

Neurology[®]

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Neurology 1991;41;372

This information is current as of March 19, 2012

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Celiac disease, brain atrophy, and dementia

P. Collin, MD; T. Pirttilä, MD; T. Nurmikko, MD; H. Somer, MD; T. Erilä, MD; and O. Keyriläinen, MD

Article abstract—We report 5 patients who developed dementia before age 60 and were subsequently found to have celiac disease (CD). Intellectual deterioration ranged from moderate to severe, and diffuse cerebral or cerebellar atrophy was found on brain CT. Diagnosis of CD was confirmed by findings of subtotal villous atrophy in jejunal biopsy specimens and positive serum reticulin and gliadin antibodies. Conspicuously, gastrointestinal symptoms were mild. The gluten-free diet failed to improve the neurologic disability except in 1 patient. CD is a multisystem disorder and may play a role in some cases of presenile dementia. Although the pathogenetic mechanisms are obscure, immunologic mechanisms are implicated

NEUROLOGY 1991;41:372-375

Neurologic disorders occur in celiac disease (CD). Peripheral neuropathy and cerebellar disease were usually reported,¹⁻³ in addition to unexplained attacks of unconsciousness and epileptic seizures.⁴⁻⁶ Dementia was described in isolated cases only.^{7,8} We now report 5 patients with CD and concomitant brain atrophy and dementia.

Methods. The study concerns adult subjects living in the district of Tampere University Central Hospital, with a total population of 420,000. In 1983, we found 2 sisters with progressive ataxia and dementia associated with CD (patients 1 and 2). Thereafter, we found 3 relatively young patients suffering from dementia and brain atrophy with concomitant CD. One patient (patient 3) was living outside our hospital's district. Thorough laboratory evaluation of the patients with diagnosed or suspected dementia consisted of exclusion of thyroid, liver, and kidney diseases, and measurement of serum cardiolipin. Serum vitamin B₁₂, erythrocytic folic acid, and serum iron concentration were determined; if these values were low, serum reticulin and gliadin antibodies were analyzed. Reticulin antibody content in serum was measured by indirect immunofluorescence⁹ and gliadin antibody content by enzyme-linked immunosorbent assay (ELISA).¹⁰ In case of positive titers, a jejunal biopsy was performed. Circulating immune complexes (C1q-ELISA)¹¹ and HLA antigens were determined in patients with mucosal atrophy. When the patients had maintained the gluten-free diet for at least ½ year, they were invited to have a control biopsy, and at that time reticulin and gliadin antibodies were determined. Neurologic symptoms were recorded to find out if the gluten-free diet had any effect on the symptoms.

All patients received a comprehensive neurologic examination, including CT of the brain, EEG, and a battery of standardized neuropsychological measures of attention, orientation, memory, conceptualization, language, praxis, and visuospatial and visuoperceptual processing. CSF analysis was carried out in selected cases.

Case reports. Patient 1. In 1978, at the age of 32, this patient was seen in a psychiatric clinic because of a 3-year history of depression, migraine headache, walking difficulty, and memory disturbances. The results of the routine neurologic examinations were unremarkable (brain CT not done). In 1983, she underwent a reexamination because her sister (patient 2) was being evaluated for severe ataxia, and there was a suspicion of a hereditary disorder. At this time she had a moderate cognitive disorder, physical signs of diffuse CNS involvement, and polyneuropathy (table 1). Brain CT revealed central and cortical cerebral atrophy and cerebellar atrophy. Erythrocyte folic acid was low. The patient reported slight gastrointestinal symptoms, such as flatulence. A jejunal biopsy specimen showed subtotal villous atrophy. When reexamined in 1988, the adherence to the diet appeared to be good, and reticulin and gliadin antibodies were normal. She was not motivated to have a control biopsy. All her neurologic symptoms had progressed, and she had profound dementia. Also, cerebral atrophy was worse on CT examination.

