# Cognitive Impairment and Celiac Disease

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**Objective:** To characterize the clinical, radiological, and electrophysiological laboratory profiles and histological features of patients who developed cognitive impairment temporally associated with celiac disease.

**Design:** Case series.

**Setting:** Referral center.

**Patients:** Patients with the onset of progressive cognitive decline within 2 years of symptomatic onset or with a severe exacerbation of biopsy-proved adult celiac disease were identified from the Mayo Clinic medical records from January 1, 1970, to December 31, 2005. Patients were excluded if an alternate cause of their cognitive impairment was identified.

**Results:** Thirteen patients (5 women) were identified. The median age at cognitive impairment onset was 64 years (range, 45-79 years), which coincided with symptom onset or exacerbation of diarrhea, steatorrhea, and abdominal cramping in 5 patients. Amnesia, acalculia, confusion, and personality changes were the most common presenting features. The average initial Short Test of Mental Status score was 28 of a total of 38 (range, 18-34), which was in the moderately impaired range. The results of neuropsychological testing suggested a trend of a frontosubcortical pattern of impairment. Ten patients had ataxia, and 4 of them also had peripheral neuropathy. Magnetic resonance imaging of the head showed nonspecific T2 hyperintensities, and electroencephalography showed nonspecific diffuse slowing. Deficiencies in folate, vitamin $B_{12}$, vitamin E, or a combination were identified in 4 patients, yet supplementation did not improve their neurological symptoms. Three patients improved or stabilized cognitively with gluten withdrawal. A detailed histological analysis revealed nonspecific gliosis.

**Conclusions:** A possible association exists between progressive cognitive impairment and celiac disease, given the temporal relationship and the relatively high frequency of ataxia and peripheral neuropathy, more commonly associated with celiac disease. Given the impact for potential treatment of similar cases, recognition of this possible association and additional studies are warranted.

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CELIAC DISEASE (CD) IS A multiorgan systemic disease that most commonly affects the gut but also affects other organs, especially the skin. Up to 10% of patients with CD and gastrointestinal symptoms have otherwise unexplained neurological symptoms,[1] and neurological involvement of CD is one proposed cause. Neurological symptoms can occur at or near the onset of gastrointestinal complaints in patients newly diagnosed as having adult-onset CD or may occur during adulthood in patients with childhood-onset CD. Ataxia, peripheral neuropathy, and seizures are neurological complications most commonly associated with CD.[2,3] Dementia temporally associated with adult-onset CD has only been previously reported in 6 patients,[4,5] with additional cognitive impairment reported in 7 others,[2,6,7] and the association between cognitive deficits and adult-onset CD remains contentious. We identified 13 patients from our institution's medical records who had close temporal onset of gastrointestinal symptoms and cognitive impairment associated with CD. Herein, we review the clinical features, laboratory findings, magnetic resonance imaging (MRI) results, electroencephalographic (EEG) results, neuropsychological profiles, and clinical outcomes of these patients, who all had biopsy-proved CD and otherwise unexplained cognitive impairment. We also perform detailed neuropathological analysis on 5 patients who either underwent a brain biopsy or a postmortem examination.

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## METHODS

### CLINICAL FINDINGS

Mayo Clinic medical records from January 1, 1970, to December 31, 2005, were electronically searched using terms for CD (*celiac disease*, *celiac sprue*, *nontropical sprue*, and *gluten-sensitive enteropathy*) and encephalopathy (*cognitive impairment*, *dementia*, and *encephalopathy*). Fifty patients for whom both search terms matched were identified. The historical records of all 50 patients were reviewed to exclude all patients without biopsy-proved CD or patients in whom an alternate cause of dementia was identified. Patients were excluded if they fulfilled the diagnostic criteria for delirium as specified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*.[8] Eighteen patients met the

