LIISA LUOSTARINEN

Neurological Manifestations in Coeliac Disease

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ACADEMIC DISSERTATION

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Coniecturalem artem esse medicinam.

Medicine is the art of guessing.

(Aulus Cornelius Celsus, De medicina)

Facito aliquid operis, ut te semper diabolus inveniat occupatum.

Always do something, so that the devil always finds you occupied.

(St. Jerome, Epistulae)

To

Markku, Justiina and Eemeli

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Abstract

The clinical picture of coeliac disease has changed over the years. Nowadays the classical symptoms, steatorrhoea, weight loss and malabsorption syndrome, are rare and in typical cases abdominal symptoms are mild or even absent. Gluten-free dieting restores the mucosal function and prevents the development of many complications associated with untreated coeliac disease.

Coeliac disease is underdiagnosed. Its estimated prevalence has been as high as 1% in recent screening studies. Coeliac disease may present itself with various extraintestinal symptoms. Neurological symptoms are the presenting feature in as many as 7% of new coeliac disease cases. In patients with ataxia of unknown origin, the frequency of coeliac disease may be as high as 17%. An association prevails, moreover, between coeliac disease and epilepsy, though the previously described syndrome of coeliac disease, epilepsy, and intracranial occipital calcifications seems to be rare in adults. Neuromuscular disorders are common even in patients with well-treated coeliac disease. The mechanisms underlying neurological disorders associated with coeliac disease are unknown. Even the impact of a gluten-free diet in modifying neurological symptoms associated with coeliac disease is uncertain.

Neurologists should be aware of neurological symptoms associated with coeliac disease and screening for the disease is warranted in cases evincing neurological symptoms of unknown origin concomitant with coeliac disease.

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Abbreviations

ARA	antireticulin antibody
AGA	antigliadin antibody
CAG	DNA triplet (cytosine-adenine-guanine)
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
DH	dermatitis herpetiformis
EmA	endomysial antibody
EMG	electromyography
ENMG	electroneuromyography
GAA	DNA triplet (guanine-adenine-adenine)
GFD	gluten-free diet
MHC	major histocompatibility complex
MUP	motor unit potential
PNS	peripheral nervous system
SWs	Sturge-Weber syndrome
tTGA	tissue transglutaminase antibody
tTG	tissue transglutaminase

List of original communications

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Introduction

Neurological symptoms in association with adult steatorrhoea have been identified since the beginning of the twentieth century. The first reports did not differentiate between tropical and non-tropical sprue, but since the introduction of the jejunal mucosa biopsy in 1957, more relevant data on coeliac disease and neurological manifestations have been available (Cooke and Smith 1966, Morris et al. 1970). The first larger study of coeliac disease and neurological complications was published in Brain in 1966 (Cooke and Smith 1966). The authors described 16 patients suffering from neuropathy, in whom jejunal biopsy had revealed mucosal villous atrophy. All 16 also had gait ataxia, and five suffered unexplained attacks of unconsciousness. The prevalence of neurological complications in coeliac disease has been reported to be as high as 35.7% (Bannerji and Hurvitz 1971). Of the 42 patients in the study in question, five had myopathy, 4 tetany, 2 peripheral neuropathy, 2 pyramidal and other long tract lesions, and 1 spinal cord degeneration, and 1 was hypokalaemic. All these patients were suffering from overt malabsorption. The investigators assumed that the aetiological factor underlying the neurological symptoms was a deficiency of vitamins or some trace elements.

The spectrum of coeliac disease has altered over the years. Nowadays most patients are asymptomatic or have only minor symptoms, whereas an overt malabsorption state is rare (Mäki and Collin 1997, Collin et al. 1997a). Patients with coeliac disease nevertheless evince neurological symptoms (Hadjivassiliou et al. 1996). The neurological disorders most often described in association with coeliac disease are cerebellar ataxia, peripheral neuropathy, and epilepsy with or without intracerebral calcifications and neuropathy (Wright 1995, Pfeiffer 1996, Perkin and Murray-Lyon 1998). The mechanisms behind the development of these neurological manifestations are obscure, and it remains to be established whether early institution of gluten-free diet (GFD) might prevent the development of neurological

manifestations in association with coeliac disease. This would warrant a more aggressive screening policy for the early detection of the disorder.

The purpose of this study was to evaluate neurological symptoms and signs in coeliac disease, and to investigate the frequency of coeliac disease accompanying selected neurological conditions. We also studied the frequency of the syndrome comprising coeliac disease, epilepsy and intracerebral calcifications in Finnish epilepsy patients. If the frequency of coeliac disease is increased in these conditions, a high index of clinical suspicion might help to find coeliac disease cases and prevent complications.

Review of the literature

What is coeliac disease?

Historical background

The typical features of coeliac disease, severe steatorrhoea and cachexia, were described by Doctor Samuel Gee in 1888. Sixty years later a Dutch paediatrian, W.K. Dicke (1950), recognised the harmful effect of ingested wheat gluten and a few years later Paulley (1954) reported small-bowel mucosal villous atrophy with chronic inflammation as a constant finding in the condition. The development of peroral intestinal biopsy in 1957 made diagnosis of coeliac disease possible (Shiner 1957). Up to that time case identification has been based entirely on the search for symptoms such as chronic diarrhoea, abdominal distension and weight loss. In the 1990`s it became apparent that coeliac disease is underdiagnosed; the clinical features of the disease have changed and silent disease is frequently found (Grodzinsky et al. 1994, Catassi et al. 1994, Mäki and Collin 1997, Fasano 2001).

