Atypical Limbic Encephalitis and its Complex Psychiatric Presentations: Implications for Diagnosis and Management

Sir,

Autoantibody-mediated encephalitis (AME) is a neurological illness caused by autoantibodies of autoimmune or paraneoplastic pathology, directed against the neuronal surface, synaptic antigens, or the intracellular proteins.[1] The onset is subacute, with the occurrence of altered mental status, seizures, and cognitive deficits, with a rapid progression. AME has been classified in different ways, including those based on anatomical sites involved or the underlying etiology, or eponymously classification too is present.[2] One such terminology is limbic encephalitis (LE), where autoimmune or paraneoplastic affection of the limbic system is implicated as the etiology. LE can manifest with diverse psychopathology, including delusions, hallucinations, irritability, aggression, anxiety, depression, and catatonic symptoms.[1-3] LE can also have atypical etiologies including nonparaneoplastic and seronegative varieties, especially during the early course of illness.[2] Psychiatric presentations of atypical variants of LE are not reported in the existing literature.

We present a case of acute seronegative nonparaneoplastic LE with complex neurological and psychiatric symptomatology including obsessions. The diagnostic implications of the clinical presentation and the integrated neuropsychiatric management required are also discussed.

CASE REPORT

A 28-year-old woman presented to the emergency department with multiple episodes of seizures, preceded by high-grade fever and headache for 10 days. There was no history of vomiting, blurred vision, or neck stiffness suggestive of meningeal irritation. The epileptic attacks started as right-sided focal seizures followed by generalized tonic–clonic seizures. The episodes were multiple, with a frequency of one episode every 2–3 h, with acute onset and offset; lasting 3–5 min; and associated with loss of consciousness, loss of posture, and postictal drowsiness. Her medical history revealed the presence of hypothyroidism. There was no history of rheumatic or chronic inflammatory conditions. There was no family history of significant medical or psychiatric illness. She developed refractory status epilepticus, which responded to a cocktail of phenytoin 300 mg/day, carbamazepine 600 mg/day, valproate 1500 mg/day, levetiracetam 3 g/day, clobazam 20 mg/day, and midazolam infusion. She was also prescribed prednisolone (50 mg/day) and acyclovir (500 mg/day) for 1 week as prophylactic medications for AME and probable viral encephalitis. The patient required intensive care unit (ICU) monitoring for 3 weeks for adequate control of seizures. Her blood biochemistry evaluation for autoimmune disorders returned normal [Table 1]. The electroencephalogram (EEG) revealed fast beta background activity with an abnormal slowing in the left-sided leads with bilateral infrequent inter-ictal epileptiform discharges. Computerized tomography (CT) of the brain revealed bilateral medial temporal lobe hyperintensities. The CT of the thorax and abdomen was taken to rule out paraneoplastic syndrome, which returned normal. Acute onset of seizure disorder, status epilepticus, lack of focal neurological deficits, and the involvement of temporal lobes pointed to a clinical diagnosis of LE.

During the ICU stay, the patient developed postictal psychosis characterized by episodes of irritability, mutism, staring, posturing, and auditory hallucinations. There were no signs of delirium. The postictal psychosis improved with quetiapine (50 mg/day) in a week's time. After discharge, over 3 months' period, she had low mood, anhedonia, ideas of worthlessness and hopelessness, and suicidal tendencies. She had repetitive and unexplained emotional outbursts. On detailed exploration, she revealed that she experienced repetitive and intrusive urges to have physical intimacy with her spouse. Though she recognized those urges to be her own, repetitive, and intrusive, she could not reveal further information such as irrationality, control, or any associated anxiety. She did not reveal any mental or motor compulsions. The mental status examination revealed depressed affect, the presence of obsessive urges of sexual content, and defects in recent memory, and visuospatial functioning, with intact executive functions, praxis, and language functions. The patient was diagnosed to have Organic Depressive Disorder (F06.32) as per the International Classification of Diseases-10th edition (ICD-10).[4] Antipsychotics were stopped, and she was started on fluoxetine (20–40 mg/day) and clonazepam (0.75 mg/day). Her mood symptoms, obsessive thoughts, and distress improved significantly in a month's

Table 1: Blood biochemistry, serology, drug levels, and autoimmune panel results

Parameter	Patient value	Normal range
Hemoglobin	12.6	11.7-15.5 gm/dL
White blood cell count	7.35	4.0-11.0 × 10^3/μL
Sodium	139.8	136-146 mEq/L
Potassium	3.42	3.5-5.5 mEq/L
Blood urea	10	15-40 mg/dL
Serum creatinine	0.72	0.5-0.9 mg/dL
Liver function tests		
Total Bilirubin	0.24	0.3-1.3 mg/dL
Direct Bilirubin	0.15	0.1-0.4 mg/dL
Serum Protein	6.3	6.7-8.6 g/dL
Serum Albumin	3.9	3.5-5.5 g/dL
AST	28	12-38 IU/L
ALT	26	7-41 IU/L
ALP	99	108-306 IU/L
Thyroid function tests		
Free T3	2.1	2.1-4.4 pg/ml
Free T4	0.95	0.8-2.7 ng/dL
TSH	1.44	0.35-5.5 μIU/ml
Random blood sugar	108	75-140 mg/dL
Blood culture	Sterile after 2 days of incubation	
Serology		
HIV	Negative	
HbsAg	Negative	
anti-HCV	Nonreactive	
VDRL	Nonreactive	
Dengue (IgM ELISA, NS1)	Negative	
Malaria (ICT Pf and Peripheral smear)	Negative	
PCR for Japanese encephalitis	Negative	
CSF analyses		
Cell count	10 cells (8 lymphocytes)	
Glucose	69	75-140 mg/dL
Chloride	123.4	102-109 mEq/L
Protein	30	15-50 mg/dL
Culture	Sterile	
HSV PCR	Negative	
Oligoclonal bands	Negative	
Autoimmune panel		
Anti-TPO	40.3	0-35 IU/ml
Anti-TG	<15	0-40 IU/ml
ANA	Negative	
CSF autoimmune panel (done twice for confirmation)		
GABA-B		
AMPA 1	Negative	
AMPA 2		
NMDAR		
VGKC		
Drug levels		
Valproate	62	50-100 μg/ml
Carabamazepine	6	4-12 mg/L

