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Steroid-responsive Encephalopathy as a Semblance of Neuroleptic Malignant Syndrome in a Patient with Schizophrenia

Sir,

The exact etiopathogenesis of schizophrenia remains unclear, but the field of psychoneuroimmunology has provided certain plausible immunological underpinnings. Lately, more attention has been paid to autoimmune encephalopathies of both rheumatic origin and those associated with autoimmune encephalitis. In contrast to the rheumatic conditions which mainly present with systemic involvement, autoimmune encephalitis syndrome usually presents with an initial clinical picture that is dominated by headache, mild hyperthermia, and frequent cerebrospinal fluid (CSF) pleocytosis and thus is often treated in line of a bacterial or viral meningoencephalitis. The second stage may be characterized by psychiatric manifestations such as altered mood and behavior, memory changes, anxiety, and insomnia or neurologically a reduced level of consciousness and seizures, with/without other severe symptoms such as autonomic instability, dyskinesias, hypoventilation, and at the end coma may ensue. The frequent occurrence of psychiatric symptoms as an initial presentation of certain autoimmune encephalitis/encephalopathy and findings of autoantibodies in such patients enthused various researchers to explore a possible autoimmune etiology of severe mental illnesses such as schizophrenia. However, the evaluation of various autoantibodies in persons with schizophrenia has remained inconclusive till date.

Although various neuropsychiatric symptoms are the common initial presentation in autoimmune encephalopathies, semblance to the neuroleptic malignant syndrome (NMS) is rarely reported. Moreover, it is a very uncommon observation that autoimmune encephalitis, which has usually an acute and progressive course of illness, presents as an episodic mental illness with a long interepisodic interval. Only two case reports of autoimmune encephalitis are available wherein a diagnosis was made after a long history of relapsing psychosis or mood disorder. Here, we report a case of steroid-responsive encephalopathy with a semblance of NMS in a patient of episodic schizophrenia.
CASE REPORT

The patient is a 61-year-old male who was diagnosed with schizophrenia 22 years ago. He presented to the accident and emergency department of our institute with complaints of high-grade fever, rigidity, stupor, mutism, autonomic instability, and poor oral intake for the last 15 days. A diagrammatic presentation of the course of illness of the index patient is shown in Figure 1. He was initially managed by the internist, with a possible diagnosis of meningoencephalitis. Apart from the hematological and blood biochemistry, a CSF examination and computed tomography of the head without contrast were done [Table 1]. The psychotropic medications were stopped, and he was empirically treated with intravenous fluids, antihypertensive, antipyretic medications, and a course of intravenous ceftriaxone and prophylactic acyclovir for the next 3 days. However, in view of a minimal response, consultation with psychiatrist and neurologist was done, and the possibility of schizophrenia with NMS was entertained. He was admitted to psychiatry inpatient section for further management. His physical examination showed a thinly built, poorly kempt man with a nasogastric tube and urinary catheter in situ. His vitals revealed body temperature of 102°F, systolic/diastolic blood pressure to be 150/90 mmHg, pulse rate of 110/min, and the respiratory rate to be 16/min. His mental status examination (using Kirby’s method) showed generalized rigidity of limbs (lead-pipe) as well as torso and minimal efforts to bring the body part in a comfortable position when placed in an awkward position. He remained mute; did not follow commands; had an expressionless face with minimal movements of eyes, reduced blink rate, largely a fixed gaze, and no response to sudden movements toward his eyes or to pain stimuli. The diagnoses of schizophrenia and NMS according to the Diagnostic and Statistical Manual – fifth edition (DSM-5) were made, and a trial of bromocriptine up to 25 mg/day was given for 10 days. Minimal improvement in the form of remission of fever and reduction of creatine phosphokinase levels to normal range was observed. Thereafter, in the next 7 weeks and in due consultation-liaison with the neurologist, adequate trials of intravenous lorazepam up to 8 mg/day in divided doses (weeks 2–3), levodopa 100 and carbidopa 25 mg (weeks 4–5), and finally, bilateral modified electroconvulsive therapy (seven therapy sessions in weeks 5–7) were tried, but they failed to elicit any further response. In view of the persistence of the rest of the symptoms, namely, rigidity, mutism, poor oral intake, minimal response to sensory stimuli, passive negativism, staring and withdrawal (akin to catatonia), and further investigations [Table 1], the differentials of a small vessel disease [Figure 2] and immune-related encephalitis/vasculopathy were entertained. Due to financial constraints, only a limited autoantibody profile was done [Table 1]. The patient showed a dramatic response to intravenous methylprednisolone (1 g/day for 5 days), and he started to communicate, regained nearly normal gait, and accepted oral feeds. The formulation of methylprednisolone was changed to oral prednisolone (40 mg/day) after a week, which is planned to be given for at least 2 months at the same dose. At the end of week 8, the patient regained urinary and fecal continence. Furthermore, symptoms of cognitive decline, as well as executive dysfunction, have been observed clinically, which will be evaluated once he stabilizes.
DISCUSSION