**Table 1. Clinical Characteristics of Patients With CD and Cognitive Impairment**

| Patient No./Sex | Age at Cognitive Decline, y | Dementia Features | Age at GI Symptom Onset, y | Type of GI Symptoms | Supportive CD Features | Lag Time Between Cognitive and GI Symptoms, y | Survival After Cognitive Decline, y |
|---|---|---|---|---|---|---|---|
| 1/M | 59 | Amnesia, confusion, and personality change | 59 | Diarrhea | None | 0 | 3 |
| 2/F | 60 | Amnesia, personality change, and apraxia | 60 | Steatorrhea and low albumin level | DH | 0 | 4 |
| 3/M | 64 | Amnesia, confusion, and personality change | 64 | Steatorrhea and weight loss | None | 0 | Alive at the age of 81 y; improved, but began to deteriorate when not eating a gluten-free diet |
| 4/F | 73 | Amnesia, confusion, and acalculia | 73 | Diarrhea | AGA, AGG, and TTG | 0 | Alive and stable at the age of 74 y |
| 5/M | 79 | Amnesia, disorientation, and acalculia | 79 | Weight loss and anemia | AGA, AGG, EMA, and TTG | 0 | Alive but deteriorating at the age of 82 y |
| 6/M | 61 | Amnesia, disorientation, personality change, and acalculia | 60 | Weight loss, fatigue, diarrhea, and steatorrhea | TTG | 1 | 1 |
| 7/M | 45 | Confusion and disorientation | 47 | Loose stool and weight loss | None | 2 | 6 |
| 8/F | 52 | Amnesia, personality change, aphasia, acalculia, and dysgraphia | 50 | Weight loss | DH | 2 | 5 |
| 9/M | 54 | Amnesia | 56 | Loose stool | None | 2 | Alive; improved and stable until AD at the age of 73 y |
| 10/M | 65 | Amnesia, confusion, disorientation, acalculia, and dysgraphia | 63 | Diarrhea | DH | 2 | 9 |
| 11/F | 70 | Amnesia | 72 | Nausea and abdominal distention | DH | 2 | 11 |
| 12/F | 72 | Amnesia, confusion, disorientation, personality change, and acalculia | 74 | Anemia | None | 2 | 8 |
| 13/M | 74 | Amnesia and acalculia | 72 | Constipation and diarrhea | AGA and DH | 2 | 6 |

Abbreviations: AD, Alzheimer disease; AGA, antigliadin IgA; AGG, antigliadin immunoglobulin G; CD, celiac disease; DH, dermatitis herpetiformis; EMA, endomysial antibody; GI, gastrointestinal; TTG, tissue transglutaminase IgA.

previously described inclusion and exclusion criteria. We further excluded any patient whose onset of cognitive symptoms (self- or family-reported) occurred more than 2 years before or after development of gastrointestinal symptoms associated with a first-time diagnosis of CD or an exacerbation of biopsy-proved adult-onset CD. Five patients had longer time lapses between the onset of gastrointestinal and neurological symptoms (3, 3, 4, 6, and 7 years). Available clinical information for the 13 remaining patients, including cognitive profiles, noncognitive neurological findings, computed tomographic or MRI findings of the brain, EEG findings, laboratory data, neuropsychological profiles, and clinical outcomes, was reviewed.

### NEUROPATHOLOGICAL STUDIES

Two patients (patients 2 and 7) underwent a right frontal lobe brain biopsy, and 3 (patients 1, 6, and 8) underwent postmortem whole brain tissue examination. In the patients who underwent postmortem whole brain tissue examination, sections from frontal, temporal, parietal, and occipital cortices, and the amygdala, hippocampus, thalamus, basal ganglia, brainstem, and cerebellum, were analyzed. In all 5 patients, 5-µm sections were stained with hematoxylin-eosin and modified Bielschowsky stain. In addition, all patients underwent immunohistochemical analysis with glial markers: glial fibrillary acid protein for astrocytes (polyclonal, 1:800; DAKO, Carpinteria, Calif). Neuronal pathological features were studied with antibodies to neurofilament protein (NF-L, clone 2F11, 1:75; DAKO), ubiquitin (polyclonal, 1:100; DAKO), α-synuclein (clone LB509, 1:200; Zymed, San Francisco, Calif), and phospho-τ (clone AT8, 1:1000; Endogen, Woburn, Mass). Prion studies were also conducted (clone 3F4, 1:5; DAKO). Additional studies were performed on patient 6, including immunohistochemistry for CD45 and CD68 (phosphoglucomutase 1 antibodies), the Luxol fast blue stain, and reverse-transcription polymerase chain reaction for *Tropheryma whippelii*.