Patient 2. This patient is the younger sister of patient one. In 1983, at the age of 36, she started to suffer from progressive balance disturbances. Neurologic evaluation revealed extensive CNS affliction and peripheral neuropathy (table 1). Brain CT showed slight cortical atrophy. Serum vitamin B₁₂ level was abnormally low (table 2). Gastroscopy showed a normal gastric mucosa, but a duodenal biopsy was not performed. Parenteral B₁₂ substitution had no effect on her neurologic condition. CD was not suspected until the diagnosis was confirmed in her sister 2 years later. At this time, serum reticulin and gliadin antibodies were positive, and a jejunal biopsy specimen showed subtotal villous atrophy. The patient had no abdominal symptoms. In 1987, a reevaluation was carried out. Her diet had not stayed completely gluten-free, but reticulin and gliadin antibodies had clearly diminished. The patient refused jejunal biopsy. She now had a profound cognitive disorder and severe spinocerebellar ataxia. Cortical atrophy had progressed on repeated CT.

From the Departments of Internal Medicine (Drs. Collin and Keyriläinen) and Neurology (Drs. Pirttilä, Nurmikko, and Erilä), Tampere University Central Hospital, Tampere; and the Department of Neurology (Dr. Somer), Helsinki University Central Hospital, Helsinki, Finland.

Received May 22, 1990. Accepted for publication in final form August 28, 1990.

Address correspondence and reprint requests to Dr. Pekka Collin, Department of Internal Medicine, Tampere University Central Hospital, SF 33520, Tampere, Finland.

Table 1. Summary of clinical features and results of investigations of the patients

Case	Cerebral	Brainstem/ cerebellar	Spinal	Peripheral	CSF	EEG	Brain CT	Course of disease
1.	Intellectual deterioration	Ataxia; intention tremor; upward gaze paresis; vertical nystagmus	Heightened patellar tendon jerks; positive Babinski sign	Absent achilles tendon jerks; diminished vibration sense distally in legs	Normal	General slowing; theta-delta paroxysms in occipital regions	Cerebral central and cortical atrophy; cerebellar atrophy	Progressive
2.	Intellectual deterioration; deficits in verbal and visual memory	Ataxia; dysarthria; horizontal nystagmus; upward gaze paresis	Positive Babinski sign	Absent achilles tendon jerks; diminished vibration sense distally in legs	Normal	General slowing; episodic theta-delta waves	Progressive cerebral cortical atrophy	Progressive
3.	Intellectual deterioration; slowing of psychomotor functions	Dysarthria; incoordination	Spasticity in legs; heightened tendon jerks in lower extremities; positive Babinski sign	Diminished pain, touch, temperature, and vibration senses below the knees; muscle weakness distally in legs	Mild leukocytosis; protein 521 mg/l	Normal background activity; outbursts of spike-and-wave discharges	Cerebellar atrophy; cerebral cortical atrophy	Death
4.	Intellectual deterioration; severe memory deficit; constructional deficits and apraxia	Slight limb ataxia	None	None	Not examined	General slowing; irritative spikes in left temporal region	Cerebral central and cortical atrophy	Progressive
5.	Deficits in numeric span and visual memory; visuomotor constructional difficulties	None	None	Diminished pain and temperature senses below the knees	Not examined	General slowing; outbursts of spike-and-wave discharges in frontal regions	Cerebellar atrophy	Slightly improved

Table 2. Laboratory findings, reticulin (ARA) and gliadin (AGA) antibodies, and small bowel histology of 5 patients with celiac disease and dementia

Case	Sex	Age at diagnosis	Hb	S-B12	E-fol	S-Fe	Histology		ARA IgA	AGA		C1Q
							BFG	AFG		IgA	IgG	
1	F	37	113	171	250	17.6	SVA	NE	1:500	+	+	+
2	F	39	145	<38	338	15.5	SVA	NE	1:100	+	+	+
3	F	41	127	100	21	14.0	SVA	Normal	1:1,000	+	NE	NE
4	F	58	138	238	36	11.4	SVA	PVA	1:500	+	+	+
5	M	43	141	323	282	20.7	SVA	NE	<1:50*	-	+	+

* ARA IgG 1:1,000.
 BFG Before gluten-free diet.
 AFG After gluten-free diet.
 SVA Subtotal villous atrophy.
 NE Not examined.
 PVA Partial villous atrophy.

Reference values: Hb: female, 120-160 g/l; male, 130-180 g/l.
 S-B12: 170-640 pmol/l.
 E-fol: 280-800 nmol/l.
 S-Fe: 8-30 μmol/l.
 ARA: <1:50.

