

# Brain White-Matter Lesions in Celiac Disease: A Prospective Study of 75 Diet-Treated Patients

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**ABSTRACT.** *Objective.* Celiac disease (CD), or gluten sensitivity, is considered to be a state of heightened immunologic responsiveness to ingested gluten proteins in genetically predisposed individuals. The gastrointestinal manifestation suggests a severe enteropathy of the small intestine with malabsorption, steatorrhea, and weight loss because of a deranged mucosal immune response. Neurologic complications occur, especially epilepsy, possibly associated with occipital calcifications or folate deficiency and cerebellar ataxia. There have been reports of brain white-matter lesions as an extraintestinal manifestation in Crohn disease and ulcerative colitis but not in CD.

*Methods.* In this study, 75 diet-treated mainly pediatric patients with biopsy-proven CD underwent prospectively clinical neurologic examinations, laboratory investigations, electroencephalography, computed tomography, and magnetic resonance imaging. The age range was 2.8 to 24.2 years with a mean of 11.6 years. The mean period of gluten exposure was 2.4 years.

*Results.* Ten patients had neurologic findings such as febrile seizures, single generalized seizures, mild ataxia, and muscular hypotonia with retarded motor development. No folate deficiency was found. The hippocampal regions showed no abnormalities. Computed tomography did not reveal any cerebral calcifications, but magnetic resonance imaging detected unilateral and bilateral T2-hyperintensive white-matter lesions in 15 patients (20%). There was no correlation between these lesions and dietary compliance or neurologic or electroencephalographic abnormalities. The mean gluten exposure time of these patients was slightly increased (not significant).

*Conclusions.* Focal white-matter lesions in the brain may represent an extraintestinal manifestation of CD. They may be ischemic in origin as a result of a vasculitis or caused by inflammatory demyelination. They seem to be more typical of pediatric CD than cerebral calcifications. Their prognostic value is unclear and needs to be elucidated in additional studies. CD should be suggested as a differential diagnosis in children with unclear white-matter lesions even without intestinal symptoms. *Pediatrics* 2001;108(2). URL: <http://www.pediatrics.org/cgi/content/full/108/2/e21>; celiac disease, neurologic complications, brain white-matter lesions, child.

ABBREVIATIONS. CD, celiac disease; EEG, electroencephalography;

CT, computed tomography; MRI, magnetic resonance imaging; AU, arbitrary units.

Celiac disease (CD), or gluten sensitivity, is considered to be a state of heightened immunologic responsiveness to ingested gluten proteins in genetically predisposed individuals. The gastrointestinal manifestation implies a severe enteropathy of the small intestine with malabsorption, steatorrhea, and weight loss associated with characteristic lesions of the small bowel mucosa, which improve after withdrawal of gluten from the diet. It often is associated with the presence of antiendomysial and antigliadin antibodies. The pathologic mucosal immune response has a background of genetic susceptibility. Investigations showed that 70% to 100% of monozygotic twins and 10% of first-degree relatives are concordant for the disease.<sup>1-3</sup> There is a strong genetic association with the human leukocyte antigen types DQ8 and DQ2 (DQA1 0501 and QQB1 0201 arranged either in cis or trans).<sup>4</sup> Neurologic complications occur in approximately 8% to 10% of adults with CD.<sup>5</sup> These include epilepsy, associated particularly with occipital calcifications and folate deficiency; cerebellar ataxia; peripheral neuropathy; myositis; neuromyotonia; myasthenic syndrome; myelopathy; and dementia accompanied by brain atrophy in adults.<sup>6-10</sup> The aim of this study was to investigate the spectrum, incidence, and risk factors of neurologic involvement of CD in a mainly pediatric cohort.