### STATISTICAL ANALYSIS

In reviewing the Short Test of Mental Status scores,[9] patients were divided into 2 groups: those with the onset of gastrointestinal and cognitive symptoms separated by 1 year or less, and those with the symptoms separated by more than 1 year. The *t* test was used to determine the difference in average scores between the 2 groups. The difference was considered statistically significant if $P<.05$.

## RESULTS

### CLINICAL

All 13 patients, 5 of whom were women, had a detailed description of their cognitive impairment (**Table 1**). The

**Table 2. Findings From a Neurological Examination, EEG, a CSF Test, and a Metabolic Workup of Patients With CD and Cognitive Impairment**

| Patient No./Sex | Short Test of Mental Status Score* | Other Neurological Findings | EEG Findings | CSF Protein Level | CSF NSE Level | Nutritional Deficiency | Diagnosis |
|---|---|---|---|---|---|---|---|
| 1/M | 29 | AT, HA, and SZ | Rhythmic δ, slowing in temporal regions, left side greater than right side | Normal | ND | None | Possible CJD; autopsy showed nonspecific gliosis |
| 2/F | 10† | AT and PN | Bitemporal slowing, right side greater than left side | Normal | ND | None | Cognitive impairment associated with CD; the biopsy specimen showed nonspecific gliosis |
| 3/M | 30 | None | Low-amplitude β waves in bilateral anterior regions | Normal | ND | Carotene | None |
| 4/F | 23 | AT | ND | ND | ND | None | Possible cognitive impairment associated with CD |
| 5/M | 18 | AT | Mild diffuse θ slowing, maximal over the left temporal region | Normal | Normal | Folate, vitamin $B_{12}$, and vitamin D | Vitamin $B_{12}$ deficiency |
| 6/M | 20 | AT, MC, and PN | ND | Elevated (55 mg/dL) | High | Folate and vitamin E | CJD vs cognitive impairment associated with CD; autopsy showed nonspecific gliosis |
| 7/M | ND | AT, MC, and SZ | Bifrontal δ slowing | Normal | ND | Folate and carotene | CJD vs cognitive impairment associated with CD; the biopsy specimen showed gliosis |
| 8/F | 28 | HA and SZ | Bitemporal θ slowing | Normal | High | None | FTLD-U; autopsy showed neuronal loss with gliosis and ubiquitin-positive inclusions |
| 9/M | 34 | AT and PN | Bifrontal slowing, δ slowing in the left temporal region, bilateral intermittent sharp waves in sleep | Elevated (58 mg/dL) | ND | Vitamin $B_{12}$ and vitamin D | None |
| 10/M | 33 | AT and MC | Normal | ND | ND | None | Possible cognitive impairment associated with CD |
| 11/F | 34 | AT and HA | ND | ND | ND | Carotene and vitamin D | None |
| 12/F | ND | None | Increase of symmetric bifrontal β activity | Normal | ND | None | None |
| 13/M | ND | AT and PN | ND | Elevated (81 mg/dL) | ND | None | None |

Abbreviations: AT, ataxia; CD, celiac disease; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalography; FTLD-U, frontotemporal lobar degeneration with ubiquitin-only immunoreactive changes; HA, headache; MC, myoclonus, ND, not done; NSE, neuron-specific enolase; PN, peripheral neuropathy; SZ, seizure.

*The total score possible was 38.

