Gluten sensitivity and neuromyelitis optica: two case reports

S Jacob, M Zarei, A Kenton, H Allroggen

Neuromyelitis optica is a clinical syndrome characterised by acute transverse myelitis plus an acute or subacute optic neuritis with or without recovery. Although once believed to be a variant of multiple sclerosis, diagnostic criteria have recently been proposed for neuromyelitis optica, making it a clinically distinct syndrome. The term gluten sensitivity refers to a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals, as indicated by circulating antibodies to gliadin. Several neurological complications have been described associated with gluten sensitivity ranging from peripheral neuropathy and cerebellar ataxia to an increased risk of epilepsy. Although myelopathy has been described in some case reports of coeliac disease, neuromyelitis optica has never been described in association with gluten sensitivity. We describe two cases of gluten sensitivity presenting as neuromyelitis optica with no previous history of significant gastrointestinal symptoms. Gluten sensitivity was confirmed by immunological and histological studies.

Neuromyelitis optica is a recognised clinical syndrome of acute transverse myelitis and optic neuritis, the exact aetiology of which has yet to be identified. A number of neurological disorders have been described in association with coeliac disease. We report two cases of gluten sensitivity, confirmed immunologically and histologically, presenting as neuromyelitis optica without a previous gastrointestinal diagnosis.

CASE REPORTS

Case 1

A 36 year old Asian woman was referred to neurologists by the surgical team under whom she was admitted with a 1 week history of abdominal and back pain. On the day prior to referral she developed difficulty in passing urine, with tingling and sensory disturbance in her trunk and legs. She was also found to be increasingly unsteady and weak.

Close questioning revealed a band like sensation in the trunk followed by the above symptoms 1 week later. She had developed reduced visual acuity with minimal eye pain 4 weeks prior to admission. Past history was unremarkable except for an unexplained mild microcytic anaemia that was treated with iron supplements. General examination was normal. Neurological examination revealed reduced corrected visual acuity of 6/48 in the right eye and 6/30 in the left eye, with pale disc margins and normal eye movements. There were no other cranial nerve signs. She had pyramidal weakness in both legs with mildly wide based gait. A hemi-sensory level to pinprick was demonstrated below D10 on the left side with reduced left toe joint position sense.

Investigations revealed haemoglobin of 10 g/dl with MCV of 67 fl. Detailed biochemical and immunological profile including cardiolipin antibodies was normal. Serum ferritin was low at 9 mcg/l (normal values 10–150 ng/ml), confirming iron deficiency. MRI scan of the brain was normal; whole spine T2W MRI showed high signal changes from D2 to the level of the conus with very faint gadolinium enhancement. CSF showed 90 white cells (95% lymphocytes, with normal immunophenotyping) with no red cells. CSF protein was 0.8 g/l and glucose 2.5 mmol/l (serum 4.5 mmol/l). No oligoclonal bands (OCB) were detected in the CSF. Blood and CSF examination showed no evidence of mycobacteria, borrelia, CMV, EBV, syphilis, or HTLV 1. Visual evoked potentials showed delay in both optic nerves.

Coeliac screen revealed IgA anti-gliadin antibody (AGA) of 55.3 IU/l (normal <11 IU/l), IgG anti-gliadin antibody (GGA) of 27.4 (normal <11), and tissue transglutaminase antibody (TTG) of 28.6 IU/l (normal <5 IU/l). Upper GI endoscopy and biopsy revealed flat erosive gastritis, severe blunting of villi with increased intraepithelial lymphocytes, and mild crypt hyperplasia. HLA typing showed HLA-DQ2, which accounts for over 90% cases of coeliac disease.

A 5 day course of intravenous methylprednisolone was given, following which sensory, motor, and visual symptoms gradually improved. Further to the results of the coeliac screen, a gluten free diet was introduced. Repeat coeliac screen (table 1) and spinal MRI 10 weeks later showed marked improvement. She was readmitted 6 months later with a recurrence of transverse myelitis. The MRI spine revealed new longitudinal high signal changes from C8 level. Repeat investigations including CSF examination returned findings similar to those of the first admission. It is interesting to note that there was an increase in the titres of anti-gliadin antibodies during this admission (table 1), in spite of an apparently gluten free diet. Again, she improved after a course of intravenous steroids and is currently making good progress in rehabilitative care.

Case 2

A 30 year old, right handed Asian woman was admitted following a 3 week history of progressive neck, back, and interscapular pain ushered in by a rapidly progressive ascending numbness and weakness of the limbs associated with urinary retention.

