition and treatment. Given the primary involvement of psychiatrists, neurologists, and internists, it behooves these professionals to have at minimum a passing awareness of the condition.

Existing literature suggests 10% of all cases of AE to be affected by catatonia.[5] Emphasizing the varied possible presentations, this issue appears concentrated among anti-NMDAR encephalitis, with 88 of the 100 cases in a larger review affected.[8] Case 3 had motor symptoms, suggestive of catatonia, and was later treated with intravenous lorazepam based on the Bush-Francis scale. Seizures, as described in the diagnostic criteria,[6] were seen in cases 2, 3, and 4, leading to treatment with multiple antiepileptic medications.

Antibodies

Among 7 cases, 2 were positive for anti-NMDAR, 2 were positive for LGI1/VGKC complex, and 2 were positive for GAD65, while 1 was seronegative.

Anti-NMDAR encephalitis. Cases 1 and 2, demonstrating anti-NMDAR encephalitis with initial manifestations of both neurologic and psychiatric symptoms, correlate with the epidemiologic data describing a predominance of this condition in young women.[7] Although this form is classically associated with teratomas, neither patient was found to have one. Both cases had CSF positive for anti-NMDAR IgG and responded well to immunotherapy that was initiated on day 13 and day 6, respectively.

The NMDA receptor is concentrated in the forebrain, hippocampus, and limbic system. Consisting of a tetrameric complex composed of 2 GluN1 subunits and a combination of 2 GluN2 or GluN3 subunits, it has been linked to learning, memory, cognition, and behavior. Current evidence suggests that IgG antibodies in the serum and CSF bind specifically to the GluN1 subunit, leading to this encephalitis.[9] One point we wish to address directly is the absence of seropositivity in case 3. Although the patient was initially labeled as having bipolar disorder with manic features, which, given the absence of antibody, cannot be fully excluded, we felt it was important to include this case given that it met the criteria for probable anti-NMDAR encephalitis and responded avidly to immunotherapy.

As the most often described subtype of AE, anti-NMDAR encephalitis may serve as the basis to discuss all types. With more reports of other types of AE, a similar pattern of phases will hopefully become apparent. Given this, we find value in reviewing the 5 distinct phases of anti-NMDAR encephalitis to allow viewing of other types using this well-established structure.[10,11]

1. **Prodromal phase.** Presenting with flu-like symptoms, anti-NMDAR encephalitis is virtually indistinguishable from many illnesses in its earliest stage.
2. **Psychotic phase.** Within a period of days to weeks, neuropsychiatric features rapidly emerge, including visual or auditory hallucinations, delusions, depression, mania, apathy, anxiety, fluctuating sensorium, hypersexuality, aphasia, amnesia, apraxia, or sleep-wake cycle disruption with severe insomnia. Coexistent neurologic features may accompany the psychiatric changes, while some manifest only weeks after. Seizures can be resistant to antiepileptic drugs and may evolve to status epilepticus (case 3). Kuppuswamy et al[12] advised choosing atypical and more sedative antipsychotics to treat psychotic symptoms. To treat mood symptoms, valproic acid was advised, with the advantage of its IV form and its induction of the release of presynaptic levels of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter postulated to be impaired by NMDAR dysfunction.[13] The use of lithium and benzodiazepines is also reported in the literature, without a clear benefit. Neuroleptics can exacerbate neuropsychiatric symptoms and cause neuroleptic malignant syndrome.[14] There is no current guideline on how to weigh the risks and benefits of using antipsychotics, which psychotropic to prefer, or the duration of treatment.
3. **Unresponsive phase.** This phase is characterized by mutism, decreased motor activity, and catatonia. Catatonic symptoms must be treated with benzodiazepines as the first-line choice, and the use of electroconvulsive therapy is controversial.
4. **Hyperkinetic phase.** This phase is seen with autonomic instability and prominent movement disorders. Labile blood pressure, cardiac arrhythmias, temperature instability, and central hypoventilation warrant admission to the intensive care unit. The classic movement disorder in this phase is oro-lingual dyskinesias with lip-smacking, tongue protrusion, and jaw movements, along with automatisms, dyskinesia, dystonia, choreoathetosis, dysrhythmia, blepharospasm, oculogyric crisis, and hemiballismus.
5. **Recovery phase.** With adequate immunotherapy and supportive care, patients may enter the rehabilitation phase of treatment. Recovery of language function and reduction in behavioral symptoms occur at the end.

Most studies show that early treatment and low severity of disease are predictors of good outcomes.[15] Relapse occurs in 15% to 24% of anti-NMDAR encephalitis patients, sometimes after several years.[8] Treatment of patients with relapse is typically similar to that of newly diagnosed patients, with a lower threshold to initiate second-line therapies early in the course of the relapse.