†This patient took the Mini-Mental State Examination instead; the total score possible was 30.

median self- or family-reported age at cognitive symptom onset was 64 years (age range, 45-79 years), with 5 patients developing simultaneous neurological and gastrointestinal symptoms (median age, 64 years; age range, 59-79 years). The median age at gastrointestinal complaint was 63 years (age range, 47-79 years), with diarrhea being the most common symptom. Five patients also had dermatitis herpetiformis. All small-bowel biopsy results showed partial or total villous atrophy consistent with CD, with no suggestions of other causes, including Whipple disease. Antigliadin antibodies (immunoglobulin A or immunoglobulin G) or tissue transglutaminase immunoglobulin A levels were positive for disease in all 4 patients tested. In patient 4, the serum tissue transglutaminase titer increased from a premorbid level of 25.4 to 124.2 U at her neurological evaluation.

## COGNITIVE IMPAIRMENT

Almost all patients had insidious subacute onset of their cognitive impairment. Three patients (patients 1, 6, and 7) had an initial rapidly progressive course. Of the 13 patients, the most common cognitive complaint was amnesia (n=12), followed by acalculia (n=7), confusion (n=6), and personality change (n=6) (Table 1). The Short Test of Mental Status was performed in 9 patients, with an average score of 28 of a total of 38 (range, 18-34) (**Table 2**). One patient scored 10 of 30 on the Mini-Mental State Ex-

**Table 3. Neuropsychological Test Performance***

| Neuropsychological Test | Patient No. 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|
| Intellectual function | WAIS-III | WAIS-R | WAIS-R† | WAIS-III | WAIS† |
| Verbal comprehension | 67 | 120 | 95 | 118 | 64 |
| Perceptual organization | 62 | 120 | 90 | 89 | 78 |
| Working memory (WAIS-III) | 55 | 106‡§ | NA | 86 | 81‡ |
| Processing speed (WAIS-III) | 69 | NA | NA | 81 | NA |
| Learning and memory | WMS-III | WMS-III | WMS | WMS-R | WMS |
| Paragraph learning | 16 | 37 | 42‖ | 63 | ≤1‖ |
| Paragraph retention | 9 | 25 | <5‖ | 9 | <5‖ |
| Visual learning (figures) | 9¶ | 91 | NA | 63 | NA |
| Visual retention | 75¶ | 9 | NA | 37 | NA |
| AVLT | | | | | |
| Word list learning | NA | 10-19 | <10 | <10 | NA |
| Word list retention | NA | 80-85 | <10 | 60-69 | NA |
| Language | | | | | |
| Receptive (token test) | <1 | NA | NA | 60-71 | NA |
| Expressive | | | | | |
| Boston Naming Test | 2-6 | NA | NA | 41-59 | NA |
| Letter fluency | <1 | NA | NA | 11-18 | NA |
| Semantic fluency | 1-2 | NA | NA | 11-18 | NA |
| Visuoconstruction (Bender-Gestalt test) | Impaired | NA | Normal | Normal | NA |

Abbreviations: AVLT, Rey Auditory Verbal Learning Test; NA, data not available; WAIS, Wechsler Adult Intelligence Scale; WAIS-R, WAIS-Revised; WAIS-III, WAIS–Third Edition; WMS, Wechsler Memory Scale; WMS-R, WMS-Revised; WMS-III, WMS–Third Edition.

*Because patients were seen clinically rather than for research purposes, neuropsychological test batteries varied. Normative data from the WAIS, WAIS-R, or WAIS-III were used for intellectual function, working memory, and processing speed and are presented as standard scores (mean, 100; SD, 15). Normative data from the Mayo's Older Americans Normative Studies were used for the remaining tasks (learning and memory, AVLT, language, and visuoconstruction) and are presented as percentiles.

†Scores reflect verbal and performance IQ from the WAIS or WAIS-R.

‡Freedom from distractibility from the WAIS or WAIS-R in keeping with the IQ test given.

§Subject also performed in the impaired range (<1 percentile) on the Stroop test.

‖Overall immediate recall (memory quotient) and delayed retention from the WMS.

