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Gut to brain: Celiac disease beyond the Intestine — A neurological case series

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Abstract

Celiac disease (CD) is an autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals, leading to small intestinal damage and malabsorption. While gastrointestinal symptoms like diarrhoea are commonly associated with CD, more than 50% of adults with the condition experience significant extraintestinal involvement, including neurological and psychiatric manifestation. The mechanisms underlying these neurological manifestations remain incompletely understood, with potential causes including gluten-mediated neurotoxicity, immune complex deposition, and associated nutritional deficiencies. In this article, we present the Indian case series highlighting immunological CNS involvement with celiac disease, where three patients, initially presenting with neurological symptoms ranging from isolated cerebellar ataxia to acute encephalopathy with psychiatric features, were diagnosed with CD. Patients showed clinical improvement following multimodal management including gluten-free diet and, in selected cases, immunotherapy. Additionally, all three patients showed substantial improvement with long-term follow-up, suggesting the importance of sustained monitoring and management in cases of neurological CD. This is a small case series from India highlighting varied neurological phenotypes associated with CD, contributing to a broader understanding of its complex presentation and management.

Keywords: Celiac disease; Neuroimmunology; Immune-mediated cerebellar ataxia; Gut-brain axis

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder triggered by the ingestion of gluten, which, in genetically predisposed people, induces damage to the small intestine and consequent malabsorption.[1] From a clinical perspective, although diarrhoea and gastrointestinal symptoms are commonly observed in early phases of the disease, they are not as frequent as in the past.[1] It is widely recognized that the characteristic gastrointestinal symptoms of the disease represents a small part of the so-called "CD iceberg", with greater than 50% of adult individuals displaying substantial extra-intestinal involvement, even in the absence of the overt CD presentation.[1] Celiac disease (CD) is considered to be a complex multi-organ disease with a high prevalence of extra-intestinal involvement. The neurological and psychiatric manifestations, include as cerebellar ataxia, epilepsy, peripheral neuropathy, headache, depression and cognitive impairment.[2] The mechanisms behind the neurological involvement in CD remain controversial. Recent evidence shows these can be related to gluten-mediated pathogenesis, including antibody cross-reaction, direct neurotoxicity, deposition of immune complexes and, in severe cases, vitamin or nutritional deficiency.[2] In this article, we report 3 cases of CD masquerading as neurological illness. The cases range from isolated cerebellar ataxia to acute encephalopathy with psychiatric symptoms. They were managed with a combination of gluten-free diet and immunomodulatory therapy. This case series highlights the importance of considering CD in patients with unexplained neurological syndromes and underscores the need for early recognition and comprehensive management.

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CASE REPORT

Patient 1

An 11 year-old, school going girl, born to non-consanguineous marriage with normal birth and developmental history, presented with one month of subacute behavioural changes, including irritability, decreased attention, persecutory delusions, and visual hallucinations, following a febrile illness. She also had one episode of generalized tonic–clonic seizure and altered sensorium. she had a history of chronic diarrhoea. At presentation, patient was stuporous and irritable and was not oriented to time, place or person. On examination, she was thin-built with a weight of 32kg and a height of 140cm, the 27th percentile for her age. Her BMI was 16.3 kg/m², which was less by one standard deviation and the 29th percentile as per her age. There was no focal neurological deficit, and we did not elicit any signs of meningeal irritation. Patient's routine blood investigations suggested a haemoglobin level of 13 g/dl, a mean corpuscular volume of 93, a TLC of 5700/mm³, and a platelet count of 245,000/mm³. The patient had a deficit for vitamin D3 with a value of 10.51 ng/mL. Investigations showed normal MRI and EEG; CSF with elevated protein (159 mg/dL) and normal cytology; and a negative autoimmune panel, including anti-NMDAR antibodies. Infectious, metabolic, toxic, and other autoimmune causes of encephalopathy were excluded based on clinical, laboratory, and imaging evaluation. Given the systemic clues of malabsorption, anti-tTG IgA (Anti-tissue Transglutaminase Immunoglobulin A) was tested and found to be strongly positive (337 U/mL; >10× ULN) along with positive endomysial antibodies (EMA) and normal total IgA levels, establishing a diagnosis of gluten encephalopathy as per the European Society for Paediatric Gastroenterology, Hepatology & Nutrition (ESPGHAN) non-biopsy criteria. The patient was treated with intravenous methylprednisolone at a dose of 1 g/day for 5 days, followed by a tapering course of oral corticosteroids along with a strict gluten-free diet—comprising elimination of wheat, barley, and rye, with substitution using rice, maize, and millet-based foods, along with dietary counselling to avoid hidden sources of gluten—resulting in progressive clinical improvement; by 3-month follow-up, she had achieved complete recovery with normalization of behaviour, improved attention span, full orientation, resolution of hallucinations and delusions, absence of seizure recurrence, resolution of diarrhoea, and significant weight gain, and had resumed school activities with age-appropriate functioning.