Anti-LGI1 encephalitis. Anti-LGI1 is by far the most common subtype, affecting middle-aged to older patients. They classically exhibit the limbic encephalitis triad: memory

disturbances, confusion, and seizures. Other hallmarks include hyponatremia, while about half of the patients have faciobrachial dystonic seizures.[16] These seizures may have been present in case 4, though the retrospective review of clinical documentation does not allow this to be fully ascertained.

Tumor association is infrequent, occurring in 11% of the patients.[17] Concerning Caspr2, the spectrum of associated disturbances is wider, with limbic encephalitis, Morvan syndrome, neuromyotonia, and painful neuropathy, and has a stronger association with cancer, notably thymoma.[18]

Case 4 was a classic presentation of anti-LGI1 encephalitis, a middle-aged male with psychosis, altered mentation, epilepsy, increased FLAIR signal in the medial temporal lobe, and fair response to immunotherapy. As occurred in his case, relapses arise in up to one-third of patients, often during the first 6 months of the disease, and are associated with worse outcomes.[19] Case 5 had a more indolent neuropsychiatric course that was ongoing for more than a year with mild elevation of N-type VGKC antibody.

Previously thought to be a disorder associated with antibodies to the voltage-gated potassium channels, recent studies revealed that the targets are the associated proteins, rather than the channel itself.[17] Most cases are associated with antibodies against LGI1 or Caspr2, but evidence suggests that other still unrecognized (double negative) antibodies to VGKC-associated proteins might be involved, explaining such diversity. Double-negative VGKC antibodies usually target intracellular epitopes and lack pathogenic potential.[20] They form the majority of the results in routine VGKC antibody testing, and, in stark contrast to finding antibodies directed against LGI1 and CASPR2, they do not predict response to immunotherapy. It has been proposed that VGKC antibody radioimmunoassay is not an effective screening test and that LGI1/CASPR2 antibody testing be utilized as a first-line test when investigating a patient for VGKC antibodies.[21]

Encephalitis with GAD antibodies. Our patients with positive GAD65 antibodies (cases 6 and 7) showed different manifestations. Case 6 was an elderly female with speech dysfunction, altered mentation with T2 FLAIR hyperintensity in the right mesial temporal lobe, EEG showing focal neurologic dysfunction in the left frontotemporal region, and PET scan negative for occult tumors. She was treated with monthly plasmapheresis and mycophenolate for encephalitis due to her relapses. Case 7 was an elderly male with stiff-person syndrome, ataxia, cognitive decline, and thymoma. Although an initial CSF panel was negative, the repeat study was positive only 3 months later, and the patient improved on immunotherapy. He eventually presented with pulmonary adenocarcinoma about a year and half later that may or may not have been associated with his encephalitis.

Typically, an intracellular protein found in the 2 isoforms GAD65 and GAD67 is suggested to be exposed during vesicular release.[2]2 Within cells, it acts as the rate-limiting enzyme for the synthesis of GABA, an inhibitory neurotransmitter. It has been theorized that GAD65 antibodies play a pathogenic role through either T cells or antibodies-mediated disruption of synthesis or exocytosis.[23] This mechanism alone, however, does not account for the varied presentations among patients with this antibody.[24]

Being associated with a wide range of neurologic disorders, it has now been suggested that the group be referred to as *GAD antibody–spectrum disorders*.[22] As the level of antibodies does not correlate with disease severity, it remains uncertain whether the antibodies are simply disease markers or act with pathological potential through the mechanisms discussed above. Two theories are under investigation. One suggests a disease-specific epitope hypothesis[25] in which antibodies targeting different protein domains account for the difference, while others suggest there may be yet other unidentified autoantibodies that account for the differences.[26]

Overall, psychiatric presentations are less frequent than with other forms of autoimmune encephalitis.[27] Although cancer is not always present at the time of diagnosis, GAD antibodies are associated with small cell lung cancer and thymoma, particularly in older male patients and those with concomitant antibodies against neuronal cell-surface antigens.[24]

CONCLUSION

With our case series, we hope to reemphasize the need for a high index of suspicion of autoimmune encephalitis among psychiatrists treating a patient with mixed neuropsychiatric symptoms. We highlight the timeline of the development of psychiatric symptoms, including altered mental status, psychosis, and mood symptoms. Due to the anecdotal nature of the case series, the frequency of psychiatric symptoms in the diagnosis of AE may not be ascertained from this case series. It also does not inform a treatment guideline. As clinicians are still exploring heterogeneity in the clinical presentation of this autoimmune disease, our series will help consultation-liaison psychiatrists to conceptualize and expand their knowledge about this interface of neurologic and psychiatric disorders. Moreover, we hope that with the addition to the number of cases discussed in the literature, larger reports can begin to use the cumulative data to establish specific terminology in which these patients can be discussed.

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