

Coeliac disease and epilepsy

C.C. CRONIN, L.M. JACKSON, C. FEIGHERY¹, F. SHANAHAN,
M. ABUZAKOUK¹, D.Q. RYDER², M. WHELTON and N. CALLAGHAN³

From the Departments of Medicine, ²Radiology and ³Neurology, Cork University Hospital, Ireland, and ¹Department of Immunology, St James' Hospital, Dublin, Ireland

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Summary

Whether there is an association between coeliac disease and epilepsy is uncertain. Recently, a syndrome of coeliac disease, occipital lobe epilepsy and cerebral calcification has been described, mostly in Italy. We measured the prevalence of coeliac disease in patients attending a seizure clinic, and investigated whether cerebral calcification occurred in patients with both coeliac disease and epilepsy. Screening for coeliac disease was by IgA endomysial antibody, measured by indirect immunofluorescence using sections of human umbilical cord. Of 177 patients screened, four patients were positive. All had small-bowel histology typical of coeliac disease.

The overall frequency of coeliac disease in this mixed patient sample was 1 in 44. In a control group of 488 pregnant patients, two serum samples were positive (1 in 244). Sixteen patients with both coeliac disease and epilepsy, who had previously attended this hospital, were identified. No patient had cerebral calcification on CT scanning. Coeliac disease appears to occur with increased frequency in patients with epilepsy, and a high index of suspicion should be maintained. Cerebral calcification is not a feature of our patients with epilepsy and coeliac disease, and may be an ethnically-or geographically-restricted finding.

Introduction

The prevalence of epilepsy among patients with coeliac disease is disputed; some studies have shown an increased prevalence,^{1,2} while others have not.³ The prevalence of coeliac disease, determined by antibody screening, among patients with epilepsy has been little studied.⁴

The existence of a specific syndrome of coeliac disease, epileptic seizures and intracranial calcification was proposed by Sammaritano and colleagues in 1988,⁵ and was confirmed in several subsequent series.^{6–9} In the largest,⁶ 5/12 patients with coeliac disease and epilepsy had cerebral calcification and, conversely, of 31 patients with epilepsy and cerebral calcification, 24 had coeliac disease. Nearly all reported cases have been from Italy, and the prevalence in other ethnic groups is uncertain.

The purposes of this study, therefore, were (i) to assess the prevalence of coeliac disease in patients attending the Seizure Clinic of Cork University Hospital, and (ii) to determine whether radiological

cerebral calcification is a feature of patients with both epilepsy and coeliac disease attending this hospital.

Methods

Part 1

Patients attending the Seizure Clinic of Cork University Hospital who were able to give informed consent were invited to undergo screening for coeliac disease; 177 were recruited. Seizure type was classified according to the scheme of the International League against Epilepsy,¹⁰ in which epilepsies are described as generalized or as partial or focal. Epilepsies may also be classified by aetiology: in idiopathic epilepsy, there is no underlying cause other than a possible hereditary disposition; symptomatic epilepsies and syndromes are the consequence

Address correspondence to Dr C.C. Cronin, Department of Medicine, Mallow General Hospital, Mallow, Cork, Ireland

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of a known or suspected disorder of the central nervous system; and cryptogenic epilepsies are presumed to be symptomatic, but the aetiology is not known. A control group of 488 consecutive patients attending an ante-natal clinic were also screened for coeliac disease. Measurement of IgA anti-endomysial antibody by indirect immunofluorescence using sections of human umbilical cord was used to screen for coeliac disease. Each patient gave informed consent. The study was approved by the Ethics Committee of Cork University Hospital.

Part 2

The hospital records of all patients attending the gastroenterology clinic of Cork University Hospital over a one-year period with a diagnosis of both epilepsy and coeliac disease were reviewed. Also, the computerized national Hospital In-Patient Enquiry (HIPE) database from 1982 to 1996 was searched for patients from Cork University Hospital with both these diagnoses. Seizure classification was as above.¹⁰ Patients were invited to undergo cranial computerized tomographic (CT) scanning if they had not had the procedure in the previous 2 years. All CT scans were assessed by a consultant neuroradiologist (DQR). Three patients were deceased; the most recent CT scans of these patients were reviewed.