## METHODS

Seventy-five diet-treated patients who attended the pediatric outpatient clinic of Frankfurt University between 1997 and 1999 were enrolled in this prospective study. The age range was 2.8 to 24.2 years with a median of 10.7 years and a mean of 11.6 years (standard deviation: 5.13). Informed consent was obtained from the patients or their parents. For all patients, the diagnosis was based on biopsies of the small intestine combined with gluten exposition. Fifty-two female patients (69%) and 23 male patients (31%) underwent clinical neurologic examination, laboratory investigation, electroencephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI). Medical history concerning concomitant diseases and perinatal problems was evaluated. The quality of dietary compliance was analyzed by a questionnaire, confirmed by the presence of gliadin antibodies (IgA) and classified into 3 groups: 1) good: no dietary mistakes, 2) moderate: 1 or 2 dietary mistakes per week, or 3) poor: more than 2 dietary mistakes per week. IgA were measured in arbitrary units (AU) by the gluten-IgA-enzyme immunometric assay (Pharmacia, Erlangen, Germany). The gluten exposure time was defined as age at diagnosis minus the age at the beginning of gluten-containing nutrition plus the time of diagnostic gluten exposition. EEG re-

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Received for publication Dec 20, 2000; accepted Apr 9, 2001.

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cording was performed with a 12-channel model (Schwarzer model E, Muenchen, Germany) with standardized program, photostimulation, and hyperventilation for 30 minutes. For CT, a Somatom plus (Siemens, Erlangen, Germany) was used and included 20 slices of 5 mm to 8 mm thickness. MRI was done with a 1.5 Tesla Magnetom Impact (Siemens) and included axial T1 and T2 spin echo sequences, as well as inversion recovery sequences with water suppression (fluid attenuated inversion recovery) of 6 mm. The temporal lobes were examined by additional coronary slices of 3 mm, with particular emphasis on the hippocampus.

## RESULTS

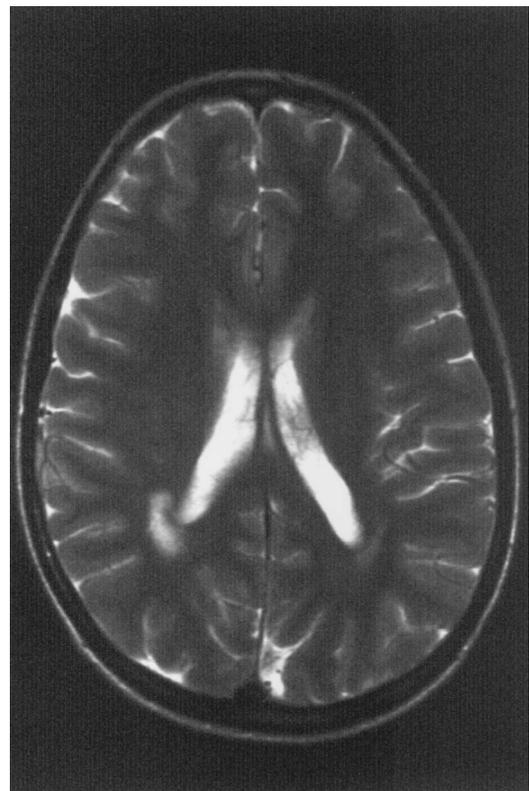
Seventy-three percent of the patients had good dietary compliance, 15% had moderate compliance, and 12% had poor compliance. Patients with poor dietary compliance showed lower iron (mean: 69.38  $\mu\text{g}/\text{dl}$ ) and ferritin (mean: 25.44 ng/ml) blood levels than patients with good (mean iron: 80.65  $\mu\text{g}/\text{dl}$ ; mean ferritin: 32.86 ng/ml) or moderate (mean iron: 85.18  $\mu\text{g}/\text{dl}$ ; mean ferritin: 29.94 ng/ml) dietary compliance. There were no differences concerning the transaminases (glutamate-oxalacetate-transaminase and glutamate-pyruvate-transaminase) in the different compliance groups. IgA levels were increased in the poor dietary compliance group (mean: 9.71 AU) compared with the good (mean: 7.45 AU) and moderate (mean: 7.78 AU) compliance groups. There was no folate deficiency in the whole cohort, and there were no compliance-related differences. The mean age at the first gluten exposure was 5.2 months. The age at diagnosis varied between 3 months and 15 years; 71% had their illness diagnosed during the first 2 years. The gluten exposure time ranged between 1 month and 15.2 years with a median of 1.2 years and a mean of 2.4 years. Analysis of the comorbidity revealed 2 patients with cystic fibrosis, 1 with diabetes mellitus (type I), 1 with autoimmune thyroiditis, 1 with thalassemia minor, 1 with alcoholic embryopathy, 1 with asphyxia at birth, and none with prematurities.