Clinical symptoms

The classical symptoms of coeliac disease are, as noted, steatorrhoea, weight loss, diarrhoea and malabsorption syndrome. Bone disorders such as bone pain and osteomalacia were also formerly common in patients with malabsorption syndrome. Nowadays, due to better recognition of the disease, malabsorption and steatorrhoea have become rare and cases with milder symptoms or even without symptoms are

diagnosed. Patients may have mild abdominal discomfort or isolated malabsorption of iron, calcium and folic acid, but deficiency of these nutrients does not constantly lead to clinical manifestations (Visakorpi et al. 1970, Bodé and Gudmand-Høyer 1996, Collin et al. 1997a, Johnston et al. 1998, Collin et al. 1999, Feighery 1999). Dermatitis herpetiformis (DH), a blistering skin disease, is one classical manifestation. Less than 10-30% of patients with DH have gastrointestinal symptoms suggestive of coeliac disease (Reunala 1998, Wills et al. 2002).

Diagnosis of coeliac disease

In untreated coeliac disease the typical findings in the small-bowel mucosa are villous atrophy, crypt hyperplasia and an increased density of intraepithelial lymphocytes (IEL). Chronic inflammatory cells are increased in the lamina propria and the enterocyte height is reduced. During a GFD these histological features improve concomitantly with clinical recovery, but reappear upon gluten challenge (Ferguson and Murray 1971, Kuitunen et al. 1982, Kaukinen et al. 1998). The first diagnostic criteria for coeliac disease were defined in 1969 by an expert board of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN). These criteria were modified in 1990 (Walker-Smith et al. 1990) The finding of characteristic small-bowel mucosal atrophy remains the basis for diagnosis and the effect of a GFD must be evidenced by clinical and in asymptomatic coeliac disease patients also by histological recovery. The presence of circulating antibodies, antireticulin (ARA), antiendomysial (EmA) antigliadin (AGA) and tissue transglutaminase antibodies (tTGA) while on gluten-containing diet and their disappearance on GFD support the diagnosis of coeliac disease.

In patients with DH, granular immunoglobulin A (IgA) deposits in the dermis are pathognomic for the disease. Most patients with DH have small-bowel villous atrophy and crypt hyperplasia consistent with coeliac disease and the rest have mucosal inflammation (Reunala 1998, Wills et al. 2002).

In the diagnosis of atypical and asymptomatic cases screening for ARA, EmA, AGA and tTGA is helpful in selecting cases for small-bowel biopsy (Table 1). Although the ELISA tTGA assay is more convenient than EmA testing, both offer a similar sensitivity or specificity, 75-100% and 94-100%, respectively (Mäki et al.

1991, Ascher et al. 1996, Sulkanen et al. 1998b, Lagerqvist et al. 2001, Bardella et al. 2001, Dickey et al. 2001). The incomplete concordance between EmA and tTGA positivity means that combination screening with both assays offers higher sensitivity. Selective IgA deficiency is common in patients with coeliac disease and since some patients even with normal serum IgA are negative for all antibodies, biopsies should still be performed in seronegative individuals at high risk of coeliac disease (Mäki et al. 1991, Ascher et al. 1996, Sulkanen et al. 1998b, Bardella et al. 2001, Dickey et al. 2001, Lagerqvist et al. 2001).

The current diagnostic criteria for coeliac disease require small-bowel villous atrophy, although the villous damage develops gradually. In the early stage of the disease these diagnostic criteria are not fulfilled, as the disease and its complications are still evolving (Mäki and Collin 1997, Kaukinen et al. 2001).

Treatment of coeliac disease

The environmental trigger in coeliac disease is ingested gluten and permanent withdrawal of gluten results in clinical and histological recovery. Cereal prolamins, wheat (gliadin), rye (secalin) and barley (hordein), are all toxic in coeliac disease, whereas oat prolamin (avenin) appears to be tolerated (Janatuinen et al. 1995, Godkin and Jewell 1998, Picarelli et al. 2001, Stern et al. 2001, Janatuinen et al. 2002). A strict GFD is recommended for the prevention of complications such as lymphoma or osteoporosis (Holmes et al. 1989, Cellier et al. 2000, Sategna-Guidetti et al. 2000, Valdimarsson et al. 2000, Mora et al. 2001). Also iron deficiency anaemia (Sari et al. 2000, Annibale et al. 2001) and quality of life (Hallert 1998, Hallert and Lohiniemi 1999) improve with a GFD. The mortality rate does not differ in well-treated coeliac disease compared with controls (Collin et al. 1994a, Corrao et al. 2001). Although GFD has not shown any effect on the metabolic control of type 1 diabetes in patients with diabetes and coeliac disease (Kaukinen et al. 1999), there is a suspicion that dieting might prevent the progression of certain other disorders associated with coeliac disease (Kaukinen et al. 2002b).

Prevalence of coeliac disease

Coeliac disease is a particularly common disorder (Table 2). In Finland, its clinical prevalence has been 0.27–0.75% (Collin et al. 1997b, Kolho et al. 1998). Recent screening studies have established prevalence figures as high as 1% in Sardinia, New Zealand and Hungary (Korponay-Szabo et al. 1999, Meloni et al. 1999b, Cook et al. 2000).

