

# Association of Multiple Sclerosis and Celiac Disease: Case Report

## Multipl Skleroz ve Çölyak Hastalığı Birlikteliği

İrem Fatma ULUDAĞ, MD,<sup>a</sup>  
Uğur KULU, MD,<sup>a</sup>  
Ufuk ŞENER, MD,<sup>a</sup>  
Yaşar ZORLU, MD,<sup>a</sup>  
Işın GÖKÇÖL ERDOĞAN, MD<sup>b</sup>

Departments of  
<sup>a</sup>Neurology  
<sup>b</sup>Biochemistry  
Izmir Tepecik Training and  
Research Hospital, İzmir

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Yazışma Adresi/Correspondence:  
İrem Fatma ULUDAĞ, MD  
Izmir Tepecik Training and  
Research Hospital,  
Department of Neurology, İzmir,  
TÜRKİYE/TURKEY  
fatmairem@yahoo.com

**ABSTRACT** The association of multiple sclerosis and celiac disease is recently described in case reports although clinical significance of this association is not clear, and it is difficult to decide whether observed neurologic abnormalities originate due to celiac disease itself or suspected accompanying multiple sclerosis. The association of multiple sclerosis and celiac disease, if present may be due to a common genetic or autoimmune basis. Our case is a 16-year-old male who developed celiac disease 2.5 years after the diagnosis of multiple sclerosis. Duodenal biopsy was positive and the patient responded well to the gluten-free diet.

**Key Words:** Celiac disease; multiple sclerosis; demyelinating autoimmune diseases, CNS; autoimmune diseases

**ÖZET** Multipl skleroz ve çölyak hastalığı birlikteliği son dönemlerde olgu sunuları ile tanımlanmış ise de bu birlikteliğin klinik önemi belirlenmemiştir. Ayrıca bu olgulardaki nörolojik bulguların çölyak hastalığından mı yoksa eşlik edebileceği düşünülen multipl sklerozdan mı kaynaklandığını belirlemek oldukça güçtür. Eğer çölyak hastalığı ve multipl skleroz tesadüfün ötesinde bir sıklıkta birlikte görülüyorsa bu durum ortak bir genetik veya otoimmün zemini yansıtıyor olabilir. Bu yazıda, klinik ve laboratuvar açıdan multipl skleroz tanısı aldıktan 2.5 yıl sonra çölyak hastalığı gelişen 16 yaşında bir erkek olgu ele alınacaktır. Duodenal biyopsisi pozitif olan hastanın glutensiz diyetle olumlu cevap verdiği gözlenmiştir.

**Anahtar Kelimeler:** Çöliak hastalığı; multipl skleroz; otoimmün demiyelinizan hastalıklar, CNS; otoimmün hastalıklar

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Celiac disease (CD) is an immune mediated, inflammatory intestinal disease triggered by gluten proteins.<sup>1</sup> Recently, white matter lesions have been described in CD patients with headache in brain magnetic resonance imaging (MRI).<sup>2,3</sup> It is suggested that these white matter lesions are “multiple sclerosis like diseases”<sup>2,3</sup> and that there can be an association between CD and multiple sclerosis (MS). To further investigate this observation, small intestine biopsy studies were carried out in patients with MS; yet no symptoms that could be associated with CD were found.<sup>4</sup> Nevertheless, in patients who were diagnosed with CD years after the diagnosis of MS, it was still considered that the association of MS and CD could represent not a coincidence but a common autoimmune or genetic

basis.<sup>2,5</sup> However it is difficult to conclude whether observed neurologic abnormalities originate celiac disease itself or due to suspected accompanying MS.

During the course of MS, the reported case was observed to have gastrointestinal symptoms which suggested an association with CD. The aim of this paper is to emphasize the association of MS and CD with our case in whom there is not only nonspecific white matter lesions which can be seen in CD, but more specific lesions concordant with MS.