Ten (13%) of 75 children had neurologic symptoms or anamnestic seizures (Table 1); 3 had febrile seizures, 2 had single generalized seizures, and 1 had a typical absence epilepsy. Two patients had a mild ataxia, and another 2 had muscular hypotonia and mild statomotor retardation. One of them had a history of asphyxia associated with a periventricular leukomalacia on MRI; the other had unknown cause and normal MRI. Their dietary compliance was good in 7 and poor in 3 patients. Their mean gluten exposure time was 1.8 years and was not elevated in comparison with the whole group.

In 12 female patients, the EEG showed low-grade general slowing. Two patients had centrotemporal

sharp waves, and 1 girl with typical absence epilepsy showed a typical 3/sec spike wave pattern. The EEG findings showed no correlation with length of gluten exposure or dietary compliance.

CT showed abnormalities in 3 patients: 1 periventricular leukomalacia, 1 astrocytoma-like lesion of the quadrigeminal plate, and 1 biparietal periventricular hypodensity. Cerebral calcifications were not observed. MRI detected the quadrigeminal plate lesion in one patient and an asymptomatic pineal cyst in another patient. The hippocampal regions showed no abnormalities. Including the girl with the CT finding of periventricular hypodensities, MRI revealed unilateral or bilateral white-matter lesions of different degrees of intensity, varying between smaller spot and larger flat lesions, in 15 patients (20%). These lesions were hyperintense in T2 and fluid attenuated inversion recovery sequences and showed biparietal and left-sided predominance (Figs 1 and 2). The localization was biparietal/occipital in 8, uniparietal left in 5, frontal in 1, and uniparieto-temporo-occipital right in 1 patient. These 15 patients—10 girls and 5 boys—had a mean age of 11.6 years, representing identically the mean age of all 75 patients. Unfortunately, none of these 15 patients had a comparable previous MRI. In 1 patient, the MRI lesions were accompanied by an anamnestic generalized seizure; in another girl, they were accompanied by a typical absence epilepsy (Table 1) with a 3/sec spike wave pattern. Three had minor EEG findings (2 low-grade general slowings, 1 centrotemporal sharp waves). None of them had neurologic symptoms at examination or a history of peri-



**Fig 1.** Larger bilateral periventricular white-matter lesions (T2 spin-echo sequence).

**TABLE 1.** Neurologic Findings and White-Matter Lesions

Finding	Patients	White-Matter Lesions
Febrile seizures	3 (30%)	0
Single generalized seizures	2 (20%)	1
Typical absence epilepsy	1 (10%)	1
Mild ataxia	2 (20%)	0
Muscular hypotonia and statomotor retardation	2 (20%)	0
Total	10 (100%)	2

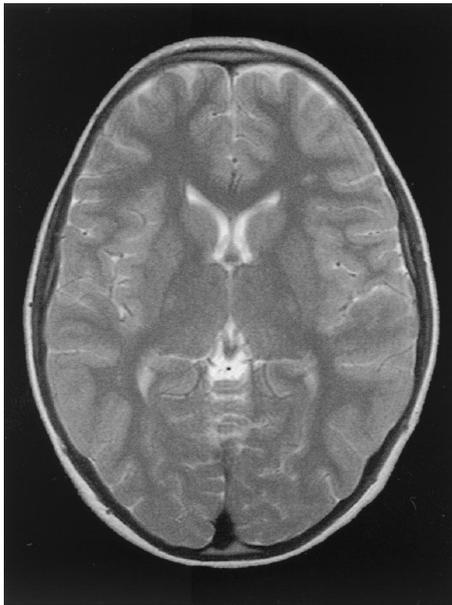


Fig 2. Small spot lesion in the left frontal white matter (T2 spin-echo sequence).