μIU – micro International Units, μg – microgram, μL – microliter, ALP – Alkaline phosphatase, ALT – Alanine transaminase, AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, ANA – Antinuclear antibody, Anti – TG – Antithyroglobulin antibody, Anti-TPO – Antithyroid peroxidase antibody, Anti-HCV – Anti-hepatitis C virus antibody, AST – Aspartate transaminase, CSF – Cerebrospinal fluid, dL – deciliter, ELISA - Enzyme-linked immune sorbent assay, GABA-B – gamma-aminobutyric acid – B, g – gram, HbsAg – Hepatitis B surface antigen, HIV – Human immunodeficiency virus, HSV – Herpes simplex virus, ICT Pf – Immunochromatographic test for *Plasmodium falciparum*, IgM – Immunoglobulin M, IU – International units, L – liter, mEq – milliequivalent, mg – milligram, ml – milliliter, ng – nanogram, NMDAR - N-methyl-d-aspartate receptor, NS1 – Dengue nonstructural protein 1, PCR – polymerase chain reaction, pg – picogram, T3 – triiodothyronine, T4 – thyroxine, TSH – Thyroid stimulating hormone, VDRL – Venereal Disease Research Laboratory, VGKC – Voltage-gated potassium channel

time [Table 2]. The patient was followed up for 3 months with no further relapses. Informed consent was obtained for patient management and write up of this report.

DISCUSSION

The above clinical scenario sheds light on the diagnostic process of atypical LE and the complex neurological and psychiatric presentations associated with atypical variants of LE. A systematic evaluation of LE can be performed along the lines of clinical assessment, autoimmune panel, EEG, and neuroimaging investigations.[5,6]

In our patient, the clinical presentation was characterized by fever prodrome; generalized seizures with rapid progression to status epilepticus; seizure refractoriness; and polymorphic psychiatric presentation, including signs of catatonia, auditory hallucinations, depressive symptoms, and obsessional urges. The prevailing literature supports that the presence of a febrile prodrome, seizures, abrupt and polymorphic psychiatric complaints, rapid illness progression, poor treatment response, memory disturbances, and focal neurological signs should rouse the possibility of autoimmune encephalitis in patients with acute psychiatric disturbances.[5-7] Our case highlights that, apart from various psychiatric complaints, obsessional urges, which lack the classical features of irrationality or compulsive behaviors, can occur in patients with LE.[2,3,8] The occurrence of obsessions and depressive symptoms can be due to the involvement of medial temporal lobes, which are implicated in both seizures and emotional regulation.[9]

The investigations for infectious, metabolic, endocrine, and drug-induced causes returned normal, ruling out common causes for encephalitis [Table 1]. Further, normal autoimmune panel eliminated common autoimmune causes for LE. Recent literature reports that rarely LE can be nonparaneoplastic and that LE can be seronegative during the early stages.[1-3] Similar to what was observed in our patient, focal or diffuse slowing and epileptiform discharges in the EEG and bilateral medial lobe hyperintensities based on neuroimaging are consistently associated with LE.[6,7]

The comprehensive pharmacotherapy of the patient comprised high-dose corticosteroids, antiepileptics, and various psychotropics. Complex psychiatric disturbances in LE shall entail the supplementation of mood stabilizing antiepileptics to control agitation, atypical antipsychotics for psychosis, and antianxiety agents.[5,7]

The limitations of our report are that autoantibodies such as Glutamic Acid Decarboxylase 65 (GAD65) and those against Gamma-aminobutyric acid–A (GABA-A) receptor were not studied as their kits were not available. Rare possibilities such as new-onset refractory status epilepticus (NORSE), febrile infection related epilepsy syndrome (FIRES), or prion diseases were not actively considered.

Nevertheless, the present report adds to the literature that LE can be atypical when it presents in nonparaneoplastic and seronegative forms. In such atypical LE, the neurological and psychiatric symptoms can be more variegated than LE with an identified etiology. A careful assessment of the clinical presentation invariably determines the appropriate diagnostic work-up of the LE patient. An early, thorough, and integrated neuropsychiatric approach will be able to overcome the difficulties in such cases. Future studies are necessary to understand the symptoms of atypical LE in greater detail, identify their etiopathogenesis, and provide scope for the effective management of its myriad neuropsychiatric manifestations.

Table 2: Scores on rating scales

Scale	Baseline			After 4 weeks of antidepressant therapy		
HDRS-17	21			7		
Y-BOCS	Obsessions	Compulsions	Total	Obsessions	Compulsions	Total
	14	4	18	5	1	6
MMSE	27			27		

HDRS-17 – Hamilton depression rating scale – 17 items, MMSE – Mini mental state examination, Y-BOCS – Yale Brown Obsessive complusive scale

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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