Patient 3. In 1978, at the age of 39, this patient was diagnosed as having dermatitis herpetiformis. Two years later, a jejunal biopsy specimen showed subtotal villous atrophy. The gluten-free diet was not strict; in 1984, she had positive reticulin and gliadin antibodies and low serum vitamin B₁₂ concentration. In 1985, she was hospitalized because of epileptic seizures,

confusion, and general muscle weakness. Now she started a strict gluten-free diet. In 1987, the jejunal biopsy specimen and serum vitamin B₁₂ concentration were normal. However, her condition deteriorated. Her speech became dysarthric, and she developed progressive spasticity in the lower extremities. The sensory disturbances progressed, and tests for

coordination became abnormal. Neuropsychological examination revealed slowing of psychomotor functions and mild-to-moderate deterioration of cognitive functions. Electro-neuromyography (ENMG) examination showed reduced sensory nerve conduction velocities. Repeated brain CTs showed steady progression of cerebral and cerebellar atrophy. She developed profound dementia and died in another hospital in 1987, 20 months after the onset of her symptoms. The immediate cause of death was pneumonia.

Patient 4. A previously healthy woman aged 58 was referred to a psychiatric clinic due to excessive salivation and tiredness. Psychological tests revealed a distinct psycho-organic syndrome. Brain CT demonstrated gross cortical atrophy and slight cerebellar atrophy. On neurologic examination, she appeared slightly disorientated and had memory difficulties and apraxia. She reported no abdominal symptoms. Erythrocyte folic acid was low (table 2). Jejunal biopsy confirmed severe mucosal atrophy. A gluten-free diet was started. After 10 months, erythrocyte folic acid was normal, and on control biopsy jejunal mucosa was normal. Despite the adequate gluten-free diet, her mental state deteriorated, and she developed extrapyramidal symptoms.

Patient 5. This patient underwent a neurologic evaluation in 1969 at the age of 27 because of generalized seizures and memory difficulties. There were no specific findings. Phenytoin and carbamazepine therapy was started. The patient gave up the anticonvulsive therapy 10 years later. In 1984 he was reevaluated; he continued to have epileptic seizures twice a year and reported some memory disturbances. The neurologic examination revealed loss of pain and temperature sensation distally in the lower extremities, but the examination was otherwise normal. ENMG confirmed mild polyneuropathy. Brain CT revealed central and cortical cerebellar atrophy. Defects in both verbal memory functions and visuoconstructive performance were recognized on neuropsychological evaluation. Reticulin and gliadin antibodies were positive in IgG class. Jejunal biopsy showed a subtotal villous atrophy. The patient started a gluten-free diet. On control examination in 1987, he refused the control biopsy. Reticulin and gliadin antibodies were normal. He was seizure-free on carbamazepine treatment. His mental status was still consistent with a psycho-organic syndrome, but some improvement was noticed.

All 5 patients had positive HLA B8 and DR3 antigens (table 3). None of the patients had clinical evidence of vascular dementia based on Hachinski's ischemic score.¹²

Discussion. There are no epidemiologic studies on the nervous-system involvement in CD. Banerji and Hurwitz¹³ described neurologic complications in 37.5% of their patients. In the majority, the complications were caused directly by malabsorption, such as osteomalacia and hypokalemia. Nowadays, it is well known that CD may present with minimal symptoms, and signs of malabsorption are often absent.¹⁴ The clues for concomitant CD in the 5 patients reported here were quite subtle. In most cases, CD was diagnosed during the neurologic evaluation. The jejunum biopsy specimens were typical for CD. Serum reticulin and gliadin antibodies were pathologic and returned to normal during the gluten-free diet. We do not find any reason to question the diagnosis of CD in these patients, although 3 patients refused the control biopsy after diet.

The number of patients suffering from primary de-

Table 3. HLA antigens of patients

Pt no.	HLA		
1	A 2,3	B 7,8	DR 2,3
2	A 3,19	B 7,8	DR 3,4
3	A 1,9	B 8,w6	DR 3
4	A 2,9	B 8,16	DR 3,4
5	A 1	B 7,8	DR 2,3

mentia in the group aged 30 to 64 years can be estimated to be about 60 in our catchment area.¹⁵ From this population we have found 4 patients with both CD and dementia. The estimated number of such patients, assuming the prevalence of CD to be as high as 1:300,¹⁶ is only 0.2. Calculated from these figures, the standardized prevalence ratio is 20 and the 95% confidence interval from 5.5 to 51.5.¹⁷ Thus, the association of CD with brain atrophy and dementia seems very unlikely to be coincidental.