Patient 2

A 42-year-old female presented with 2 years of progressive gait imbalance, limb ataxia, tremulousness, scanning/explosive speech and cognitive decline, with a history of diet-related recurrent diarrhoea, weight loss and fatigue worsening with wheat intake. On examination, Patient was conscious and mute. Patient had head titubation with truncal as well as limb ataxia. Extrapyramidal signs were present in the form of bradykinesia and rigidity. Routine Blood work-up and CSF came out to be normal. MRI Brain revealed vermian-predominant pancerebellar atrophy with midbrain hyperintensities involving the tectum and tegmentum (FIGURE 1). CECT of the abdomen and thorax was done to screen for paraneoplastic cerebellar degeneration, which came out normal. In view of diarrhoea and weight loss which were related to dietary changes, Anti-tTG was sent, which came out to be 220U/mL (>10 times elevated) with normal IgA levels . Findings were suggestive of CD in the appropriate clinical and serological context, and the diagnosis was further supported by jejunal biopsy demonstrating Marsh grade II changes (Figure 2). She was initiated on IV immunoglobulin (IVIG) induction at a total dose

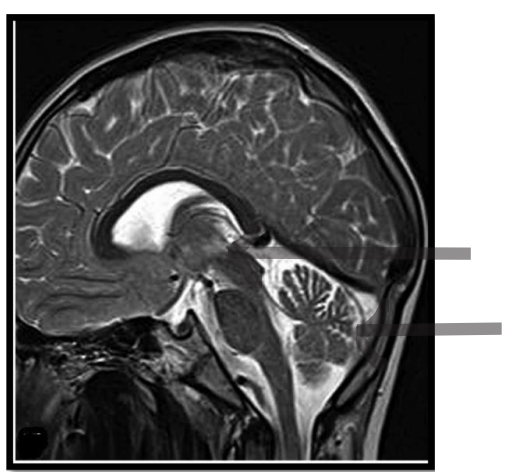

Figure 1. MRI Brain revealed vermian predominant pancerebellar atrophy with midbrain hyperintensities involving tectum, tegmentum.

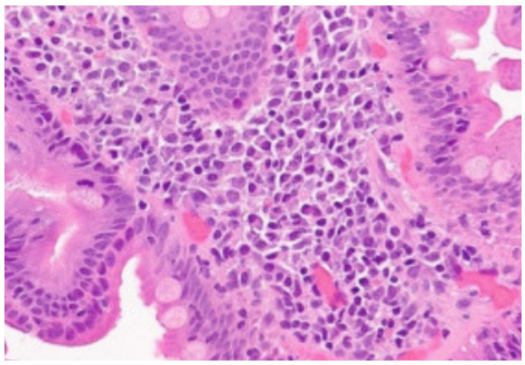

Figure 2. Intraepithelial lymphocytosis with crypt hyperplasia without villous atrophy. Modified Marsh-Oberhuber classification: Grade 2.