¶Patient received picture rather than figure memory.

amination.[10] Patients with the onset of neurological symptoms within 1 year of gastrointestinal symptoms had a lower average Short Test of Mental Status score of 24, compared with an average of 32 among the rest ($P<.02$). There was no association between Short Test of Mental Status score and number of cognitive domains affected. Neuropsychological test results were available for 5 of the 13 patients (**Table 3**). Two patients (patients 9 and 11) had learning inefficiency, 1 (patient 10) had memory deficits more than learning inefficiency, and the other 2 (patients 8 and 12) had global cognitive impairment.

Surprisingly, 3 patients (patients 1, 6, and 7) were initially diagnosed as having possible Creutzfeldt-Jakob disease (CJD) because of a rapidly progressive course and the constellation of subacute dementia and ataxia, and myoclonus and seizure in 2 each. In addition, 4 patients (patients 2, 4, 6, and 7) were diagnosed as having "celiac dementia" during their evaluation.

## ADDITIONAL FEATURES

Among complications known to be associated with CD, gait ataxia was the most common symptom (10 of 13 patients), followed by peripheral neuropathy, myoclonus, seizure, and headaches. All patients with peripheral neuropathy or myoclonus also had ataxia, and 1 patient had all 3 symptoms. Only 2 patients had cognitive impairment without other neurological symptoms.

## TEST FINDINGS

Electroencephalography was performed in 9 patients, and showed focal or diffuse slowing in 6. Two patients had nonspecific frontal changes, and only 1 had a normal EEG result. Computed tomography of the head showed generalized atrophy in 4 patients (patients 7, 10, 11, and 12) and dense basal ganglia calcification in 1 (patient 11). Magnetic resonance imaging was performed in 7 patients and similarly showed generalized atrophy in 6 and frontal atrophy in 1 (**Figure 1**). On MRI, 3 types of changes were observed: confluent periventricular changes (Figure 1A), patchy cortical and subcortical areas of T2 hyperintensities (Figure 1B), and both (Figure 1C and D). In 1 patient, there were unilaterally increased T2 hyperintensities in the thalamus, with progression noted on subsequent MRI (Figure 1E and F).

Cerebrospinal fluid was obtained from 10 patients, and 2 had an elevated protein level. Because of clinical suspicion for a prion disease, neuron-specific enolase levels were obtained from 3 patients. Two patients had elevated levels of neuron-specific enolase, suggestive of CJD; the 14-3-3 level was tested in only 1 of these patients, and was normal.

Nutritional deficiency was identified in 6 patients (Table 2), including deficiencies of vitamin $B_{12}$ in 2 patients and of folate in 3 patients. The vitamin E level was checked in 3 patients and was low in 1. Two other pa-

