DOI: 10.7860/JCDR/2015/13299.6743

Case Report

Internal Medicine Section

Gluten Sensitivity – A Potentially Reversible Cause of Progressive Cerebellar Ataxia and Myoclonus - A Case Report

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ABSTRACT

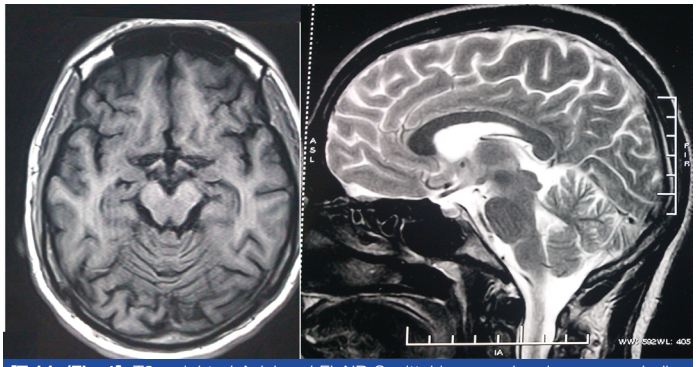
Gluten sensitivity is an umbrella term used for diverse clinical manifestations occurring as a result of abnormal immunological reactivity to dietary gluten in genetically susceptible individuals. Celiac disease is the most well-known but not the only manifestation of gluten sensitivity. Myoclonus with Ataxia is a rare manifestation of gluten sensitivity and should be considered in the differential diagnosis of all patients with idiopathic sporadic ataxia. The presence of gluten-related immune markers in normal population however complicates the reliable diagnosis of gluten related neurological disorders and clinical improvement on gluten free diet can serve as a diagnostic tool for this disease. We report a case of sporadic progressive cerebellar ataxia with myoclonus with positive antigliadin antibodies, which improved with a trial of gluten free diet. This case highlights an important diagnostic and therapeutic principle in management of late onset idiopathic ataxia.

Keywords: Celiac disease, Idiopathic sporadic ataxia, Immune markers, Neurological disorders

CASE REPORT

A 35-year-old nondiabetic, nonhypertensive male laborer presented to us with a one year history of gradually progressive slurring of speech, clumsiness of hands and unsteadiness of gait. He denied any motor weakness or loss of sensation in the limbs but complained of tremulousness of the hands with clumsiness in doing fine work and a tendency to sway to either side while walking, with occasional falls. Within 4-5 months of the onset of the illness, he was unable to walk without support and his speech had become progressively more difficult to understand. He also complained of forgetfulness and difficulty in calculating and handling money but there was no history of fits, headache, hallucinations, delusions or any change in behaviour or personality. He also complained of chronic diarrhea with 6-7 semisolid, non-foul smelling loose stools without blood or mucus per day for almost the same duration. Diarrhea was not associated with vomiting, abdominal pain, loss of appetite, weight loss or fever. He was a product of a non-consanguineous marriage and there was no family history of any similar illness in the parents or siblings. Besides the habit of tobacco chewing he had no other addiction.

On examination, patient was fully conscious and alert. His vitals were stable and systemic examination was normal. Higher mental functions were essentially normal (MMSE-27/30). All the cranial nerves were intact with normal fundus examination and full ocular movements without nystagmus. There was no motor or sensory deficit. Deep tendon reflexes were normal except for pendular knee jerks and plantars were bilaterally flexor. He had bilateral cerebellar signs with scanning speech, finger nose in coordination, dysdiakokinesia and a typical broad based ataxic gait. Frequent, irregular, non-stimulus sensitive myoclonic jerks were also observed in both the lower limbs (right> left).



[Table/Fig-1]: T2 weighted Axial and FLAIR Sagittal images showing pancerebellar atrophy

On laboratory evaluation, haemogram, blood counts and ESR were normal but occasional macrocytes were seen on peripheral blood smear. Routine blood chemistry including blood sugar, LFT, KFT, serum electrolytes, lactate and Vitamin B12 levels were in the normal range. Blood examination was negative for VDRL, HIV, hepatitis B surface antigen (HbsAg), antibodies to hepatitis C virus (anti HCV). Workup for vasculitic profile was negative for ANA, dSDNA, p-ANCA, c-ANCA, RA factor. CRP, serum calcium and ACE and TFT levels were in the normal range. ECG, X-ray chest, CT chest, and ultrasound abdomen were normal. Routine stool examination was also normal. Blood test was positive for antigliadin antibody but negative for anti TTG (tissue trans-glutamase) antibody. Nerve conduction studies were in the normal range. EEG was normal and did not reveal any spike or polyspike discharges in association with the myoclonic jerks. MRI brain showed marked pancerebellar atrophy [Table/Fig-1]. Duodenal biopsy normal and did not show any villous atrophy.

In view of a history of progressive cerebellar ataxia and myoclonus being accompanied by chronic diarrhea and a positive blood test for antigliadin antibody, a diagnosis of gluten sensitive disorder was entertained. The patient was advised to follow a strict gluten free diet, following which his loose motions abated within a few days and he was discharged home with the advice to remain compliant with his diet plan. On a follow up 3 months later, his gait ataxia and dysarthria had improved by around 40% and he was able to walk unsupported.