Results

Part 1

Serum samples were obtained from 177 out-patients (80 male, 97 female). Mean age was 36 years (range 14–80 years), and median age of onset of epilepsy was 14 years (range <1–63 years). Of the 177 patients recruited, 38% had generalized tonic-clonic seizures, 28% complex partial, 10% complex partial with secondary generalization and 9% had generalized myoclonic epilepsy. Seventy-seven patients (44% of total) had idiopathic seizures, 71 (40%) had cryptogenic seizures and 29 (16%) had symptomatic seizures.

Of 177 patients screened, four female patients tested positive for endomysial antibody (Table 1; patients 1–4, Table 2). In patient 1, coeliac disease had been diagnosed in childhood, but she had been non-compliant with gluten restriction since adolescence. The other three patients had not been suspected of having coeliac disease at the time of screening. However, patient 2, in the interim between venesection and receipt of the screening results, complained of loose stools and abdominal bloating, and investigations revealed coeliac disease. Patient 3 had no gastrointestinal symptoms, but had an occult iron

deficiency anaemia. Patient 4 was asymptomatic. All four patients had a low duodenal biopsy per gastro-scope. Histological findings in each case were typical of coeliac disease (Table 1). Therefore, the frequency of coeliac disease among this sample of epilepsy patients is 1 in 44; in patients with epilepsy of undetermined cause (idiopathic or cryptogenic), the frequency of coeliac disease is 1 in 37.

The mean age of the 488 control patients was 27.7 years (range: 14–48 years). Two patients tested positive for endomysial antibody (1 in 244).

Part 2

A total of 16 patients (6 male, 10 female) with both epilepsy and coeliac disease, who had attended or were attending Cork University Hospital, were identified. Four patients were identified from the screening study (patients 1–4, Table 2), five from the gastroenterology clinic (patients 5–9) and seven from the HIPE database (patients 10–16). In seven patients, the diagnosis of epilepsy was made before that of coeliac disease, in seven patients, coeliac disease was diagnosed first, and in two patients, the two conditions were diagnosed at about the same time. The median age of detection of coeliac disease was 32 years (range <1–79 years), and of epilepsy, 20 years (<1–67 years). Five patients had onset of epilepsy during childhood. Seizure type is documented in Table 2. Six patients continued to have seizures, and seven patients had been seizure-free for at least one year; three patients were deceased. One patient's CT scan showed lacunar infarcts, and three showed generalized cerebral atrophy. Twelve patients had a normal scan appearance.

Three patients are deceased (patients 14–16, Table 2). Patient 14, with known coeliac disease, presented with simple partial seizures with motor signs (Jacksonian epilepsy) and was found to have non-Hodgkin's lymphoma, a recognized complication of coeliac disease. Patient 15 developed epilepsy and multiple sclerosis 3 years after diagnosis of coeliac disease. Patient 16 developed signs of dementia at age 60 years; at age 62, she presented with dermatitis herpetiformis, and jejunal biopsy showed sub-total villous atrophy. During her last year of life, she had recurrent grand mal epileptic seizures.

Discussion

Coeliac disease and epilepsy

In 1966, Cooke and Smith described 'unexplained attacks of unconsciousness' in five patients with coeliac disease.¹¹ Chapman *et al.* reported a prevalence of epilepsy among patients with coeliac disease of 5.5%,¹ and Holmes described a 3.5% prevalence.²

Table 1 Laboratory findings in patients with coeliac disease detected at screening

Patient	1	2	3	4
Hb (normal range: 12–15 g/dl)	12.5	14.6	10.0	13.5
Serum ferritin (17–320 µg/l)	301	31	7	134
Serum vitamin B ₁₂ (150–750 pmol/l)	432	236	400	526
Serum folic acid (4–22 nmol/l)	7.7	15.2	9.2	12.1
Small-bowel histology	sub-total villous atrophy	sub-total villous atrophy	partial villous atrophy	sub-total villous atrophy