Table 1. Sensitivity and specificity of IgA-class EmA, ARA, tTGA and IgA- and IgG-class AGA tests

Author	IgA-EMA	IgA-ARA	IgA-tTGA	IgA-AGA	IgG-AGA
Sensitivity (%)					
Mäki et al. 1991	92	92		31	46
Ascher et al. 1996	98	89		91	96
Sulkanen et al. 1998	93	92	95	85	69
Lagerqvist et al. 2001	100		100	89	89
Bardella et al. 2001	100		100	95	
Dickey et al. 2001	81		75		
Specificity (%)					
Mäki et al. 1991	95	95		87	89
Ascher et al. 1996	100	72		99	69
Sulkanen et al. 1998	100	96	94	82	73
Lagerqvist et al. 2001	100		97	96	78
Bardella et al. 2001	97		98	89	
Dickey et al. 2001	97		98		

Table 2. Prevalence of coeliac disease

	Population		Prevalence of coeliac disease	Screening method	Biopsy-pro
Author	**Study group / Area**	**N**			
Catassi et al. 2000	Students / Sardinia	2096	0.91%	AGA + EmA	yes
Collin et al. 1997b	Clinical cases / Finland	147000	0.27%	Risk groups	yes
Cook et al. 2000	Adults / New Zealand	1064	1.2%	EmA	yes
Gomez et al. 2001	Adults / Argentina	2000	0.55%	AGA + EmA	yes
Hovdenak et al. 1999	Blood donors / Norway	2096	0.33%	AGA + EmA	yes
Hovell et al. 2001	Rural community / Australia	3011	0.40%	EmA	yes
Johnston et al. 1997	General population / Ireland	1823	0.82%	AGA +ARA+ EmA	yes
Kolho et al. 1998	Adults, hospital staff / Finland	1070	0.75%	EmA	yes
Korponay-Szabo et al. 1999	Preschool children / Hungary	427	1.2%	EmA	yes
Meloni et al. 1999b	Schoolchildren / Sardinia	1607	1.1%	AGA+EmA	yes
Riestra et al. 2000	General population / Spain	1170	0.26%	AGA + EmA	yes
Weile et al. 2001	Blood donors / Sweeden	1866	0.27%	AGA + EmA	yes
	Blood donors / Denmark	1573	0.25%	AGA + EmA	no
Volta et al. 2001a	General population / Italy	3483	0.49%	EmA	yes

Pathogenesis of coeliac disease

Genetic factors

Susceptibility to coeliac disease is determined particularly by genetic factors. HLA genes side by side with non-HLA genes predispose to the disease (Sollid et al. 2001, Greco et al. 2002). The disease is strongly associated with the HLA DQ2 haplotype encoded by alleles DQA1*0501 and DQB1*0201. Approximately 90% of coeliac disease patients share this HLA DQ2 haplotype compared to 20-30% found in the population in general (Sollid et al. 1989, Tosi et al. 1983, Polvi et al. 1996, Tuysuz et al. 2001). Most DQ2-negative coeliac disease patients express the DR4-DQ8 (DQA1*0301, DQB1*0302) haplotype (Polvi et al. 1998, Perez-Bravo et al. 1999, Tuysuz et al. 2001). These haplotypes are also common in various autoimmune disorders such as insulin-dependent diabetes mellitus, autoimmune thyroiditis and Sjögren`s syndrome (Dalton and Bennett 1992, Krzanowski 1992). Since more than 95% of coeliac disease patients share the HLA DQ2 or DQ8 haplotype, the absence of this haplotype might be used to exclude coeliac disease in clinical practice (Kaukinen et al. 2002b).

Immunological and pathogenetic aspects

It is widely accepted that immunological mechanisms are involved in the development of the mucosal damage seen in coeliac disease. In untreated patients there are signs of activation of mucosal cellular and humoral immune systems (Sollid 1989, Peña et al. 1998). The principal environmental trigger is ingested gluten, but additional factors may be required. Enteric adenovirus infection has been suspected to be a part in the causation of coeliac disease (Kagnoff et al. 1987). Gluten-specific HLA DQ2 and DQ8 restricted T-cells are present in lesions of the small-bowel mucosa (Lundin et al. 1993, Przemioslo et al. 1995). Tissue transglutaminase is

considered to be possibly the unique autoantigen for coeliac disease (Dieterich et al. 1997). In active coeliac disease the expression of tTG is increased and the enzyme enhances the binding of gliadin peptides to HLA DQ2 and DQ8 molecules through deamination of glutamine residues (Bruce et al. 1985, Molberg et al. 2001). This results in better binding affinity and increased T-cell reactivity (Mollberg et al. 1998). Secretion of interferon-ν and other inflammatory cytokines by activated lamina propria T-cells can damage the small-bowel mucosa. It has also been suggested that antibodies against tissue transglutaminase may play a direct role in the pathogenesis of coeliac disease. In an in vitro model tTG has been seen to inhibit epithelial differentiation on the crypt villous axis (Halttunen and Mäki 1999).

Extraintestinal manifestations

Extraintestinal symptoms and complications

Patients with coeliac disease may also have atypical and extraintestinal symptoms (Holmes 1996) (Table 3). DH being the most common extraintestinal manifestation. This is a blistering skin disease with predilection sites on elbows, knees, buttocks and scalp. The rash resolves on a GFD (Reunala et al. 1984, Reunala 1998). Coeliac disease patients may also have dental enamel defects (Aine et al. 1990), and suffer from infertility or unfavourable outcome of pregnancy (Meloni et al. 1999a, Martinelli et al. 2000). Patients with untreated coeliac disease are at risk of significant complications such as small-bowel lymphoma and osteoporosis (Cooper et al. 1982, Kemppainen et al. 1999, Meyer et al. 2001). It is not clear whether these disorders are atypical symptoms of coeliac disease or consequences of malabsorption of nutrients.