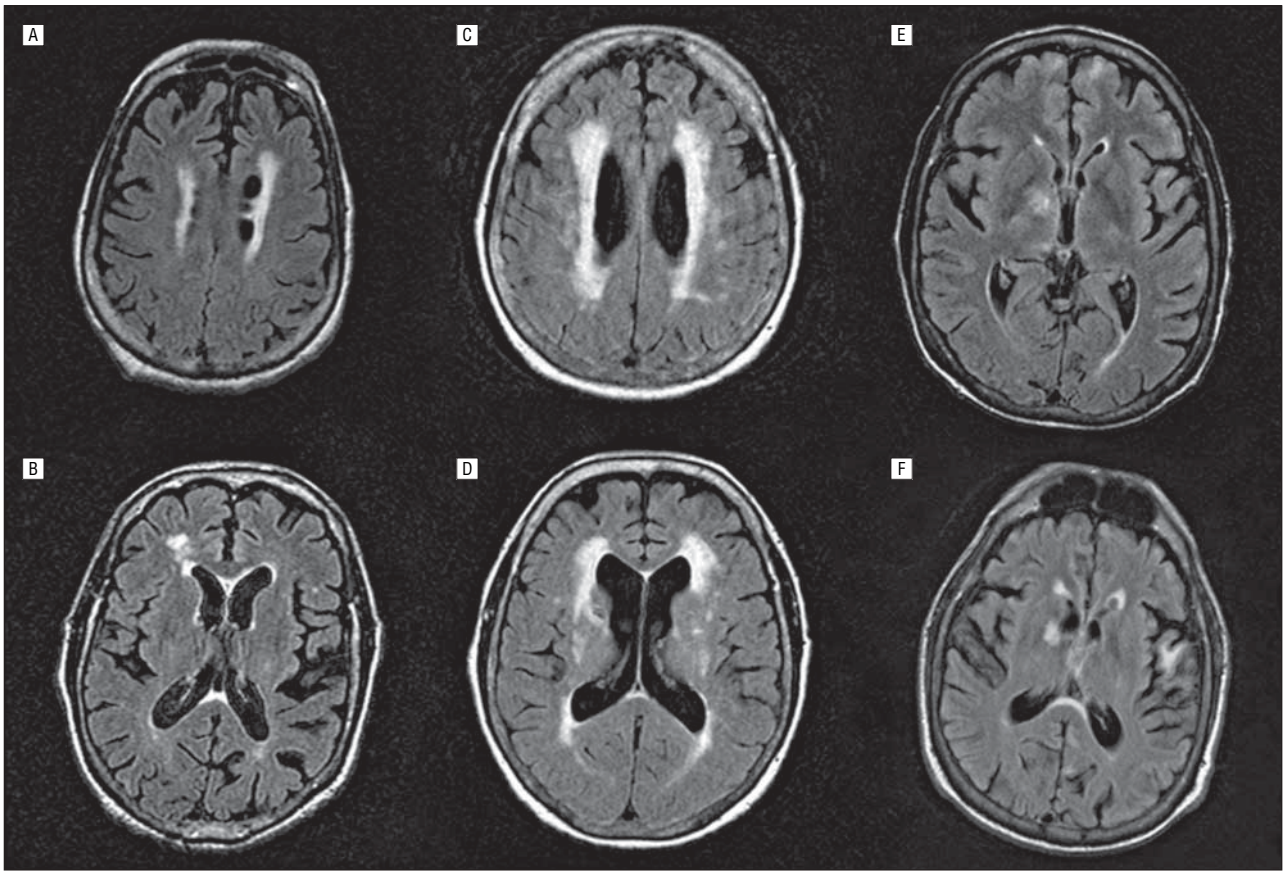


**Figure 1.** Magnetic resonance imaging (MRI) findings of patients with celiac disease and cognitive impairment; fluid-attenuated inversion recovery images are shown. A, Confluent areas of periventricular T2 hyperintensities were seen in patient 4. B, Scattered foci of T2 hyperintensities involving bilateral subcortical regions were found in patient 9. C and D, Both types of MRI changes were found in patient 11. E and F, The temporal sequence of subcortical and thalamic changes in patient 6 revealed increased intensity in the subcortical lesion and expansion of the lesion in the left temporal lobe 4 months later.

tients were already receiving vitamin E supplementation. Five patients identified with deficiencies were treated with oral supplementation (folate or vitamin $B_{12}$, D, or E), except for patient 5, who received intramuscular vitamin $B_{12}$ injections. None of the patients experienced cognitive improvement with supplementation alone, despite confirmed normalization of serum vitamin $B_{12}$ and folate levels. Paraneoplastic antibodies were absent in all 5 patients (patients 4-6, 8, and 9) tested.

## FOLLOW-UP

During follow-up, 10 patients deteriorated cognitively and 9 died of complications associated with their progressive dementia. Among the patients who deteriorated, the mean duration of disease was 5.9 years after the onset of cognitive impairment (median, 6 years; range, 1-11 years). Four patients (patients 2, 7, 8, and 12) underwent repeat small-bowel biopsies that showed partially treated CD, and 5 (patients 5, 6, 10, 11, and 13) had persistent gastrointestinal symptoms. Two patients improved cognitively with a gluten-free diet: 1 (patient 9) remained cognitively stable for 10 years until he developed probable Alzheimer disease, and the other (patient 3) remained stable for 10 years until he gave up his dietary restrictions. One patient (patient 4) remained neurologically stable with her cognitive deficits and ataxia 6 months after gluten withdrawal. The gastrointestinal and cognitive symptoms of patient 6 improved transiently while providing total parenteral nutrition, but again declined with increased oral intake. Only 1 patient (patient 7) was treated with plasma exchange, but the patient's condition failed to improve.