Just over a year prior to the present admission, she had suffered from left optic neuritis. The following investigations were then normal or negative: gallium scan, serum and CSF ACE levels, CSF OCB, and detailed autoimmune profile. Gluten antibodies were not measured at that time. Brain MRI was entirely normal except for a swollen optic nerve on the left that was seen to be atrophied on subsequent MRI scans. Intravenous methylprednisolone (1 g) was given for 3 days with no clinical improvement. Seven years previously, the patient had been investigated for transient self limiting jaundice for which no cause was found, while 15 years ago she had been given a diagnosis of irritable bowel syndrome. Other aspects of the history including family history were unremarkable.

Abbreviations: AGA, IgA anti-gliadin antibody; GGA, IgG anti-gliadin antibody; TTG, tissue transglutaminase antibody
General examination was normal. Cranial nerves were intact except for marked left optic atrophy with relative afferent pupillary defect. Corrected visual acuity was 6/6 on the right and 1/60 on the left. The patient had severe pyramidal weakness in all limbs, which was particularly marked in the right leg. Deep tendon reflexes were pathologically brisk, but plantar responses were flexor. She had a sensory level at D2 for pinprick.

MRI of the whole spine with gadolinium showed an extensive panmyelitis with swelling of the cord and diffuse high signal extending from the medulla to the conus medullaris with several areas of patchy contrast enhancement and focal low signal on T1, suggesting focal necrosis (fig 1A). Brain MRI was entirely normal.

CSF examination showed an inflammatory pattern with high protein (1.86 g/l) and pleocytosis (496, 75% lymphocytes). Further investigations in search of an inflammatory/infective cause were unremarkable. Extensive biochemical and immunological investigations including antineuronal antibodies were normal or negative. However ESR was slightly raised (28 mm/h). Chest, abdomen, and pelvic CT scan were normal. Screening tests for gluten sensitivity showed AGA of 143 IU/l (normal value <11 IU/l); GGA, IgG anti-gliadin antibodies (normal value <11 IU/l); TTG, tissue transglutaminase (normal value <5 IU/l).

The patient received intravenous methylprednisolone (1 g daily for 3 days), followed by a reducing dose of prednisolone over 5 weeks, with significant clinical improvement. MRI scans 1 and 2 months later (fig 1B and C, respectively) showed decreased cord swelling and reduction of high signal changes throughout the cord with no appreciable enhancement. Repeat coeliac screening tests showed remarkable improvement (table 1). We have been informed by her rehabilitation team that the patient suffered another relapse whilst under their care. She had not been very compliant with the gluten free diet and has since been commenced on azathioprine. Anti-gliadin antibody titres were not measured during this relapse.

**DISCUSSION**

Neuromyelitis optica was initially described by Eugene Devic and Fernand Gault in the late 19th century. Initial reports considered neuromyelitis optica to be a variant of multiple sclerosis, but more recent case series have suggested distinct clinical, CSF, and MRI findings and new diagnostic criteria (table 2). The predominant involvement of optic nerves and spinal cord with relative sparing of the cerebral white matter, more severe attacks, longitudinally extensive spinal MRI lesions, CSF pleocytosis, and the absence of CSF oligoclonal bands appear to distinguish neuromyelitis optica from multiple sclerosis. Neuromyelitis optica can remain a monophasic illness or evolve into a multiphasic pattern with recurrent relapses. Both our cases fulfil the diagnostic criteria for neuromyelitis optica proposed by previous authors.

Specific aetiological causes of neuromyelitis optica have not been identified, although connective tissue disorders, tuberculosis, and acute disseminated encephalomyelitis have been associated with it.

**Table 1** Response of gluten antibodies to treatment

<table>
<thead>
<tr>
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<th>Case 1</th>
<th>Case 2</th>
<th>Case 2</th>
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<tbody>
<tr>
<td></td>
<td>Week 1 Week 2 Week 12 Relapse Week 1 Week 4 Week 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGA, IU/l</td>
<td>55.3</td>
<td>42.5</td>
<td>16.3</td>
</tr>
<tr>
<td>GGA, IU/l</td>
<td>27.4</td>
<td>11.8</td>
<td>8</td>
</tr>
<tr>
<td>TTG, IU/l</td>
<td>28.6</td>
<td>27.2</td>
<td>9.6</td>
</tr>
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</table>

AGA, IgA anti-gliadin antibodies (normal value <11 IU/l); GGA, IgG anti-gliadin antibodies (normal value <11 IU/l); TTG, tissue transglutaminase (normal value <5 IU/l).