Table 3. Complications and atypical symptoms in coeliac disease

Symptom / complication	Author	No of coeliac disease cases	Frequency of disorder
Defects in bone mineralisation			
Dental enamel defects	Aine et al. 1990	40	83 %
Osteoporosis, lumbar spine	Meyer et al. 2001	128	34 %
Osteopenia, lumbar spine			38 %
Osteoporosis, lumbar spine	Kemppainen et al. 1999	77	26 %
Osteopenia, lumbar spine			35 %
Unfavowrable outcome of pregnancy			
History of miscarriages	Martinelli et al. 2000	12	33 %
Child small for gestational age			41 %
Child died in the first week of life			25 %
Arthritis			
Arthritis	Lubrano et al. 1996	200	26 %
Sacroilitis	Usai et al. 1995	22	63.6%
Malignancy			
Lymphoma	Cooper et al. 1982	314	6.3%
Miscellaneous			
Vitamin B12 deficiency	Dahele and Ghosh 2001	39	41 %
Lymphocytic gastritis	Feeley et al. 1998	70	10 %
Hypothyroidism	Sategna-Guidetti et al. 2001	241	12.9%

Table 4. Frequency of coeliac disease in associated diseases and symptoms

Disease or symptom	Author	Cases	Frequency of coeliac disease	Screening method	Biopsy-proven
Immunological diseases					
Addison`s disease	O`Leary et al. 2002	44	12.2%	EmA	Yes
Autoimmune thyroiditis	Berti et al. 2000	172	3.4%	EmA	Yes
Autoimmune thyroid disease	Collin et al. 1994b	83	4.8%	AGA + ARA+ EmA	Yes
	Cuoco et al. 1999	92	4.3%	AGA + EmA	Yes
	Sategna-Guidetti et al. 1998	152	3.3%	EmA	Yes
Autoimmune hepatitis	Volta et al. 1998	181	2.8%	AGA + EmA	Yes
Alopecia areata	Corazza et al. 1995	256	1.2%	AGA + EmA	Yes
Diabetes mellitus, type 1	Aktay et al. 2001	218	4.6%	EmA	Yes
	Collin et al. 1989	195	4.1%	ARA	Yes
	Gillett et al. 2001	230	7.7%	EmA + tTGA	Yes
	Matteucci et al. 2001	74	1.4%	AGA + EmA	Yes
	Not et al. 2001	491	5.7%	EmA	Yes
	Cronin et al. 1997	101	5.0%	EmA	Yes
	Talal et al.1997	185	2.2%	EmA	Yes
Juvenile chronic arthritis	Lepore et al. 1996	119	2.5%	EmA	Yes
Primary biliary cirrhosis	Kingham and Parker 1998	67	6.0%	Medical records	Yes
	Dickey et al. 1997	57	7.0%	EmA	Yes
Sjögren`s syndrome	Iltanen et al. 1999	34	14.7%	Biopsy	Yes

Disease or symptom	Author	Cases	Frequency of coeliac disease	Screening method	Biopsy-proven
Malignancy					
Non-Hodgkin´s lymphoma	Catassi et al. 2002	653	0.92%	EmA	No
Chromosomal diseases					
Down`s syndrome	Book et al. 2001	97	10.3%	EmA	No
	Bonamico et al. 2001	1,202	4.6%	AGA + EmA	No
	Carnicer et al. 2001	284	6.3%	AGA + EmA	Yes
	Gale et al. 1997	51	3.9%	AGA	Yes
	Mackey et al. 2001	93	3.2%	Ema	Yes
	Zachor et al. 2001	75	6.7%	AGA + EmA	Yes
Turner´s syndrome	Ivarsson et al. 1999	87	3.4%	AGA + EmA	Yes
	Bonamico et al. 1998	37	8.1%	AGA + EmA	Yes
Infertility					
Infertility	Meloni et al. 1999a	99	3.0%	AGA + EmA	Yes
	Collin et al. 1996	150	2.7%	ARA + AGA	Yes
Unexplained infertility	Meloni et al. 1999a	25	8.0%	AGA + EmA	Yes
Gastroenterological associations					
Cryptogenic hypertransaminasaemia	Volta et al. 2001b	110	9.2%	Ema + tTGA	Yes
Lymphocytic colitis	Matteoni et al. 2001	27	15 %	Medical records	Yes

Associated disorders

Coeliac disease has been reported as occurring in close association especially with various autoimmune disorders. Associations with type 1 diabetes mellitus, autoimmune thyroid diseases, alopecia areata, primary biliary cirrhosis, autoimmune hepatitis, primary Sjögren`s syndrome and Addison`s disease have been described (Table 4). Recent studies have pointed out high prevalence of coeliac disease and some of these disorders described in association with it may be only coincidental. Association with Down`s and Turner`s syndrome has also been described (Table 4).