Apart from the presence of a long gap between the occurrence of psychotic episodes in the absence of any systemic disease, initially this case appeared to be a typical one. However, the subacute onset of the current episode with a rapid progression within 3 months despite psychopharmacotherapy and progression to treatment-resistant NMS (the yellow and red flags for possible autoimmune encephalitis)[7] along with elevation of erythrocyte sedimentation rate, diffuse slowing of electroencephalogram (EEG) in frontal and temporal regions, and the neuroimaging findings led us to consider an autoimmune etiology.

Table 1: Physical investigations of the patient during inpatient management

| Investigation                  | Result                                                                 |
|--------------------------------|------------------------------------------------------------------------|
| Complete hemogram              | Hemoglobin (g/dL) 12.0 (day 1), 11.6 (day 5), 9.6 (day 21), 9.0 (day 45), 9.9 (day 56) |
|                                | Total leucocyte count (mm$^3$) 8480 (day 1), 6220 (day 5), 5110 (day 21), 9230 (day 45), 12890 (day 56) |
|                                | Differential leucocyte count (neutrophils/lymphocytes/monocytes/cosinophils in %) 67/24/6/3 (day 1), 62/30/6/0 (day 5), 69/21/7/1 (day 21), 75/11/13/1 (day 45), 87/9/3 (day 56) |
|                                | Platelet count (per mm$^3$) 1,000,000 (day 1), 1,06,000 (day 5), 1,50,000 (day 21), 2,87,000 (day 45), 1,97,000 (day 56) |
| Liver function test            | SGOT/PT (U/L) 31/72 (day 1), 34/60 (day 15), 18/27 (day 45), 21/17 (day 56) |
|                                | Bilirubin (mg/dL) (total/direct/indirect) 0.5/0.12/0.48 (day 1), 0.46/0.02/0.37 (day 15), 0.68/0.15/0.53 (day 45), 0.36/0.08/0.28 (day 56) |
|                                | Proteins (g/dL) (total/albumin/globulin) 6.67/2.70/3.96 (day 1), 7.28/2.85/4.43 (day 15), 6.84/2.78/4.06 (day 45), 5.36/2.76/2.60 (day 56) |
| Prothrombin (s) time/control time/INR 12.4s/12.1s/1.03 |
| Kidney function tests          | Urea/creatinine (mg/dL) 73/1.16 (day 1), 107/1.01 (day 15), 51/0.93 (day 21), 32/0.91 (day 45), 69/0.77 (day 56) |
|                                | Serum sodium/potassium (mmol/L) 142/3.97 (day 1), 141/4.52 (day 15), 129/5.11 (day 21), 136/4.55 (day 45), 137/3.70 (day 56) |
| Urine culture/sensitivity      | Escherichia coli growth (day 21), Pseudomonas aeruginosa growth (day 37), E. coli growth (day 56) |
| CPK-NAC (g/L)                  | 918 (day 2), 394 (day 5), 261 (day 10) |
| Thyroid function test          | FT3 1.65 pg/mL, FT4 1.10 ng/dL, TSH 8.20 mIU/L |
| Anti-TPO antibodies            | 1.83 IU/mL |
| ESR                            | 107 mm in first hour |
| VDRL/HIV/HBsAg/HCV ELISA       | Non-reactive |
| Serum homocysteine             | 9.34 μmol/L |
| CSF examination                | CSF microcopy (WBC/RBC) Nil/425 cells/mm$^3$ - hemorrhagic tap (day 2) |
|                                | 05/80 cells/mm$^3$ - cytopsin smears showed occasional lymphonuclear cells (day 45) |
|                                | CSF biochemistry (sugar/protein/chloride in mg/dL) 68/35/135 (day 2) |
|                                | 87/33/121 (day 45) |
|                                | CSF Culture/Sensitivity No growth seen (days 2 and 45) |
|                                | Special staining (Gram’s staining/ZN staining/India ink staining) Negative (days 2 and 45) |
|                                | Anti-NMDA antibodies Negative (day 45) |
| Ultrasoundography of abdomen and pelvis | Lithogenic bile with microolithiasis within gall bladder |
| Neuroimaging                    | NCCT brain Features suggested senile atrophy with chronic end vessel ischemic changes (day 7) |
|                                | MRI brain and MR-angiography Small-vessel ischemic changes involving bilateral corona radiata and centrum semi-ovale. Microbleeds involving bilateral basal ganglia and pons-chronic hypertensive microvascular changes. Diffuse cerebra atrophy. Subtle narrowing in bilateral ICA causing < approx. 30% stenosis. (day 40) |
| EEG                            | Diffuse slowing observed in frontal and temporal leads |
| ANA/dsDNA                      | Negative |
| RA factor                      | 7.2 IU/mL (normal range=0-20I U/mL) |
Furthermore, the absence of systemic manifestations and negative autoantibodies ruled out possible rheumatic encephalitis. Although CSF, EEG, and neuroimaging profile were not conclusive for an autoimmune encephalitis, which may occur due to a range of factors,[8-10] the presence of cerebral small-vessel disease too suggested a primary immune-based vasculitis and encephalitis. The presentation in the index patient remarkably differed from the previously reported cases which had a younger age of onset of illness,[2-6] had a female predominance,[2,3,5,6] and had a seizure or other neurological symptoms at the initial presentation.[2,3,6] The nonevaluation of a panel of other autoantibodies was a limitation in this case, and a definitive diagnosis based on a brain biopsy was not feasible. The future course of management for this patient would be a course of cyclophosphamide with/without rituximab, evaluation of cognition and executive functions with standard tools, and rehabilitation. To conclude, autoimmune encephalitis forms a close differential diagnosis for various neuropsychiatry syndromes, including, rarely, the NMS and hence, one should suspect an autoimmune pathology in cases of unusual clinical presentation or resistance to traditional treatments.

