Metabolic Opsoclonus Myoclonus Syndrome in a Patient of Crohn's Disease: Lessons Learnt

Sir,

A 51-year-old man, on intermittent mesalamine and oral steroids for Crohn's disease, underwent surgery (intestinal resection and anastomosis) for small bowel obstruction. Three weeks later, he was hospitalized for subacute-onset dizziness, vomiting, palpitations, irritability, agitation, and disturbed sleep. Magnetic resonance imaging of the brain showed a small gliotic lesion in the left frontal lobe, consistent with an ischemic stroke he had in the past. Laboratory investigations showed hypokalemia (serum potassium 2.9 mEq/L); complete blood count, blood glucose, liver, renal and thyroid function tests, serum sodium, urinalysis, and cerebrospinal fluid analysis were normal. In addition to the treatment of hypokalemia, in-hospital management included several drugs such as escitalopram, levosulpiride, olanzapine, risperidone, lorazepam, trihexyphenidyl, betahistine, prochlorperazine, donepezil, citicoline, piracetam, amiodarone, pantoprazole, and ondansetron. His clinical status deteriorated, and a few days later, he had incomprehensible speech, imbalance in walking, and involuntary jerky movements of limbs. The chronology of clinical features is depicted in Figure 1.

Neurological examination of the patient showed normal alertness, opsoclonus, blepharoclonus, ataxic speech, generalized muscle wasting, mild rigidity, quadriparesis (Medical Research Council grade III), multifocal myoclonus, exaggerated deep tendon reflexes, flexor plantar response, and Chvostek's sign [Video 1]. Furthermore, laboratory investigations showed high creatine phosphokinase (1758 IU/L), hypocalcemia (corrected calcium 3.9 mg/dL), hypomagnesemia (0.3 mg/dL), elevated parathormone (223 ng/L), and low 25-hydroxy vitamin D (13.2 ng/mL). Revised management included discontinuation of the aforementioned drugs, correction of electrolyte abnormalities (hypokalemia, hypocalcemia, and hypomagnesemia), clonazepam, vitamin D, thiamine (500 mg/day), and other multivitamin supplements. Within five days, he showed remarkable clinical improvement [Video 2]; opsoclonus was replaced by downbeat nystagmus which later subsided, and myoclonus abated. A month later, he was given empirical intravenous methylprednisolone (1 g/day) for five days followed by gradually tapering course of oral steroids over the next six months, because he had persistent cerebellar ataxia (Scale for the Assessment and Rating of Ataxia score 16) and elevated anti-glutamic acid decarboxylase (anti-GAD) level (25.64 IU/mL; normal <10 U/mL). Serum VDRL, HIV, HBsAg, anti-HCV, paraneoplastic antibody panel, and anti-tissue transglutaminase were negative. A whole-body FDG-PET scan did not show evidence of neoplasia. At 2-year follow-up, he had mild disability due to cerebellar ataxia (Scale for the Assessment and Rating of Ataxia score was 8).

Thus, the patient had opsoclonus myoclonus syndrome (OMS). The typical clinical features of OMS include opsoclonus (involuntary, chaotic, multi-vector eye movements that are not interrupted by inter-saccadic intervals), multi-focal spontaneous and action myoclonus, gait instability, and behavioral symptoms or other encephalopathic features. Acute-to-subacute onset vertigo, vomiting, and gait instability are the most common presenting symptoms.[1] Some patients have prominent cerebellar signs, though it is very difficult to separate them from myoclonus. A high