Coeliac disease and the central nervous system

Coeliac disease and ataxia

There is some controversy as to the concomitant occurrence of coeliac disease and ataxia of unknown origin (Table 5). In all studies in question the diagnosis of coeliac disease was confirmed by small-bowel biopsy. Hadjivassiliou and colleagues in 1996 reported 16% of patients with ataxia of unknown cause to be suffering from coeliac disease. Pellecchia and colleagues (1999a) found three (12.5%) coeliac disease cases among 24 ataxic syndromes of indefinite origin. Bürk and associates (2001) found a coeliac disease frequency of 1.9% in patients with idiopathic cerebellar ataxia. In conflict with these findings, a group under Combarros (2000) failed to find any cases of coeliac disease in a cohort of 32 patients with idiopathic cerebellar ataxia. In that study, none of the patients was positive for gliadin, reticulin, endomysium or tTG antibodies. Likewise Bushara and associates (2001) found no definite coeliac disease cases among 26 patients with sporadic ataxia or in 24 patients with dominant cerebellar ataxia. However, the number of patients in these two studies was small. To summarise, the frequency of coeliac disease was significantly increased only in the studies by Hadjivassiliou (1996) and Pellechia (1999a). The others could not confirm

this finding of an increased frequency of coeliac disease in association with ataxia of unknown origin.

Hadjivassiliou and associates (1999) have pointed out the problematic nature of the diagnosis of coeliac disease. They widened the spectrum of gluten intolerance in neurological disorders and recommended a definition of gluten sensitivity as a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals. The disease is not restricted to the gut, but can manifest itself as DH or in neurological symptoms. Sometimes extraintestinal symptoms precede the diagnosis of coeliac disease. The patient may have increased levels of circulating antibodies against gliadin and the HLA genotype associated with coeliac disease without yielding small-bowel biopsy findings compatible with the diagnosis of coeliac disease. Gluten sensitivity in this form has been described in association with sporadic cerebellar ataxia (Table 5, Bushara et al. 2001, Bürk et al. 2001). Hadjivassiliou and colleagues (1998) identified increased titres of gliadin antibodies in 28 adult outpatients with ataxia. Patients with identified causes of ataxia were excluded. Only 11 had biopsy-proven coeliac disease and an additional two evinced lymphocytic infiltration in duodenal biopsy. Out of these 28 patients, 23 (82%) had the HLA DQ2 genotype and the remaining five had DR4-DQ8. In other words, all had HLA compatible with coeliac disease. The clinical syndrome of ataxia was characterised by mild upper limb ataxia but moderate to severe gait ataxia and male predominance. The mean age at onset of ataxia was 54 years. In addition, the investigators found a correlation between duration and severity of ataxia and the presence of cerebellar atrophy. In a study by Pellechia (1999a), no cases of gluten sensitivity were detected in the absence of histological changes typical of coeliac disease. Clinically, no distinctive neurological features were found in ataxia patients with or without coeliac disease.

A progressive set of neurological symptoms characterised by cerebellar ataxia, posterior column dysfunction and peripheral neuropathy is occasionally found related to vitamin E deficiency in cases of ataxia associated with untreated symptomatic coeliac disease. Clinical improvement or stabilisation of symptoms has been achieved with vitamin E therapy in some coeliac disease cases (Mauro et al. 1991, Beversdorf et al. 1996). However, obvious malabsorption has been rare or even absent in all

recent studies describing the association of coeliac disease and ataxia (Ward et al. 1985, Hadjivassiliou et al. 1996 and 1998, Pellechia et al. 1999a, Bürk et al. 2001).

Pellecchia and associates (1999b) have reported one patient with cerebellar ataxia associated with coeliac disease responding to a GFD, but there are also reports of GFD failing to show improvement of ataxia syndrome (Cooke and Smith 1966, Hermaszewski et al. 1991, Muller et al. 1996). Progression of ataxia symptoms has been documented in a patient with poor dietary compliance (Kristoferitsch 1987).

Table 5. Ataxia in association with coeliac disease

Author	Study population, (N)	Screening method	Summary of results
Bürk et al. 2001	Adults	AGA + EmA	
	Idiopathic ataxia, (104)		10.6% (11/104) AGA positive 1.9% (2/104) biopsy finding consistent with coeliac disease 4.8% (5/104) inflammatory changes but otherwise normal mucosal architecture in biopsy
Combarros et al. 2000	Adults	AGA + EmA + ARA + tTGA	
	Idiopathic ataxia, (32)		None of these patients was positive in screening tests
Bushara et al. 2001	Adults	AGA + EmA	
	Sporadic ataxia, (26) Hereditary ataxia, (24)		27% (7/26) AGA-positive, all EmA-negative 37% (9/24) AGA-positive, all EmA-negative Biopsy: 15/16, 8 normal and 7 (4 with sporadic ataxia) inflammatory changes, villous blunting, but no crypt hyperplasia; no confirmed coeliac disease cases
Hadjivassiliou et al. 1996	Adults	AGA	
	Sporadic ataxia, (25)		68% (17/25) AGA-positive Biopsy: 13/17, 4 normal, 5 non-specific duodenitis, 4 (16%) with findings consistent with coeliac disease
Pellechia et al. 1999a	Adults	AGA + EmA	
	Idiopathic ataxia, (24)		12.5% (3/24) AGA-positive, biopsy confirmed coeliac disease
	Hereditary ataxia, (23)		Screening tests normal
	Total of 211 patients with ataxia of unknown origin		**4.3% (9/211) biopsy-proven coeliac disease**