of 2 g/kg administered over 5 days, followed by maintenance immunosuppression with oral mycophenolate mofetil (MMF), gradually uptitrated to 1 g twice daily, with ongoing clinical and laboratory monitoring. She was put on a gluten-free diet. At discharge, the patient did not report significant improvement in the neurological symptoms. On subsequent follow-up, she regained her speech with spastic dysarthria, but she was able to communicate, and she could walk with minimal support with swaying on either side. She continued on oral MMF. On 3rd follow-up she would carry on her day-to-day activities and would help in household chores and could take better care of her children. Assessment using the Scale for the Assessment and Rating of Ataxia (SARA), suggested severe ataxia at baseline (approximately 28/40), which improved to moderate severity (approximately 14/40) on follow up.

Patient 3

A 37-year-old lady presented to us with a 2-year history of progressive imbalance in day-to-day activities such that she experienced side-to-side swaying while walking, which increased when walking through narrow passages. She experienced tremulousness in her hands, which would increase on activities like carrying a tray of glasses filled with water, causing spillage of water. It was associated with chronic diarrhoea and weight loss. Examination revealed undernutrition (BMI 15.1 kg/m^2), scanning speech, abnormal saccades, and bilateral cerebellar signs (impaired coordination and dysdiadochokinesia) with normal motor and sensory systems. An MRI of the brain showed vermian-predominant cerebellar atrophy, and routine workup was unremarkable. Considering chronic progressive pancerebellar ataxia with chronic diarrhoea without a positive family history Anti-tTG was sent, which came out to be strongly positive 200 U/ml(>10 times elevated) along with positive endomysial antibodies (EMA) and normal IgA levels. Diagnosis was confirmed using jejunal biopsy, which revealed intraepithelial lymphocytosis with crypt hyperplasia and moderate villous atrophy (Marsh Grade 3b) (Figure 3). The patient was started on IV immunoglobulin induction(2 g/kg administered over 5 days), following which her ataxia reduced to some extent. She was put on maintenance immunomodulator therapy with oral MMF (500mg twice/day), and on subsequent follow-up her ataxia reduced considerably. She was able to do most of her ADLs with minimum difficulty. Assessment using the Scale for the Assessment and Rating of Ataxia (SARA), suggested moderate to severe ataxia at baseline (approximately 22/40), with improvement to mild to moderate severity (approximately 10/40) on follow-up. This case demonstrated the strongest clinicopathological correlation, with biopsy-proven disease and classical neurological features.

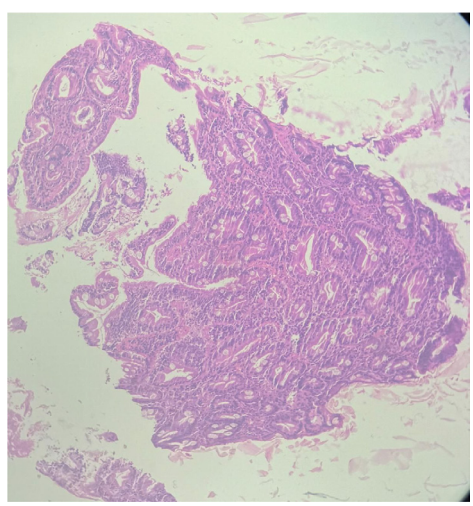

Figure 3. Intraepithelial lymphocytosis with crypt hyperplasia and moderate villous atrophy. Modified Marsh-Oberhuber classification: Grade 3b