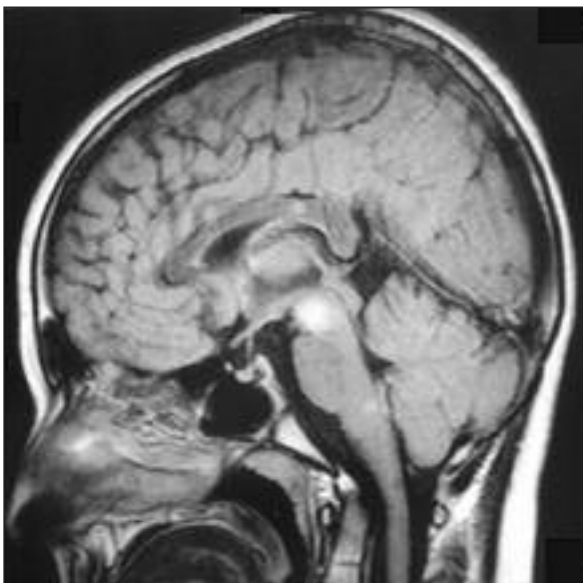
### CASE REPORT

The 16-year-old male patient presented with right arm and leg numbness, diplopia and dizziness to İzmir Tepecik Training and Research Hospital Neurology Clinic in May 2008. He was hospitalized for further investigations and an informed consent was obtained. His history revealed that the patient was first hospitalized in September 2004 in the pediatrics clinic of the hospital after he complained for numbness in the right arm and leg. He was diagnosed with MS according to Mc Donalds criteria<sup>6</sup> and received 1000 mg/day methylprednisolone for 10 days (Figure 1a and 1b). Although his weakness in his right arm and leg had improved almost completely, he again started to complain about the

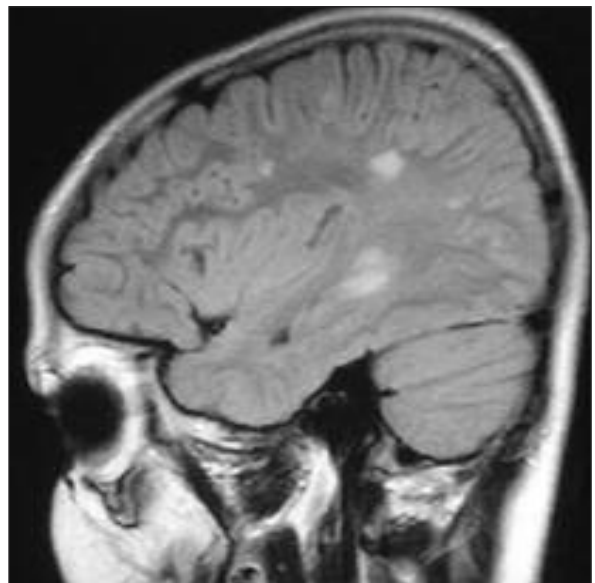
same problem in March 2005. In brain MRI there was no new or contrast enhancing lesions and the patient did not receive any treatment. The weakness in the right arm and leg improved spontaneously within 10 days. In January 2007, the patient consulted to the pediatric gastroenterology clinic of the hospital due to complaints of stomach ache and odorous, foamy, and dark colored diarrhea accompanied by weight loss of 18 kilograms in three months. He was diagnosed with CD by intestinal biopsy, and serum immunological markers. He was put on a gluten-free diet he benefited significantly.

The patient had no remarkable previous medical problems other than CD and MS. In the family history of the patient was unremarkable.

When admitted to our clinic in May 2008, the general physical examination of the patient was normal. In the neurological examination, there was slight right hemiparesis, the tendon reflexes were hyperactive in both lower extremities and the plantar response was extensor on the left. There was no other pathologic neurologic examination findings. Complete blood count, routine serum biochemistry analysis and erythrocyte sedimentation rate were normal. In the brain MRI, contrast enhancing lesions were found (Figure 2a, 2b and 2c). Cervical