Coeliac disease and epilepsy

An association between coeliac disease and epilepsy has been reported in many studies (Table 6). In 1966 Cooke and Smith described five (31%) patients with unexplained falls of unconsciousness out of 16 patients with neuropathy and small bowel biopsy findings compatible with a diagnosis of coeliac disease. Chapman and colleagues (1978) detected an increased prevalence of epilepsy (5.5 %) in patients with coeliac disease compared to controls, whereas a group under Hanly (1982) reported a frequency equal to that in the general population. Fois and associates (1994) showed a 1.2% prevalence of coeliac disease in paediatric epilepsy patients. Recently, Cronin and associates (1998) reported an increased prevalence of coeliac disease in adult Irish patients attending an epilepsy clinic. Of 177 patients screened for coeliac disease, four (2.3%) had biopsy-proven disease. This finding was statistically significant compared to the frequency in the control group (0.4 %), which consisted of pregnant women.

Sammaritano and associates (1985) first proposed a new syndrome including coeliac disease, epilepsy and intracranial calcifications. Visakorpi and colleagues (1970) had described such a patient 15 years earlier. Since then, evidence for the existence of this particular syndrome has been accumulating from many case reports and small series of patients, most of them from Italy (Ventura et al. 1991, Ambrosetto et al. 1992, Gobbi et al.1992a and 1992b, Bye et al. 1993, Magaudda et al. 1993, Piattella et al. 1993, Tiacci et al.1993, Fois et al. 1993 and 1994, Lea et al. 1995, Cernibori and Gobbi 1995, Toti et al. 1996, Bernasconi et al. 1998, Hernandez et al. 1998, Molteni et al. 1988, Calvani et al. 2001). Gobbi and colleagues (1992b) reported the largest series of patients with the new syndrome (Table 7). They found that as many as 77% (24/31) of patients with epilepsy and posterior cerebral calcifications of unexplained origin were suffering from coeliac disease. They further showed that such calcifications can be found in 42% (5/12) of patients with coeliac disease and epilepsy. In a recent work by Cronin and colleagues (1998) none of their 177 epilepsy patients screened for coeliac disease had cerebral calcifications on cerebral tomography scanning. In the study by Fois and associates in 1994 the frequency of this syndrome in paediatric patients with epilepsy was found to be 0.4%.

The pathology of calcifications in association with coeliac disease is uncertain (La Mantia et al. 1998). Originally these patients were thought to be atypical variants of the Sturge–Weber syndrome (SWs), but unlike SWs, they often have bilateral brain calcifications, the nevus flammeus is lacking and brain CT scans show no contrast enhancement or lobar hemispheric atrophy such as are virtually always present in SWs (Ambrosetto et al. 1992, Gobbi et al. 1992 b, Magaudda et al. 1993, Piattella et al. 1993). It has been proposed that the calcifications may be associated with low serum folate levels (Molteni et al. 1988, Gobbi et al 1992a and 1992b Piattella et al. 1993, Ventura et al.1991) but not necessarily (Magaudda et al. 1993). Little is known regarding the histology of the brain in the association of epilepsy with coeliac disease and intracerebral calcifications. A group under Bye (1993) reported one case in which there was cortical vascular abnormality with patchy pial angiomatosis, fibrosed veins and large microcalcifications, which were similar though not identical to SWs. Toti and associates (1996) reported a case in which X-ray spectroscopy revealed calcium (43%) and silica (57%) in calcified lesions.

Epilepsy in association with coeliac disease has been partial with or without secondary generalisation in most cases (Gobbi 1992a and b, Labate et al. 2001). Localisation has been often temporal, but many cases with occipital lobe epilepsy have also been described, especially in connection with occipital calcifications (Chapman et al. 1978, Ambrosetto et al. 1992, Bernasconi et al. 1998, Labate et al. 2001). The classification of epilepsy type is in most studies inadequate.

The course of epilepsy has been variable and the impact of GFD is not obvious (Molteni et al. 1988, Ambrosetto et al. 1992, Gobbi 1992b, Cernibori and Gobbi 1995, Hernandez et al. 1998).

Table 6. Epilepsy and coeliac disease

Frequency of coeliac disease in patients with epilepsy

Author	Study population	N	Method	Frequency of coeliac disease
Cronin et al. 1998	Hospital-based, seizure clinic adult epilepsy population	177	EmA, small-bowel biopsy	2.3% (4/177) in all epilepsy patients 2.7% (4/148) In patients with cryptocenic or idiopathic epilepsy
Fois et al. 1994	Hospital-based, paediatric patients	783	AGA + EmA, small-bowel biopsy	1.1% (9/783)
Labate et al. 2001	Hospital-based, paediatric patients		AGA + EmA, small-bowel biopsy	
	partial epilepsy with occipital paroxysms	25		8% (2/25)
	partial epilepsy with centrotemporal spikes	47		No positive antibodies

Frequency of epilepsy in patients with coeliac disease

Author	Study population	N	Method	Frequency of epilepsy
Chapman et al. 1978	Treated coeliac patients	185	Questionnaire + interview, neurologist	5.5% (2 grand mal + 7 temporal lobe)
	Control group, general practice patients	165	Questionnaire + interview, neurologist	0 %
Holmes 1996	Adult coeliac patients	340	Medical records	3.5%
Hanly et al. 1982	Coeliac patients, mean age 21 years, range 2-76	197	Questionnaire, Symptoms suggestive of epilepsy + EEG	Idiopathic epilepsy 1% (2/197) Post-traumatic epilepsy 1% (2/197)