## NEUROPATHOLOGICAL FINDINGS

Histological analysis of the brain tissue from the 2 patients (patients 2 and 7) who underwent brain biopsy showed only nonspecific gliosis. A comprehensive histological analysis of 2 patients (patients 1 and 6) who underwent postmortem examination also showed evidence of only gliosis in the patients (**Figure 2**). Patient 8 had diffuse gliosis in addition to the presence of τ- and α-synuclein–negative, but ubiquitin-positive, inclusions in the frontal and temporal cortices and hippocampal dentate granular cell layer, in keeping with a pathological diagnosis of frontotemporal lobar degeneration with ubiquitin-only immunoreactive changes.[11]

In 1 patient (patient 7) who underwent a brain biopsy, brain tissue was surgically implanted in a primate to rule out transmissible prion disease; the result was negative. The brain of patient 6 was additionally examined at the National Prion Disease Pathology Surveillance Center, and prion disease was ruled out. In all 5 patients, Biel-

schowsky silver stain, τ, neurofilament, α-synuclein, and prion immunohistochemistry results were negative.

## COMMENT

We describe 13 patients with concurrent onset of cognitive impairment and adult-onset CD. Most of these patients had common neurological complications of CD, such as ataxia and seizure, suggesting a possible link, direct or indirect, between CD and cognitive decline. While the first consideration for the cause of cognitive impairment may be nutritional deficiencies, the absence of any neurological improvement or stabilization after supplementation, and demonstrated normalization in some patients, argues against nutritional deficiency as the sole cause of the encephalopathy. On the contrary, 3 patients had at least stabilization, with significant improvement in 2, of their cognitive deficits with gluten withdrawal, similar to others' experience.[6,7] However, the strongest arguments for an association between the cognitive impairment and CD are the close temporal relationship between the onset of CD-associated gastrointestinal and cognitive symptoms and the constellation of other CD-associated neurological symptoms. It seems more than mere coincidence that in 5 patients the onset of CD and cognitive impairment was simultaneous.

A total of 13 patients have been previously described as having cognitive decline associated with CD. Cooke and Smith[2] first described a dementia-like syndrome in 2 patients with childhood-onset CD. More recently, Collin et al[5] described 5 patients with adult-onset CD, dementia, and brain atrophy. Four of these patients demonstrated general slowing on EEG, similar to ours, and 3 had spike-and-wave discharges. By combining our series with theirs, only 1 of 14 patients with CD and cognitive impairment had a normal-appearing EEG. Nevertheless, no EEG finding was characteristic among all patients, other than nonspecific slowing. Findings of confluent periventricular changes and discrete foci on MRI were equally nonspecific, but both have been observed in 10 patients with CD who experienced headaches[12] and in 1 patient with cognitive changes.[7] Thalamic involvement has also been described,[12] suggesting that it may be more common than the frequency of 1 in 13 we observed.

The mechanism of cognitive impairment remains elusive in CD. Patients with CD and ataxia but no cognitive complaints did poorer on neuropsychological testing than age- and sex-matched control subjects,[13] suggestive of a chronic neuropathological process. Neuropsychometric testing in our patients always revealed involvement of frontosubcortical networks, although in 3 patients other domains were also affected. A larger cohort of patients with a more consistent battery is necessary to generalize this finding. Pathologically, Kinney et al[4] provided the only detailed autopsy study of a patient who developed CD and dementia at the age of 55 years. Similar to 4 of our patients with histological studies, the only remarkable finding was nonspecific gliosis in the subcortical and deep white matter. Folate, vitamin $B_{12}$, and vitamin E deficiencies have all been identified in patients with dementia suspected to be associated with CD. Yet, supplementation invariably failed to stabilize or reverse the cognitive decline. Thus, such nutritional deficiency is likely a consequence of malabsorption associated with CD enteropathy, but deficiency in a yet unidentified micronutrient[5] remains a plausible explanation.