The cause of CNS involvement in CD is unsettled, but several alternative explanations, such as nutritional, toxic, genetic, and immunologic factors, deserve attention.

There is no unequivocal evidence that vitamin B₁₂, folic acid, or pyridoxine deficiency would be the primary cause of neurologic complications.¹⁸ Two of our patients presented with indisputable vitamin-B₁₂ deficiency and 3 with folic-acid deficiency (table 2). Appropriate diet therapy was not beneficial in these patients. This was especially evident in patient 2, whose condition deteriorated despite aggressive vitamin-B₁₂ substitution therapy for 2 years. However, the deficiency of some unknown nutrient cannot be excluded as a cause of the nervous system degeneration.⁸

CD is particularly associated with HLA B8, DR3, and DR7 antigens.¹⁹ All our patients presented with B8 and DR3 antigens (table 3). Yakura et al²⁰ 1st reported the possibility of linkage of dominantly inherited spinocerebellar ataxia with the HLA antigens, and there are other reports of genetic linkage of spinocerebellar ataxia with the HLA locus in some families.²¹ It is highly possible that spinocerebellar degeneration and CD share a common genetic origin. Immunologic mechanisms are supported by the presence of circulating immune complexes in the sera of 4 of our patients (all tested).

Kaplan et al²² described a patient with axonal neuropathy whose neurologic symptoms improved during a gluten-free diet, but there are also reports that a gluten-free diet does not slow the progression of the neurologic disease.^{1,2,8} In our patients, the adherence to the gluten-free diet was usually good. Still, neurologic symptoms deteriorated, with 1 exception (table 1). It is possible that the diagnosis of CD was delayed for many years, perhaps even decades, and we do not know if an earlier dietary intervention would have changed the poor prognosis in our patients.

In conclusion, there may be an association of CD and dementia, especially in the patients developing an intellectual deterioration at a relatively young age.

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Clinical and molecular genetic study of a large German kindred with Gerstmann-Sträussler-Scheinker syndrome

P. Brown, MD; L.G. Goldfarb, MD; W.T. Brown, MD, PhD; D. Goldgaber, PhD; R. Rubenstein, PhD; R.J. Kascsak, PhD; D.C. Guiryo, MD; P. Piccardo, MD; J.W. Boellaard, MD; and D.C. Gajdusek, MD

Article abstract—We have verified, by full open reading frame sequencing, the presence of an amino-acid-altering mutation in codon 102 of the scrapie amyloid protein gene in three affected members of a large and well-documented German family with experimentally transmitted Gerstmann-Sträussler-Scheinker syndrome. In addition, we identified the mutation by partial sequencing or DNA restriction enzyme analysis in three of 12 presently healthy family members with an affected parent, and none of 12 members without an affected parent. Thus, a total of six of 15 family members at risk for the disease (including the three established cases) had the same codon 102 mutation, a proportion consistent with the autosomal dominant inheritance pattern of disease expression. It is undetermined whether the mutation influences susceptibility to infection by an exogenous agent or is itself a proximate cause of disease.

NEUROLOGY 1991;41:375-379

Gerstmann-Sträussler-Scheinker syndrome (GSS) is a transmissible spongiform encephalopathy of predominantly familial occurrence, characterized by a usually

slowly progressive spinocerebellar dysfunction and dementia, and the neuropathologic findings of multicentric amyloid plaques and a variable degree of

From the Laboratory of CNS Studies (Drs. P. Brown, Goldfarb, Guiryo, Piccardo, and Gajdusek), NINDS, National Institutes of Health, Bethesda, MD; the Institute for Basic Research in Developmental Disabilities (Drs. W.T. Brown, Rubenstein, and Kascsak), Staten Island, NY; the Department of Psychiatry (Dr. Goldgaber), State University of New York, Stony Brook, NY; and the Institute for Brain Research (Dr. Boellaard), University of Tübingen, Tübingen, Germany.

Received June 11, 1990. Accepted for publication in final form August 6, 1990.

Address correspondence and reprint requests to Dr. Paul Brown, Building 36, Room 5B21, National Institutes of Health, Bethesda, MD 20892.

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Neurology 1991;41;372

This information is current as of March 19, 2012

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