Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 8 Issue 7 July 2025

Case Report

Central Nervous System White Matter Lesions in Biopsy-Defined Celiac Disease and Immunoglobulin A Deficiency

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Received: May 27, 2025

Published: June 12, 2025

Abstract

Focal white matter lesions in the central nervous system may occur in celiac disease, possibly due to a vascular cause or inflammatory demyelination likely reflecting a broad multi-system immune-mediated process. A 21 year old female developed a complex neurological syndrome, but had no intestinal symptoms or weight loss. Initial studies were abnormal with iron deficiency anemia and osteopenia with vitamin D3 deficiency. In spite of a slightly reduced serum immunoglobulin A level, screening tests for celiac disease were positive including raised serum antibodies to IgA tissue transglutaminase. Subsequent small intestinal mucosal biopsies showed features of untreated celiac disease. A gluten-free diet led to weight gain, resolution of abnormal serological tests and repeat small intestinal biopsies showed improvement. Unfortunately, neurological changes persisted. Adult celiac disease may occur more frequently than is currently appreciated in neurological disorders characterized by focal white matter lesions. Added long-term studies are needed to determine if a gluten-free diet can significantly improve accompanying neuropsychiatric changes.

Keywords: Celiac disease; Multiple Sclerosis; Demyelination

Introduction

Neurological disorders may develop in patients with already established adult celiac disease [1-3]. Extra-intestinal features may include anemia, coagulopathy, metabolic bone diseases (eg., osteopenia), infertility, skin disorders (eg., dermatitis herpetiformis) and neuropsychiatric syndromes. Some reported neurological complications include epilepsy, sometimes with occipital calcifications, cerebellar ataxia, peripheral neuropathy, myelopathy and dementia, often with accompanying brain atrophy in adults [4-6]. Antibody-positive myasthenia graves has also been noted [7], suggesting shared autoimmune phenomena, possibly related to antibody cross-reactivity, immune-complex deposition and direct neurotoxic effects of some gluten peptides. These systemic and neurological changes could reflect a broad multi-system immune-mediated disorder (rather than an immune-based small intestinal disease alone) [8]. Alternatively, some neurological changes may result directly from impaired absorption of specific nutrients (eg., peripheral neuropathy). In the present report, a patient with a complex neurological syndrome was discovered to have underlying celiac disease and deficiency of immunoglobulin A in the absence of intestinal symptoms or weight loss.

Case Report

A 21-yr-old female was initially referred to a multiple sclerosis clinic in our university teaching hospital with disturbed gait, apraxing hand movements and altered speech, all noted to have slowly deteriorated during the prior 3 to 4 years. Since then, she was observed to walk with a very wide gait and fluency of her speech had slowed. Her mother also noted a flat affect with a lack of interest in most of her prior daily living activities, including reading and

knitting. Her exam revealed an ataxic gait, slowed speech and a depressive mood with apathetic facial features. No motor or sensory impairment was observed. Deep tendon reflexes were normal in the upper extremities and brisk in the lower extremities. She did not have dysdiadochokinesia or dysmetria. Mini-mental status testing (for cognitive impairment) revealed a normal score. There were no intestinal symptoms, including diarrhea, constipation or weight loss.

Laboratory studies showed a mild iron deficiency anemia [9] with a hemoglobin or 10.8g per L; borderline vitamin D3 levels, i.e., 25-OH-vitamin D3, 19.5 ug per L (normal, 20 to 120 ug per L) and mild osteopenia, with normal

levels of vitamin E. Her serum anti-gliadin IgA was 87 (normal, up to 50.0 RU per ml); serum anti-IgA transglutaminase was 52 (normal, < 20 U per ml) with a decreased serum IgA level of 0.46 (normal, 0.70 to 4.0 g per L) consistent with serum IgA deficiency [10]. HLA testing revealed that she was carrying DQ2 (A1*0501, B1*0201) heterodimer. Nerve conduction studies revealed a mild peripheral motor neuropathy. Magnetic resonance imaging (MRI) showed a cerebral white matter lesion that was hyper-intense on T2 weighted images and hypo-intense on T1 weighted images. A peri-ventricular white matter lesion was also present. Spinal images were normal.

Because of iron deficiency anemia, osteopenic bone disease and positive serological screening studies for celiac disease, a small intestinal mucosal biopsy was done and showed characteristic features of untreated celiac disease with moderate to severe architectural changes consisting of flattened villi and expanded hyperplastic crypts along with increased lamina propria lymphocytes and plasma cells as well as increased numbers of intra-epithelial lymphocytes.