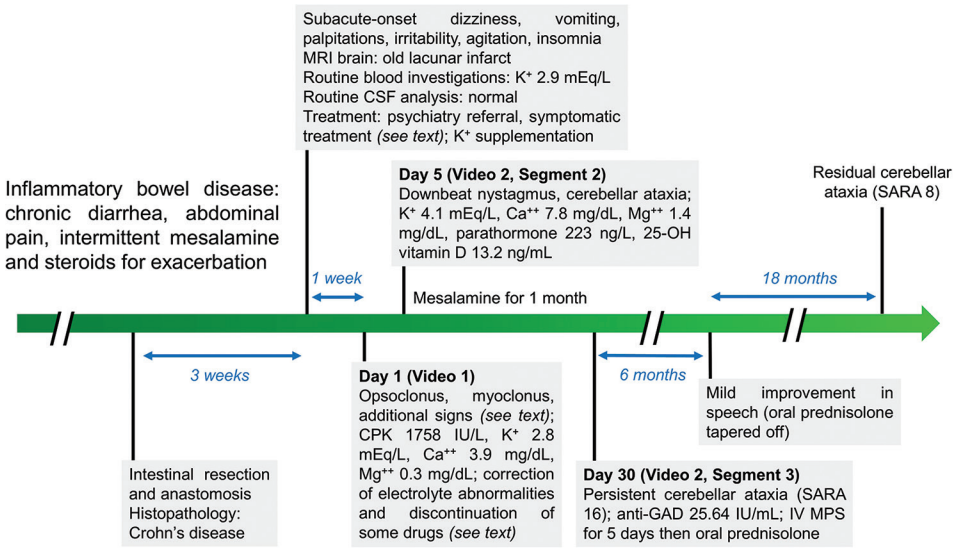

Figure 1: Chronology of clinical features and relevant investigations. Day 1 is the day when the patient sought our medical attention. Ca^{++} = calcium, CPK = creatinine phosphokinase, CSF = cerebrospinal fluid, GAD = glutamic acid decarboxylase, K^{+} = potassium, Mg^{++} = magnesium, SARA = Scale for the Assessment and Rating of Ataxia

proportion of published literature on OMS (prior to the COVID-19 era) is on paraneoplastic etiology. This is widely considered a reporting bias, and most of the adult cases are in fact para-infectious or idiopathic (presumed post-infectious).[2] The toxic and metabolic causes are seldom reported and not included in large studies.[3]

Crohn's disease is a chronic inflammatory disease that affects the gastrointestinal tract. Patients of Crohn's disease are at risk of developing hypocalcemia, hypomagnesemia, and deficiency of multiple vitamins due to impaired absorption.[4] The electrolyte and metabolic disturbances may aggravate after surgery (especially if it involves intestinal resection). Patients affected by hypocalcemia or hypomagnesemia may present with tetany, trismus, opisthotonus, chorea, seizures, and encephalopathy.[5] Additional neurological features of hypomagnesemia include tremor, myoclonus, hyperreflexia, downbeat nystagmus, and cerebellar ataxia.[5,6]

Stiff-person syndrome, cerebellar ataxia, limbic encephalitis, epilepsy, OMS, persistent nystagmus, or overlap of these disorders are attributed to anti-GAD when it is detected in high titer in the serum (>10,000 IU/mL by enzyme-linked immunosorbent assay) or the CSF (>100 IU/mL). These disorders respond to immunotherapy, albeit partially.[7] Low-titer anti-GAD may be found in several autoimmune disorders, including type 1 diabetes mellitus. An alternative explanation of neurological features is often found when anti-GAD is detected in low titer.[7]

Returning to the present case, some clinical features such as rigidity, muscle weakness, and hyperreflexia can be attributed to neuroleptic toxicity, hypokalemia, and hypomagnesemia, respectively. While it is difficult to ascertain a single etiological explanation for OMS in this patient, there are several lessons to be learnt. This case highlights the importance of investigating a patient's symptoms in the context of medical history. Upon failure of identifying a cause of patient's initial symptoms through investigations, the management focused on symptomatic treatment that included a psychiatry referral and several drugs. Perhaps a focused medical history and thorough neurological examination would have guided appropriate investigations. Early recognition and treatment of hypocalcemia and hypomagnesemia would have prevented clinical deterioration. Upon correction of these electrolyte disturbances, there was a dramatic improvement in ocular abnormalities and myoclonus. Considering anti-GAD a marker of autoimmunity, the patient was empirically treated with steroids. However, low-titer anti-GAD lacks specificity for neural autoimmunity. Furthermore, its role in the pathogenicity of cerebellar ataxia is not clearly established.[8] It is known that delayed treatment of hypomagnesemia may lead to persistent cerebellar signs[9]; this is the likely explanation of the patient's residual deficits. No other explanation was found for cerebellar ataxia through investigations.

This case illustrates that OMS can be caused by metabolic derangements, such as hypomagnesemia and hypocalcemia. One must be cognizant of the neurological manifestations of these electrolyte abnormalities, as delayed correction may lead to grave consequences.

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.

Suvorit S. Bhowmick[1,2]

[1]Movement Disorders Clinic, Vadodara Institute of Neurological Sciences, Vadodara, Gujarat, [2]Neurology Clinic, Sir Sayjirao General Hospital, Vadodara, Gujarat, India

Address for correspondence: Dr. Suvorit S. Bhowmick, Movement Disorders Clinic, Vadodara Institute of Neurological Sciences, Vadodara, Gujarat, India.
E-mail: tutai1985@gmail.com

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