**Table 2** Diagnostic criteria for neuromyelitis optica

<table>
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<tr>
<th>Absolute criteria</th>
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<tr>
<td>Optic neuritis</td>
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<tr>
<td>Acute myelitis</td>
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<tr>
<td>No evidence of clinical disease outside optic nerve or spinal cord</td>
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<tr>
<td>Supportive criteria</td>
<td></td>
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<tr>
<td>Major</td>
<td></td>
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<tr>
<td>Negative brain MRI at onset</td>
<td></td>
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<tr>
<td>Spinal MRI with signal abnormalities &gt;3 vertebral segment lengths</td>
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<tr>
<td>CSF pleocytosis &gt;50 cells/mm³ or &gt;5 neutrophils/mm³</td>
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<tr>
<td>Minor</td>
<td></td>
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<tr>
<td>Bilateral optic neuritis</td>
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<tr>
<td>Severe optic neuritis with visual acuity worse than 6/60 in at least one eye</td>
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<tr>
<td>Severe, fixed, attack related weakness (MRC grade &lt;2) in one or more limbs</td>
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Diagnosis requires all absolute criteria and one major or two minor supportive criteria.

![Figure 1](http://jnnp.bmj.com/)

T2W MRI images of cervical and thoracic spinal cord at the time of presentation (A) and 1 (B) and 2 months (C) after treatment with intravenous methylprednisolone. The scans show that high signal changes and severe cord oedema seen in the initial scan improved within the next 2 months. These radiological changes were matched by clinical improvement of the patient.
Neurological complications are a recognised, though controversial and relatively unusual manifestation of established coeliac disease, occurring in 6–10% of cases. The initial case series was published on 16 adults with established coeliac disease. However, neurological symptoms and in particular ataxia, may be the presenting manifestation of gluten sensitivity. Other neurological disorders associated with coeliac disease include peripheral neuropathy, myopathy, myoclonus, cerebral atrophy and dementia, cerebral vasculitis, brain stem encephalitis, and an increased risk of epilepsy (usually associated with cerebral calcifications). Neurological manifestations were initially thought to be due to nutritional deficiencies secondary to malabsorption, but they are now being increasingly thought of as an autoimmune phenomenon due to gliadin antibodies.

The histopathological changes of coeliac disease have been categorised into three types. Marsh type I includes infiltrative lesions, type II includes infiltrative and hyperplastic lesions, and partial sub (total) villous atrophy constitutes type III. Our two patients had type III and type I, respectively, on histology.

Myelopathy has been rarely described in association with coeliac disease. Cooke and Smith found that nine out of 16 patients with clinical evidence of adult coeliac neuropathy had myelopathic changes on histopathological examination. The changes were described as spongiform or non-spongiform demyelination of the posterior and posterolateral columns, with variable axonal degeneration sometimes resembling motor neuron disease. At that time this was believed to be due to subacute combined degeneration (though there was no evidence of vitamin B12 deficiency) or Wallerian degeneration. Interestingly, all these patients had lower motor neuron signs in the form of reduced reflexes and flexor plantars.

Neuromyelitis optica (Devic’s syndrome) has not been described as a major neurological manifestation in coeliac disease. We believe that our two cases are the first to be described with gluten sensitivity. Since gluten sensitivity is relatively common, it would be difficult to prove causation of a relatively rare neurological syndrome. Serial measurements of TTG and IgA anti-gliadin antibodies in both patients showed a decrease in levels following a course of intravenous methylprednisolone and the introduction of a gluten free diet. In the first patient, these titres rose at the time of first relapse (table 1), suggesting that there may be a causative association. (The most common reason for a rise in antibodies is non-adherence to a gluten free diet.) These cases highlight the importance of coeliac screening in cases of unexplained transverse myelitis and optic neuritis. Although both our cases had subtle pointers in the past history towards coeliac disease (iron deficiency anaemia and irritable bowel syndrome), this was never diagnosed.

Both our cases demonstrated the HLA types linked with coeliac disease, with some similarity to the HLA types linked with Devic’s syndrome (HLA-DRB1*0802, PB1*0501, DPB1*0202).

We suggest that patients who present with myelitis with or without optic neuritis should, as part of their work up, also be investigated for possible gluten sensitivity in order to explore this association further.

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