A



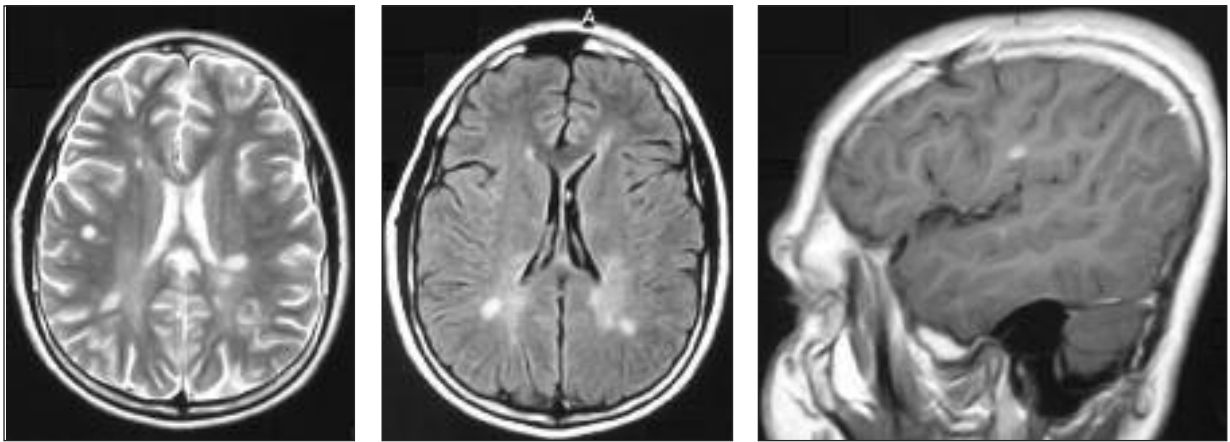
B

**FIGURE 1:** Fluid attenuated inversion recovery magnetic resonance imaging of the brain in sagittal plane demonstrates brain stem, callosal (A) and cerebral (B) multiple sclerosis lesions.

and thoracic MRI were normal. Cerebrospinal fluid was not studied. Thyroid function tests, vitamin B12, folic acid, anti-streptolysine O, C-reactive protein, angiotensin converting enzyme, Lyme immunoglobulin M and immunoglobulin G antibody levels were normal. Anti-tissue transglutaminase (tTG) immunoglobulin A (<2) was negative, anti-gliadin antibody (AGA) level was 1/160 and anti-endomysial antibody (EMA) level was 1/60. Peak P100 latency of the visual evoked potentials was delayed, but the amplitude was normal. In gastrointestinal system (GIS) endoscopy, there was grade A esophagitis. In the hematoxylin-eosin stained duodenal biopsy preparation examined under x10 (Figure 3a) and x40 (Figure 3b) magnification, no

significant changes were seen in mucosal crypts or villous architecture. Mild lymphoplasmocytic cell infiltration was observed in lamina propria and marked lymphocyte infiltration was seen in surface epithelium. Staining with CD3 marker under x40 magnification revealed these characteristics more clearly (Figure 3c). These findings were consistent with Type 1 CD according to Marsh criteria.<sup>7</sup>

In his last admission to our clinic, the patient's acute MS attack was treated with daily 1000 mg methylprednisolone for 10 days. Right hemiparesis improved but the patient experienced another MS relapse with the same clinical features after three months and started to have immunomodulator therapy.



**FIGURE 2:** Brain magnetic resonance imaging in T2 weighted (A), fluid attenuated inversion recovery (B) and post contrast (C) sequences. In T2 weighted (A) and fluid attenuated inversion recovery (B) sequences, periventricular and right parietal lesions are seen, and in post contrast T1 sequence gadolinium enhancement in the right parietal lesion are seen.



**FIGURE 3:** In the hematoxylin-eosin stained duodenal biopsy preparation examined under x10 (3a) and x40 (3b) magnification and x40 times magnification following CD3 marker (3c). Intraepithelial lymphocyte infiltration in mucosa with normal villous and epithelial architecture (3a), lymphoplasmocytic cell infiltration in lamina propria and marked lymphocyte infiltration in surface epithelium (3b) are seen. In the examination following the CD3 marker under x40 magnification, these characteristics were seen more clearly (3c).

