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.

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...
Letters to Editor

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

| Parameter                      | Patient value | Normal range            |
|--------------------------------|---------------|-------------------------|
| Hemoglobin                    | 12.6          | 11.7-15.5 g/dL          |
| White blood cell count        | 7.35          | 4.0-11.0 x 10^6/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       | 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) | 75-140 mg/dL. |
| Glucose                        | 69            |                         |
| 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                          | Negative      |                         |
| VGKC                           |               |                         |
| Drug levels                    |               |                         |
| Valproate                      | 62            | 50-100 µg/ml            |
| Carbamazepine                  | 6             | 4-12 µg/mL              |

IU – micro International Unit, 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.

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 anti-anxiety 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.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Table 2: Scores on rating scales

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

\(^{HDRS-17} – \) Hamilton depression rating scale – 17 items, \(^{MMSE} – \) Mini mental state examination, \(^{Y-BOCS} – \) Yale Brown Obsessive compulsive scale
Sir,
Mirtazapine is an antidepressant with antagonistic action on alpha 2 noradrenergic receptors and postsynaptic serotonergic receptors (5HT2 and 5HT3).\(^1\) It is considered to be one of the safest antidepressants in terms of side effects like involuntary movements. In fact, mirtazapine is one of the medications found useful in alleviating drug-induced akathisia and recommended in Parkinson’s disease.\(^2,3\) However, there is literature, mostly case reports, suggesting that at least a few subjects are intolerant to mirtazapine and may develop involuntary movement disorders such as akathisia, dystonia, and dyskinesia.\(^4\) There is no literature implicating mirtazapine with tremors, chorea, or parkinsonism.\(^5\) Here, we describe a case of mirtazapine-induced tremors.

A 60-year-old female came to the outpatient psychiatry department of our hospital with complaints of low mood, reduced interest in daily activities, loss of interest in previously rewarding or enjoyable activities, restlessness, easy fatigability, and reduced sleep and appetite for last 1 week, precipitated by the death of a close relative. The patient had a history of two depressive episodes in the last 3 years, treated with sertraline for a few months, which she had discontinued after experiencing improvement in her symptoms. There was no family history of psychiatric disorders. She had hypertension and was recently started on telmisartan and hydrochlorothiazide along with cilnidipine. Her blood investigation showed profound hyponatremia (117 mmol/L), and hence, she was shifted to cilnidipine and nebivolol by general physician alongside sodium correction with tolvaptan.

Her psychological condition showed significant improvement within 2 days, with improvement in sodium level (137 mmol/L). She was prescribed oral lorazepam 2 mg/day for residual sleep problems and anxiety. In view of persisting sleep disturbances, at first week follow-up, lorazepam was stopped and mirtazapine 7.5 mg at bedtime was initiated. After 2 days of starting...