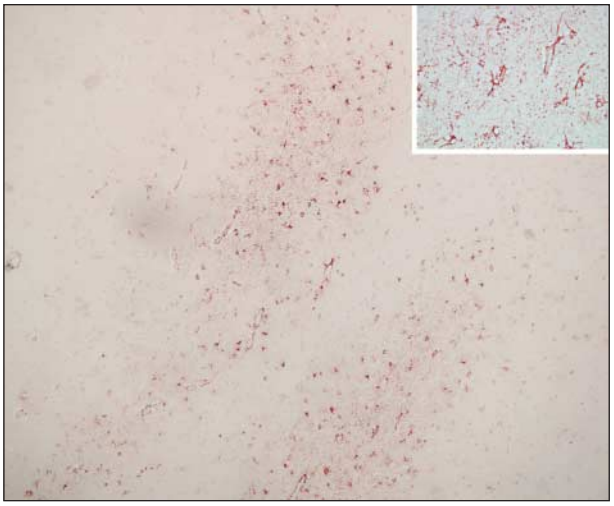

**Figure 2.** Areas of widespread gliosis in a biopsy specimen taken from patient 7 (original magnification ×5). The inset shows high-power staining of astrocytes with anti–glial fibrillary acid protein antibodies (original magnification ×40).

Autoimmunity involving the central nervous system is another possible mechanism. Hadjivassiliou and coworkers demonstrated strong staining of healthy human Purkinje cells[14] and targeting of tissue transglutaminase in brain specimens[15] by serum samples from patients with gluten-related ataxia. The involvement of tissue transglutaminase antibody in cognitive impairment may be supported clinically by the positive titer in our patients and the titer elevation along the progressive decline in patient 4. Last, a chance occurrence of CD and a yet unidentified progressive cognitive decline remain possible. Celiac disease is highly prevalent in the general population, occurring at 0.75%,[16] and pathological examination in 1 of the patients demonstrated findings of frontotemporal lobar degeneration with ubiquitin-only immunoreactive changes. We speculate that this was a coincidence, but further studies looking for clinical features of CD in patients with frontotemporal lobar degeneration and ubiquitin staining in the brain specimens of patients with antemortem CD will be necessary before we come to a final conclusion. Nevertheless, the simultaneous onset of cognitive impairment and CD in patients with similar clinical profiles would make mere chance occurrence rather unlikely.

Not unexpectedly, cognitive impairment associated with CD was never the initial clinical diagnosis, although it was later diagnosed in some. The lack of uniform response to gluten withdrawal was likely complicated by compliance, because noncompliance and biopsy-proved evidence of only partial treatment were common. We were surprised at the fact that CJD was considered a likely diagnosis in almost a third of the patients. A prion disease was a reasonable consideration given the presenting signs of subacute dementia, ataxia,

myoclonus, and seizure, and, in 2 patients, an elevated neuron-specific enolase level. In 1 patient in whom CJD was suspected, MRI of the head further revealed asymmetrically increased T2 changes in the anterior and pulvinar regions of the thalamus. While the symmetric "pulvinar sign" is associated with variant CJD, an asymmetric pulvinar sign is uncommon.[17] Hence, we suggest that a workup for CD and possibly gluten withdrawal be at least considered in patients with CJD.

In summary, we provide a more detailed report on the possible association between CD and cognitive impairment than previous series. While we hypothesize on the association and the causative pathogenesis, the fact remains that some of our patients did respond to gluten withdrawal. With nearly half of brain biopsy specimens lacking specific features to aid in the diagnosis of dementia in 1 recent series,[18] a reevaluation of the role of CD in causing cognitive impairment has the potential of expanding the narrow spectrum of the treatable dementia.

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