## DISCUSSION

Celiac disease is a gluten sensitive enteropathy. The mean prevalence is 0.5-1% in the general population. It's main target is the small intestine, but different systems can also be involved. CD is a T cell mediated autoimmune disease. It can start at any age and is three times more frequent in women. The initial symptom is diarrhea in 50% of adults. Weight loss, hypoalbuminemia and edema, hypocalcaemia, vitamin deficiency, osteomalacia, blood and bone anomalies are other possible symptoms. Neurological involvement is seen in 6-10% of the adults with CD. Among the most common neurological problems associated with CD are peripheral neuropathy, cerebellar ataxia, epilepsy, dementia, multiple sclerosis, neuromyelitis optica and migraine.<sup>8,9</sup> Depression and other psychiatric symptoms have also been reported as common complications of CD occurring in about one third of patients. Common symptoms include apathy, excessive anxiety and irritability.<sup>8</sup> Neurological symptoms may be related to metabolic, genetic, immunologic and nutritional factors.<sup>8</sup>

In CD, several antibodies can be measured such as AGA, anti-EMA, anti-tTG and anti-reticulon (ARA).<sup>10</sup> The improvement with gluten-free diet and the abnormalities in the small intestine biopsy are diagnostic. In the small intestine biopsy, the pathology of the disease can range from infiltrative lesions characterized by increased intraepithelial lymphocytes with normal architecture to a completely flat mucosa.<sup>1</sup> The Marsh classification, as modified by Oberhuber and colleagues, is used to grade the severity of these lesions.<sup>11</sup> Villi atrophy is reported in other disorders, and diagnosis of celiac disease is, therefore, confirmed only by clinical symptoms, a positive serology, or histological improvement after commencement of a gluten-free diet.<sup>1</sup>

The prevalence of other autoimmune diseases is also high in CD. Among these are insulin dependent diabetes mellitus, thyroid diseases, Sjögren syndrome, Addison disease, autoimmune liver diseases and

cardiomyopathy.<sup>10</sup> For these associations, the genetic tendency related to the human leukocyte antigens and CD itself as an etiologic factor for the autoimmune diseases have been blamed.<sup>10</sup> When CD is observed together with other autoimmune diseases, first the symptoms of the other autoimmune disease are seen in the patient. Within this period, CD which does not show any clinical symptom is named as "silent CD".<sup>2,3</sup> The autoimmune disease accompanying CD improve with a gluten-free diet.<sup>2,3</sup>

Multiple sclerosis and CD are both Th1 mediated diseases and recent data suggest that a defect in a regulatory T cell subset (CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T cells) is involved in the pathogenesis of both diseases.<sup>12-14</sup> However there is little information about the frequency of CD in MS and it has been reported that the jejunal biopsies are normal in patients with MS.<sup>4</sup> In 2008, Ferro et al.<sup>5</sup> reported a case of MS having headache complaints first, and later diagnosed as "silent CD". Pengiran Tengah et al.<sup>3</sup> published two cases having white matter lesions like MS in brain MRI without any cerebrospinal fluid oligoclonal band positivity and the patients were later diagnosed "silent CD". Hadjivassiliou et al found that 10 patients who had brain white matter lesions but not diagnosed with MS. The patients responded to low gluten diet in different levels, and three of these patients were diagnosed with CD.<sup>2</sup> Kieslich et al.<sup>15</sup> observed focal white matter lesions in the brain MRI of 20% of the children who had CD diagnosis and neurologic involvement.<sup>15</sup>

Our patient's first gastrointestinal symptom occurred two years after the diagnosis of MS. Similarly in previously reported cases, CD, when accompanied by another autoimmune disease, is generally "silent" for a time period. The difference of this case from previously reported ones is that, there is not only focal white matter lesions but more importantly the definitive diagnosis of MS. Additionally, our aim is to emphasize that this case of MS coexistent with CD can point out a tendency to Th1 mediated diseases and MS patients with gastrointestinal symptoms should be investigated with further blood survey tests.

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