natal problems such as prematurity or asphyxia. There was no correlation between the occurrence of these lesions and the dietary compliance (10 had good, 2 had moderate, and 3 had poor dietary compliance). The mean gluten exposure time of these 15 patients was slightly increased (2.69 years; median: 1.8 years) in comparison with the 60 patients without periventricular lesions (2.35 years; median: 1.2 years). The incidence of white-matter lesions in 62 patients with a gluten exposure time of <4 years was 17.4%; in the 13 patients with a gluten exposure time of more than 4 years, the incidence was higher (30.1%). Using Fisher-Yates exact test statistical evaluation revealed no significance ( $P = .445$ ).<sup>11</sup>

### DISCUSSION

Neurologic complications of CD have been known for a long time as a consequence of vitamin deficiency (B<sub>12</sub>, E, D, folic acid, pyridoxine). Today, CD is diagnosed earlier and severe malabsorption is rare. Nevertheless, neurologic symptoms are found in intestinal symptomatic as well as in intestinal asymptomatic CD. Hadjivassiliou et al<sup>12</sup> found positive antigliadin antibodies as a marker of gluten sensitivity in a high proportion (57%) of patients with undiagnosed neurologic diseases, especially patients with ataxia and peripheral neuropathy, in a general neurology outpatient clinic. The frequency of proven CD in this group was 16%. It was suggested that gluten sensitivity should be considered as a state of heightened immunologic T- and B-lymphocyte-based responsiveness to ingested gluten proteins in genetically predisposed individuals.<sup>13</sup> The brain seems to be particularly vulnerable.

In patients with established CD, epilepsy, with an incidence of 1% to 6%, is the most frequent neurologic complication, often associated with bilateral occipital calcifications.<sup>7-9</sup> Additional complications such as cerebellar ataxia or peripheral neuropathy

are very rare in childhood.<sup>9,10,14</sup> In our study, we found 2 patients with mild ataxia (0.03%) and 6 with seizures (0.08%), but these seizures were in 3 instances of anamnestic febrile seizures and 1 of typical absence epilepsy, unlikely to be linked to CD. Occipital calcifications were not observed. As to our 15 patients with white-matter lesions, similar, mostly symptomless, lesions have been described in inflammatory bowel diseases. Lesions were observed in 42% of 48 adult patients with Crohn disease and in 46% of 24 adult patients with ulcerative colitis versus an incidence of 16% in the control group.<sup>15</sup> Unfortunately, there are no available age-matched data concerning periventricular white-matter lesions in nonceliac children. A case of progressive leukoencephalopathy with fatal course in an adult with CD was described by Beyenburg et al,<sup>16</sup> but mostly symptomless white-matter lesions have not been described in CD.

White-matter lesions may represent an extraintestinal manifestation of the underlying autoimmune process. They may be ischemic in origin, as a result of a vasculitis, or caused by inflammatory demyelination. In this context, reports of multiple sclerosis in patients with inflammatory bowel disease are of special interest.<sup>17-19</sup> They may represent an extreme form of cerebral vulnerability to the underlying autoimmune process.

### CONCLUSION

Brain white-matter lesions seem to be more typical of pediatric CD than of cerebral calcifications. They occurred without specific neurologic symptoms and were independent of dietary compliance or gut symptoms. The duration of gluten exposure may be important, but the correlation in this series was not significant. Risk factors of these lesions and their prognostic value are unclear and need to be elucidated in additional studies. CD should be suggested as a differential diagnosis in children with unclear white-matter lesions even without intestinal symptoms.

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