Table 7. Coeliac disease, epilepsy and intracerebral calcifications of unknown origin

Author	Study population (N)	Main results
Cronin et al. 1998	Adult patients with coeliac disease and epilepsy (16)	No cases with intracerebral calcifications
Fois et al. 1994	Paediatric patients with epilepsy (783)	1.1% (9/783) coeliac disease 0.4% (3/783) coeliac disease and intracerebral calcifications 33% (3/9) epilepsy and coeliac disease with intracerebral calcifications, partial epilepsy
Gobbi et al. 1992 a	Epilepsy and cerebral calcifications of unknown origin (10) Age from 14 to 32 years	60% (6/10) had coeliac disease Mainly focal epilepsy
Gobbi et al. 1992 b	43 patients, mean age 16.4, range 5-31 years Epilepsy and intracerebral calcifications of unknown origin (31) Coeliac disease and epilepsy (12)	77% (24/31) coeliac disease 42% (5/12) intracerebral calcifications Most had partial epilepsy
Magaudda et al. 1993	Bilateral occipital calcifications (20) Mean age 15, range 6-32 years	95% (19/20) epilepsy 40% (8/20) coeliac disease, 16/20 with biopsy Most with partial epilepsy

Coeliac disease and dementia

An association of coeliac disease with dementia has been described in a few case reports (Cooke and Smith 1966, Kinney et al. 1981). In 1991, Collin and associates reported a series consisting of 5 patients who developed dementia before the age of 60 and were subsequently found to have coeliac disease. Intellectual deterioration ranged from moderate to severe, and diffuse cerebral or cerebellar atrophy was found in brain CT. The diagnosis of coeliac disease was confirmed by findings of subtotal villous atrophy in jejunal biopsy specimens and positive serum reticulin and gliadin antibodies. Apparently, gastrointestinal symptoms were mild. The gluten-free diet failed to improve the neurologic disability except in one patient. In contrast, Hallert and Åström (1983) found no consistent signs of cognitive impairment in adult patients with untreated coeliac disease. Frisoni (1997) found no difference in the prevalence of coeliac disease in Alzheimer's disease or cognitively unimpaired elders, suggesting that the immune changes in coeliac disease are unlikely to play a role in Alzheimer's disease. The question of a possibly increased frequency of dementia in patients with coeliac disease and mechanisms behind this possible association remains open.

Coeliac disease and the peripheral nervous system

Coeliac disease and neuropathy

In 1966 Cooke and Smith described 16 patients with adult coeliac disease and neuropathy. The series consisted of 11 men and five women and in all cases the diagnosis of coeliac disease was confirmed by jejunal biopsy. In two of the cases, diarrhoea was a presenting feature and neuropathy was considered an incidental finding at the first clinical examination. In four cases, neuropathy was the presenting symptom and in the remaining nine neuropathy developed while they were under

treatment for their gastrointestinal symptoms. Ten out of the 16 patients were on a gluten-free diet, but no positive responses in neuropathy findings were detected in this study. Neuropathy was unlikely to be the result of vitamin-B_{12} deficiency, because most patients had a normal serum vitamin-B_{12} level and in several patients the neuropathy developed or even continued to progress when they were taking parenteral vitamin-B_{12}. Since this study several case reports and small patient series have evidenced an association between coeliac disease and neuropathy (Cooke et al. 1966, Binder et al, 1967, Bundey 1969, Kaplan et al. 1988, Murphy et al. 1998, Simonati et al. 1998).

In 1971, Bannerji and Hurwiz described peripheral nervous system manifestations in seven (16.7%) out of 42 patients with coeliac disease. Two (4.7%) had peripheral neuropathy. In most cases the neuropathy was described as chronic axonal and affecting both sensory and motor nerves, but also cases with demyelinating neuropathy were described. Recently Hadjivassiliou and colleagues (1997) described nine patients with a neuromuscular disorder as a presenting feature of coeliac disease. Six patients had axonal sensorimotor polyneuropathy (of whom two presented with a pure motor neuropathy), one had mononeuropathy multiplex and one had Guillain-Barré type acute polyneuropathy. Sensory deficits were more pronounced than motor findings in the six patients with axonal polyneuropathy. These nine patients yielded no clinical or biochemical evidence of malabsorption at the onset of the neuropathy and the investigators suggested an immunological explanation for neuromuscular disorders in genetically susceptible patients. In a study of Usai and colleagues (1996), five (20%) out of 25 coeliac disease patients showed signs of autonomic neuropathy, this frequency being similar to that observed in other studies in patients with digestive motility disorders or irritable bowel syndrome.

In a study by Hadjivassiliou and associates (1997) the role of GFD was uncertain in modifying symptoms and findings of neuropathy in coeliac disease. In some case reports the symptoms have disappeared after introducing GFD (Kaplan et al. 1988, Polizzi et al. 2000), but in some cases there has been no benefit and symptoms have progressed during GFD (Tietge et al. 1997, Simonati et al. 1998).