Table 1: Summary of the cases

Patient	Age/ Sex	Presentation	GI Features	Anti-tTG	Biopsy	MRI	Treatment	Outcome
1	11/F	Encephalopathy + psychosis + seizure	Diarrhea	337 U/mL	Not done	Normal	Steroids + GFD	Full recovery
2	42/F	Cerebellar ataxia + cognitive decline	Diet-related diarrhea	220 U/mL	Marsh II	Vermian atrophy+ Midbrain hyperintensity	IVIG + MMF + GFD	Gradual improvement
3	37/F	Progressive cerebellar ataxia	Diarrhea + weight loss	200 U/ml	Marsh 3b	Vermian atrophy	IVIG + MMF + GFD	Gradual improvement

GFD: Gluten free diet, MMF : mycophenolate mofetil, IVIG: intravenous immunoglobulin

DISCUSSION

Several psychiatric and neurological disorders have previously been described to be over-represented in patients with CD, most commonly depression. However, there are only a few case reports of celiac disease presenting as acute encephalopathy. Acute presentations of immune-mediated cerebellar ataxias may be misdiagnosed as post-infective cerebellitis; in many cases, an infectious aetiology is suspected clinically, although it is not substantiated by serological or laboratory evidence.[3] Immune-mediated cerebellar ataxias (IMCAs) are a heterogeneous group of disorders characterised by subacute onset, prominence of a 'midline' cerebellar syndrome with vermian involvement on imaging, and evidence of organ-specific autoimmunity with frequent co-occurrence of other autoimmune diseases.[4] Emerging evidence suggests that a significant proportion of idiopathic sporadic cerebellar ataxias may in fact represent immune-mediated disorders, with implications for early identification and immunotherapy. In contrast to the 'global' cerebellar dysfunction of genetic and degenerative ataxias, IMCAs are characterised by a 'midline' cerebellar phenotype with gait ataxia disproportionate to limb, speech and ocular manifestations.[7]

All three patients described here had serological evidence of gluten sensitivity, and two also had enteropathy in keeping with CD. The novelty of this report is the prompt identification of the diagnosis by keeping a high index of suspicion with treatment effectiveness using immunomodulator therapy. Given the observational nature of this case series, improvement cannot be attributed solely to immunotherapy. Gluten-free diet, nutritional correction, and natural disease course may have contributed. On the other hand, gluten encephalopathy responded well to pulse methylprednisolone therapy with a short course of oral steroids. The elimination of gluten sensitivity-related antibodies can take up to 6 months, provided strict adherence to the diet.[6] Thus, relying on a gluten-free diet alone may worsen the clinical picture and prevent us from addressing a treatable cause of ataxia. Given the rapidity of progression, such cases as described here require immediate treatment with immunotherapy to prevent further cerebellar insult whilst the gluten-free diet starts to have an effect. A growing base of retrospective and observational evidence supports the use of various immunotherapy treatments in the management of IMCAs, in addition to the removal of any antigenic stimulus. These include steroids, IV immunoglobulins, mycophenolate and rituximab.[7] Clinical improvement was observed across cases; however, it is important to note that this improvement occurred in the context of multimodal therapy.

Our findings underscore the importance of recognizing CD as a multi-organ disorder, where neurological symptoms may be the predominant or initial manifestation, rather than the classic gastrointestinal signs. This case series aims to raise awareness among clinicians about the need for a high index of suspicion for CD in patients with unexplained neurological symptoms and to consider immunotherapy viz. IV immunoglobulin and corticosteroids as viable treatment options for such cases.

This study has several limitations. It represents a small, uncontrolled case series, and

improvement cannot be confidently attributed to immunotherapy alone. A gluten-free diet remains a major therapeutic component, and natural disease fluctuation along with correction of nutritional deficiencies may also have contributed to the observed outcomes. Furthermore, the current evidence base supporting the use of IV immunoglobulin and mycophenolate mofetil in gluten-related neurological disease remains limited. These observations support the evolving concept of the gut–brain axis, wherein celiac disease can manifest as a primarily neurological disorder requiring multidisciplinary evaluation and management.

DISCLOSURE

Ethics: Written informed consent was obtained from all patients or their guardians for publication of clinical details.

Conflict of interest: None

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