She also was treated for her depressive mood with sertralin 50 mg daily and risperidone 1 mg daily.

Three months later, her mood was improved, her iron deficiency anemia resolved and her serological studies including levels of anti-gliadin IgA and anti-IgA tissue transglutaminase were in the normal range. A repeat small intestinal biopsy showed improvement in mucosal architecture with re-appearance of intestinal villi consistent with a gluten-free diet treatment effect and confirmation of a gluten-sensitive lesion. Weight had increased by 4 kg. Seven months later, nerve conduction studies were not normal, but were reported to be minimally improved. Other neuropsychiatric alterations, however, were not significantly changed.

Discussion

This patient presented with a complex central nervous system disorder and focal white matter MRI imaging features thought to represent an extra-intestinal feature of adult celiac disease either due to vasculitis or inflammatory demyelination [11]. Detection of iron deficiency anemia and osteopenic bone disease had suggested possible impaired absorption and led to serological (anti-gliadin and anti-tissue transglutaminase) screening for celiac disease antibodies along with HLA definition of DQ2 (often found in celiac disease). Of note, her total serum IgA level was also decreased, occasionally noted in adult celiac disease [10]. Of special significance in this patient, there were no intestinal symptoms such as diarrhea, abdominal pain or weight loss that might have suggested an underlying intestinal disorder typical of classical celiac disease.

Celiac disease is an immune-mediated small intestinal disorder commonly associated with other systemic autoimmune changes, such as the immune-

mediated skin disorder, dermatitis herpetiformis, along with other autoimmune neurological disorders including antibody-positive myasthenia gravis [8]. A wide array of neuropsychiatric disorders have been recorded in celiac disease [1-5,12] characterized by disordered gait, apraxia, cerebellar and other different cognitive abnormalities (including apathy and depression). Some of these were also observed in the present patient despite no intestinal symptoms or weight loss.

Focal white matter lesions in the central nervous system may represent a distinct extra-intestinal manifestation of celiac disease. Prior clinical investigators have suggested that focal white matter

lesions may have a vascular or inflammatory demyelinating cause [11]. In adult celiac disease, some neurologic features may be related to a vitamin or nutrient deficiency due to small intestinal disease leading to impaired absorption. Here, the patient did not have folic acid, vitamin B12 or vitamin E deficiencies, only iron deficiency anemia and osteopenia, possibly related to mild vitamin D deficiency. Different forms of cognitive impairment may be the initial manifestation of celiac disease [1-3,5].

In the present patient cognitive changes were not established using the mini-mental test but she was apathetic and demonstrated apraxia of hand functions. Apraxia has rarely been described in celiac disease [12], here with only minimal improvement after 7 months of a gluten-free diet.

The causes of cognitive and psychiatric changes in celiac disease are not well established. An immune-based etiology has been widely considered, especially with the detection of anti-gliadin antibodies in the cerebrospinal fluid in patients with gluten sensitivity and altered neurological function. Although these antibodies may occur in celiac disease *per se*, neurological changes do not always occur. Moreover, this patient was even more clinically complex, with both serum immunoglobulin A deficiency and biopsy-defined celiac disease [10].

Further studies are needed in well documented celiac disease to define the precise frequency of different neuropsychiatric disorders and their pathogenesis.

Although demyelination is often typical of imaging changes in multiple sclerosis, similar white matter changes may be detected in amyotrophic lateral

sclerosis, a disorder sometimes rarely associated with celiac disease or mimicking celiac disease [6,7,13]. More recently, a specific genetic correlation has been defined with 3 novel risk genes [14]. The authors indicated that functional enrichment analysis in this study suggested these shared risk genes involve 4 pathways including membrane trafficking, vesicle-mediated transport, endoplasmic reticulum to Golgi apparatus anterograde transport, and transport to the Golgi apparatus [14].

Conclusion

In the present case, biopsy-defined adult celiac disease was documented without intestinal symptoms, including diarrhea or weight loss, despite the presence of a profound and complex neurological disorder. Neurological symptoms that are not readily explained should lead to a thorough evaluation including exclusion of adult celiac disease. Added longer term studies are needed, however, to determine if a gluten-free diet in this setting can fully or partially ameliorate the neurological findings.

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