A previous study from this hospital did not, however, detect an increased frequency of epileptic seizures among coeliac disease patients.³ Many cases of coeliac disease with absent, mild or atypical features are unrecognized, and previous studies examining patients with diagnosed coeliac disease may not be representative. The prevalence of coeliac disease among epilepsy patients, rather than the converse, may provide a more rigorous assessment of the association between the two conditions. With the advent of reliable tests, it is now possible to screen for coeliac disease with a high degree of accuracy; serum IgA endomysial antibody is considered the most sensitive and specific screening test available.¹² Only one study has used sensitive antibody screening methods to determine the prevalence of coeliac disease among patients with epilepsy.⁴ Fois *et al.* reported a frequency of coeliac disease of 1 in 87 among patients attending an Italian paediatric epilepsy clinic.⁴ The results of the present study indicating a frequency of coeliac disease of 1 in 44 in the total group, and of 1 in 37 in patients with epilepsy of undetermined cause, suggest a significant association between the two conditions.

In contrast, in the control group of 488 women attending an ante-natal clinic, only two serum samples were positive for endomysial antibody. The control group used has a number of shortcomings. It is not comparable to the epilepsy patient group in age or in gender distribution. In the patients with positive sera, coeliac disease was not confirmed by biopsy. Individuals with untreated coeliac disease have an increased incidence of infertility and of spontaneous abortion,^{13,14} and may be under-represented in a group of pregnant females. Many immunologically-mediated conditions undergo remission during pregnancy, although this has not been demonstrated for coeliac disease. A number of other studies have examined the prevalence of coeliac disease in the general population. A large study from Italy suggested a figure of 1 in 300.¹⁵ The sole population-based study from Ireland suggests a prevalence of coeliac disease of the order of 1 in 150.¹⁶ The prevalence figures obtained in patients with epilepsy in this study strongly indicate that coeliac

disease occurs with greater frequency than in the general population.

The mechanism of the association is unknown and any suggestions are speculative. Coeliac disease is an immunologically-mediated condition related to intolerance to dietary gluten. Many immunological abnormalities have been described in patients with epilepsy.¹⁷ Epilepsy occurs in immune-mediated conditions such as SLE, IgA deficiency and myasthenia gravis more often than would be expected by chance.^{17,18} A number of immunoglobulin abnormalities have been described in epilepsy patients, in part related to anti-convulsant therapy,¹⁹ and epilepsy patients have a high prevalence of antinuclear and anticardiolipin antibodies.²⁰ Immunoglobulin infusion is of proven benefit in some patients with epilepsy, particularly in children.²¹ Epilepsy in a subset of patients may, therefore, be the result of an immune process, and the association between coeliac disease and epilepsy may be a reflection of the tendency of immunologically-mediated conditions to occur together. Neurological syndromes other than epilepsy may also be associated with coeliac disease.²² A suggested mechanism is that the antibodies associated with coeliac disease may be themselves neurotoxic or, alternatively, may be a marker for a neurotoxic immunological process.²²

A high index of suspicion for coeliac disease should exist in patients with epilepsy. Any patient with epilepsy with gastrointestinal or constitutional symptoms, no matter how mild or non-specific, or with any evidence of malabsorption, should be screened for coeliac disease. Untreated coeliac disease may account for poor seizure control, through impaired drug absorption and possibly through occult malabsorption of vitamins and nutrients. Low serum folic acid²³ and vitamin D²⁴ concentrations should not be automatically attributed to anti-convulsant therapy. There are suggestions that a gluten-free diet may have a beneficial effect on seizure control.^{6,25} In addition, the institution of a gluten-free diet, even in asymptomatic patients without apparent consequences of coeliac disease is worthwhile. An increased risk of gastrointestinal malignancies, particularly small-bowel lymphoma,²⁶ of osteoporosis,²⁷

Table 2 Clinical features and investigations in 16 patients with coeliac disease and epilepsy