DISCUSSION

Gluten sensitivity includes a spectrum of multisystem disorders occurring due to an autoimmune reaction to gluten [1]. Gluten is a protein composite of gliadin and glutein present along with starch in grain like wheat, barley and rye. Gluten sensitivity has a strong genetic association and is seen more commonly in association with HLA DQ2 and DQ8 positivity [2]. In genetically predisposed individuals, antibodies are formed by intestinal mucosal T-lymphocytes, leading to inflammation of the intestines [2]. Coeliac disease, a common cause of malabsorption, results from gluten sensitivity with a reported incidence of 1 in 113 persons in the US [3]. A study from

north India reported a prevalence of 1 in 310 individuals [4]. Overall prevalence of gluten sensitivity is probably much higher, since coeliac disease is frequently referred to as 'iceberg disease' [2]. Various other disorders associated with gluten sensitivity include: enteropathy associated T cell lymphoma and other extra-intestinal manifestations like anaemia, short stature, dental enamel defects, osteoporosis, infertility, autoimmune thyroiditis, Type 1 diabetes mellitus, dermatitis herpatiformis and neurological disorders [5].

Accurate prevalence of neurologic complications due to gluten sensitivity is not known. In patients with established celiac disease, the reported prevalence of neurologic complications ranges from 10-22.5% [6]. Evidence of sensorimotor axonal neuropathy can be found in upto 60% of the cases on electrophysiologic testing. Hadjivassiliou et al., in a study of 500 patients with gluten antibody positivity, found ataxia (with or without myoclonus and palatal tremor), neuropathy (sensorimotor axonal, small fiber neuropathy, motor neuropathy mononeuritis multiplex and sensory neuronopathy) and other neurologic manifestations like epilepsy, myopathy, myelopathy, encephalopathy and uncommonly chorea, stiff person syndrome and neuromyotonia [7].

'Gluten ataxia' was the term first used to describe idiopathic cases of sporadic ataxia with positive antigliadin antibodies [8]. A high prevalence of antigliadin antibody positivity has been observed among patients with sporadic ataxia as compared to healthy volunteers. However, there is still no definite consensus regarding the strength of association between ataxia and antigliadin antibody positivity, since some studies report a strong correlation while others fail to support this observation [6]. Clinically, gluten ataxia is usually purely cerebellar in nature with a pancerebellar involvement (gait ataxia, limb ataxia and dysarthria) with an insidious onset, the average age at presentation being 53 years. Rarely, cerebellar ataxia may occur in association with myoclonus, palatal tremor, chorea or opsoclonus [7]. In our case the ataxia was accompanied by myoclonus. In patients with neurologic manifestations, gastrointestinal symptoms are detectable in 10% of the cases only, but biopsy evidence of coeliac disease can be found in upto one-third of the patients. In our case, the patient had a history of chronic diarrhea but the intestinal biopsy was normal.

MR imaging shows cerebellar atrophy in around 60% of the cases, as was observed in present case also. MR spectroscopic studies may show evidence of abnormal cerebellar neuronal physiology. A significant difference in mean N-acetylaspartate/creatine levels has been observed between patients with gliadin antibodies and healthy controls [9]. Gluten free diet improves the MRS changes.

Serological tests used to confirm the diagnosis of gluten sensitivity include: IgA anti gliadin antibody, IgA anti tissue trans-glutaminase (Anti-TTG) and anti endomysial antibodies. These tests are however, not adequately sensitive and specific to categorically confirm or rule out the diagnosis of gluten sensitivity related disorders. Anti TTG and endomysial antibodies are specific for enteropathy but these are often undetectable in patients with neurological manifestations. In order to overcome these shortcomings, various trans-glutaminase isoenzymes have been studied. Antibodies to TG2 isoenzyme are seen with enteropathy, and can be detected in up to one third (38%) of the patients [6]. Antibodies to TG3 are associated with dermatitis and antibodies to TG6 with neurologic manifestations, but these tests are not routinely available [10]. Even small bowel biopsy in patients with celiac disease has been reported to range from a normal mucosa to gross enteropathy to a pre-lymphomatous stage [6].

Diagnosis of gluten ataxia is confirmed if there is stabilization or improvement of symptoms on a gluten free diet. Since, loss of cerebellar purkinje cells may result in irreversible damage, the duration of ataxia prior to the diagnosis, is a good predictor of response to gluten free diet. Early management increases the chances of improvement. Immunosuppressant therapy may be considered in cases with no improvement on a gluten free diet [6]. In present case, significant improvement in ataxia following a gluten free diet strongly supports the diagnosis of gluten ataxia. Disappearance of serum antibodies to gluten are the best marker of strict adherence to gluten free diet. It takes about 6-12 months for antibodies to disappear. Clinical improvement is usually seen after a year on gluten free diet and continues over 2 year period. Our patient's ataxia improved by around 40%, within 3 months of being on a gluten free diet.

CONCLUSION

Apart from enteropathy and dermatitis, neurologic manifestations can also be encountered in cases with gluten sensitivity. Gluten related neurologic dysfunction may occur with or without gastrointestinal symptoms and can be missed if it occurs in isolation. Since gluten ataxia is a potentially treatable and reversible disorder, all patients presenting with sporadic, unexplained subacute or chronic cerebellar ataxia should be tested for serological evidence of gluten sensitivity. Patients testing positive for antigliadin and anti TG antibodies, should be put on a strict gluten free diet to reduce disability and arrest further disease progression.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 02, 2015**
Date of Peer Review: **May 08, 2015**
Date of Acceptance: **Jun 15, 2015**
Date of Publishing: **Nov 01, 2015**