**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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Central Pontine/Extrapontine Myelinolysis Presenting with Manic and Catatonic Symptoms

Sir,

Central pontine myelinolysis (CPM) is a neurological disorder associated with demyelinating lesions in the central pons. It is usually caused by electrolytic disorders, especially rapid correction of severe hyponatremia.[1] Systemic disorders such as chronic alcoholism, hepatic failure, severe burns, malignant neoplasms, and hemodialysis also predispose to this condition. It may coexist with extrapontine myelinolysis (EPM), where it involves lesions outside pons, i.e., in caudate and lentiform nuclei, putamen, thalami, cerebellum, hippocampus, and cerebral cortex. It often presents with dysphagia, dystarthis, quadriplegia, encephalopathy, or coma. Such cases may additionally develop tremors, dystonia, cogwheel rigidity, ataxia, mutism, myoclonus, etc. Besides neurological symptoms, CPM may also present with neuropsychiatric symptoms such as personality changes, inappropriate affect, emotional lability, disinhibition, catatonia, psychosis, and delirium, as described in some reports.[2-4] None of the previous reports have suggested an occurrence of prominent manic symptoms followed by catatonia in patients with central pontine/extrapontine myelinolysis (CPEM). We describe a unique case of an elderly man with such a presentation after rapidly corrected hyponatremia.

CASE REPORT

A 72-year-old man was admitted to the cardiothoracic surgery unit floor for aortic valve repair and coronary artery bypass graft. He had history of hypertension and coronary artery disease along with rheumatic aortic stenosis for the last 30 years. He had no psychiatric illness and denied any substance use in the past. During preoperative workup, his serum sodium was found to be low (114 mmol/L), but he was asymptomatic. Serum sodium levels repeated over the next couple of days remained unchanged. During surgery, his serum sodium level decreased to 104 mmol/L. As per intraoperative notes, serum sodium was rapidly corrected with intravenous 3% saline. His serum sodium levels were 134 and 139 mmol/L, respectively, on postoperative days 1 and 2. His postoperative course was uneventful from the cardiac surgery perspective. However, on