Patient	Sex (M/F)	Age (years) at diagnosis of coeliac disease	Age (years) at diagnosis of epilepsy	Epilepsy type	Epileptic features on EEG: yes (Y) or no (N)	CT scan appearance	Anti-convulsant drug treatment	Seizure control
1	F	<1	<1	Complex partial	N	Normal	Carbamazepine, lamotrigine	Continuing seizures
2	F	41	20	Generalized myoclonic	Y	Normal	Clonazepam	Continuing seizures
3	F	73	4	Complex partial	N	Lacunar infarcts	Phenytoin, vigabatrin	Continuing seizures
4	F	49	18	Generalized tonic-clonic	N	Normal	Phenobarbitone, valproate	Continuing seizures
5	F	34	22	Generalized tonic-clonic	NA	Normal	Phenytoin, valproate	Seizure-free
6	M	<1	20	Generalized tonic-clonic	Y	Normal	Phenytoin, valproate	Continuing seizures
7	F	29	5	Generalized tonic-clonic	NA	Normal	None	Seizure-free
8	F	4	22	Generalized tonic-clonic	Y	Normal	Carbamazepine	Seizure-free
9	F	36	27	Generalized tonic-clonic	Y	Normal	Phenytoin	Seizure-free
10	M	4	20	Complex partial	Y	Normal	None	Seizure-free
11	M	<1	<1	Generalized tonic-clonic	Y	Normal	Phenobarbitone, phenytoin	Continuing seizures
12	M	30	6	Complex partial with secondary generalization	Y	Normal	Carbamazepine	Seizure-free
13	M	<1	37	Generalized tonic-clonic	N	Normal	None	Seizure-free
14	M	50	64	Simple partial with motor signs	NA	Cerebral atrophy	–	Deceased
15	F	41	44	Generalized tonic-clonic	NA	Cerebral atrophy	–	Deceased
16	F	62	67	Generalized tonic-clonic	NA	Cerebral atrophy	–	Deceased

Patients 1–4 were those detected in screening study; patients 14–16 had symptomatic seizures. NA, not available.

and of infertility and recurrent abortions^{13,14} are among the complications of coeliac disease that may be averted, or at least improved, by a gluten restriction. Even in patients who cannot or will not comply with gluten restriction, care can be taken to ensure repletion of iron, folic acid and fat-soluble vitamins, and to detect complications as early as possible.

Coeliac disease, epilepsy and cerebral calcification

Anecdotal reports suggested the existence of a specific syndrome of coeliac disease, epileptic seizures and cerebral calcification,⁵ the existence of which was confirmed by several later series.⁶⁻⁹ While most reported cases have been from Italian centres, it has been suggested that this syndrome is not peculiar to there, and that cases elsewhere may be unrecognized.²⁸ Coeliac disease in patients with cerebral calcification is frequently asymptomatic and detected only by screening.^{6,8} In most patients, epilepsy was diagnosed during childhood, and was apparent before diagnosis of coeliac disease.⁶ Nearly all subjects with the syndrome have partial seizures, frequently of the occipital lobe type, and these are often poorly responsive to anti-convulsant drugs.⁶ Calcification is typically bilateral, and occurs in the cortical/subcortical regions in the parieto-occipital lobes.^{6,8} Occipital lobe seizures may also occur in coeliac disease patients without cerebral calcification.⁷

The syndrome of coeliac disease, epilepsy and intracranial calcification appears to be relatively common in Italy. For example, in a multi-centre series, 5/12 patients with epilepsy and coeliac disease had intracerebral calcification.⁶ In a review of 128 patients attending a coeliac disease clinic, five patients had epilepsy, of whom four had cerebral calcification.²⁵ In a large paediatric epilepsy clinic, nine patients had coeliac disease, of whom three had cerebral calcification.⁴ It is generally agreed that Ireland has a high frequency of coeliac disease.^{16,29} In this series, the features of epilepsy were not similar to those reported in patients with coeliac disease and intracranial calcification. The proportion with partial seizures was similar to that in the overall clinic population. No patient had either occipital lobe seizures or cerebral calcification on CT scanning. Therefore, the syndrome of coeliac disease, epilepsy and intracranial calcification did not occur in a relatively large series of 16 patients with both coeliac disease and epilepsy. To confirm that the syndrome is either ethnically or geographically restricted requires further study in other population groups.

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