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.[1] 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.[2-4] 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.[5,6] 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.

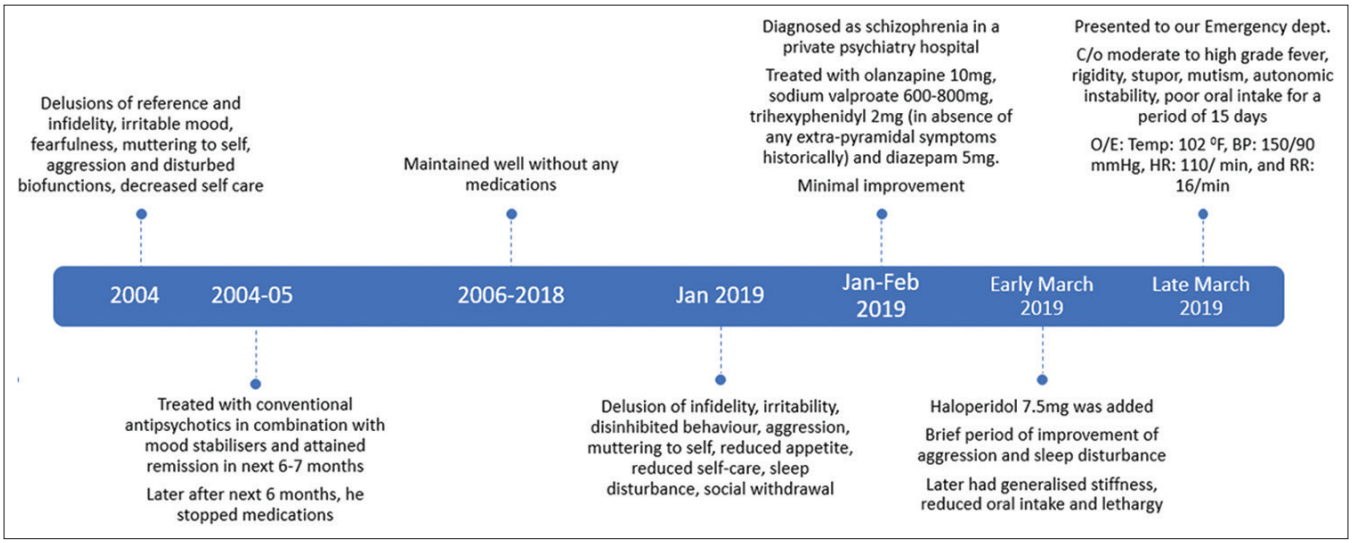

Figure 1: Diagrammatic presentation of the course of illness of patient

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/eosinophils 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)	1,00,000 (day 1), 1,06,000 (day 5), 1,50,000 (day 21), 2,87000 (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)	0.6/0.12/0.48 (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 (µg/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 microscopy (WBC/RBC)	Nil/425 cells/mm^3 - hemorrhagic tap (day 2) 05/80 cells/mm^3 - cytospin 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)
Ultrasonography of abdomen and pelvis		Lithogenic bile with microlithiasis 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)

SGOT – Serum glutamic oxaloacetic transaminase; SGPT – Serum glutamic pyruvic transaminase; CPK-NAC – N-acetyl-cystein activated creatine phosphokinase; anti-TPO – anti-thyroid peroxidase antibodies; ESR – Erythrocyte sedimentation rate; VDRL – Venereal disease research laboratory test; HIV – Human immunodeficiency virus; HBsAg – Hepatitis B surface antigen; HCV – Hepatitis C virus; FT3 – Free triiodothyronine; FT4 – Free thyroxine; TSH – Thyroid stimulating hormone; INR – Internationalized normalized ratio; CSF – Cerebro-spinal fluid; WBC – White blood cell; ICA - Internal carotid artery; RBC – Red blood cell; ZN staining – Ziehl neelsen Staining; NCCT – Non-contrast computed tomography; MRI – Magnetic resonance imaging; NMD – N-methyl-D-aspartate; EEG – Electroencephalography; ANA – anti-nuclear antibodies; dsDNA – anti-double strand DNA antibodies; RA Factor – Rheumatoid Factor

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.

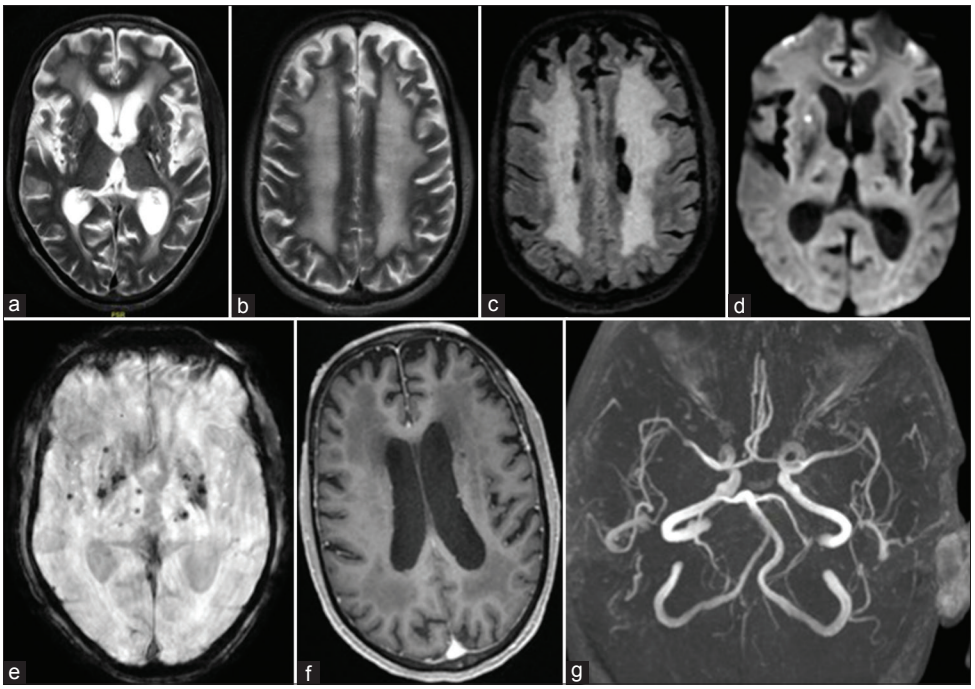

Figure 2: The axial T2 images (a and b) and axial FLAIR image (c) show diffuse confluent periventricular and lobar white matter hyperintensities. Prominent perivascular [Virchow-Robin (VR)] spaces noted at bilateral basal ganglia. The axial diffusion-weighted image (d) shows an acute lacunar infarct at right putamen. The SWAN image (e) shows microhemorrhages at bilateral basal ganglia and thalami. The postcontrast T1MPRAGE (f) and TOF MR (time of flight magnetic resonance) angiogram (g) are unremarkable. The image features are consistent with diffuse small-vessel disease

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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