Coeliac disease and myopathy

There is little information concerning muscle diseases in association with coeliac disease. In 1971, Bannerji and Hurwitz described myopathy in five (11.9%) out of 42 patients with coeliac disease. All of them also had vitamin D deficiency, which was considered to be the aetiological factor. There are also recent case reports dealing with an association of coeliac disease with osteomalacia or rickets and myopathy (Hardoff et al. 1980, Russel 1994, Cimaz et al. 2000). In these cases, myopathy improved after GFD. Coeliac disease has also been described in association with inflammatory myositis (Vilppula and Aine 1984, Marie et al. 2001), inclusion body myositis, neuromyotonia (Hadjivassiliou et al. 1997) and muscle dystrophy (Meini et al. 1995, Stenhammar et al. 1995), but these observations may be only coincidental.

Possible pathogenesis of neurological complications in coeliac disease

Both immunological and genetic factors contribute to the pathogenesis of coeliac disease. The genetic susceptibility locus is in the major histocompatibility complex (MHC) region, and the disease is closely associated with the HLA-DQ alleles DQA1*0501 and DQB1*0201. A recent study showed that a large proportion (70 %) of patients with sporadic ataxia and antigliadin antibodies carried coeliac disease-associated HLA alleles (Bürk et al. 2001). HLA DQ2 is strongly associated with other autoimmune diseases which, also supports the conception that there may be shared and immunologically mediated mechanisms contributing to the mucosal and neural tissue damage. Hadjivassiliou and associates (2002) have shown that patients with gluten ataxia have antibodies against Purkinje cells and antigliadin antibodies cross-react with epitopes on Purkinje cells. On the other hand, immunolocigal mechanisms may also contribute to the development of epilepsy (Aarli 1993).

There are few reports of neuropathological findings in patients with coeliac disease (Cooke and Smith 1966, Finelli et al. 1980). The most common alterations are myelin loss in peripheral nerves, nerve roots and spinal tracts and patchy neuronal loss in spinal ganglia, anterior horns, sensory ganglia and basal ganglia. In the

cerebellum pathological changes include focal neuronal loss especially affecting Purkinje and dentate cells. Hadjivassiliou and colleagues (1998) have reported two cases with necropsy findings. In one case of gluten ataxia neuropathological examination showed patchy loss of Purkinje cells in cerebellar cortex, astrocytic gliosis in the cerebellar white matter, vacuolation of the neuropil, and diffuse infiltrate mainly of T-lymphocytes within the cerebellar white matter and the posterior columns of the spinal cord. However, the diagnostic criteria of coeliac disease were not fulfilled because the duodenal mucosa was normal despite the presence of anti-gliadin antibodies. The neuropathological findings indicated that an inflammatory process may result in neural tissue damage. However, neuropathological examination in another coeliac disease case described by these investigators (1998) revealed degeneration of the posterior columns of the spinal cord without inflammation of the central nervous system.

One possible cause for neurological symptoms in association with coeliac disease is vitamin malabsorption. This was certainly formerly the case when coeliac disease patients suffered mostly from overt malabsorption. It is well established that nowadays coeliac disease may be silent and overt malabsorption is rare. However, subclinical metabolic disturbances remain a possibility (Alwitry 2000, Dahele and Ghosh 2001, Hallert et al. 1981, Harding et al. 1982, Kokkonen and Similä 1979, Rude and Olerich 1996, Stene-Larsen et al. 1988).

So far there is no evidence-based data on the mechanisms underlying different neurological manifestations in association with coeliac disease, but it has been suggested that genetic and immunological factors and sometimes malabsorption of nutrients might contribute to development of neurological symptoms.

Aims of the study

The purpose of the present study was to evaluate neurological manifestations in association with coeliac disease. The specific objects were:

I To study neurological manifestations as presenting features of adult coeliac disease

II To study the frequency of coeliac disease in patients with cerebellar ataxia of unknown origin

III To asses whether coeliac disease is over represented in Finnish hospital-based epilepsy population and to ascertain the frequency of the syndrome involving coeliac disease, epilepsy and intracerebral calcifications

IV To examine the frequency and characteristics of neuromuscular findings in adult patients with coeliac disease

Subjects and methods

Subjects

All patients were referred to the Departments of Neurology or Internal Medicine at Tampere University Hospital. Table 8 presents the subjects included in studies I-IV. Patients included in studies I and IV were adult coeliac disease patients detected at the Department of Internal Medicine. All had definite coeliac disease diagnosed according to the revised diagnostic criteria of the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN). The diagnosis of dermatitis herpetiformis was based on the typical rash and finding of granular IgA deposits in the uninvolved skin. In study IV, 50 consecutive coeliac disease patients were selected and 26 consented to participate. The control group included all the 58 patients with confirmed gastro-oesophageal reflux disease (coeliac disease excluded) on a waiting list for anti-reflux surgery at the Department of Surgery at Tampere University Hospital; 23 consented to take part.

Patients in studies II and III were collected from the Department of Neurology. The medical files of all consecutive adult patients with a diagnosis of late-onset cerebellar ataxia of unknown origin referred to the neurological unit at Tampere University Hospital during the years 1995-1997 were reviewed in study II and all were invited to participate in the study. The design of the study is presented in Figure 1. For study III, the medical records of 900 consecutive adult patients with a diagnosis of epilepsy who attended at the Department of Neurology in Tampere University Hospital during the years 1992-1993 were reviewed. Those still living (n=782) were divided into three groups. Group I included 147 patients who did not fulfil the diagnostic criteria of epilepsy defined as at least two spontaneous seizures.

These patients were excluded from the study. Group II comprised 435 patients who had symptomatic epilepsy. These patients were also excluded from the study. Group III included 199 patients who had possible cryptogenic epilepsy, 25.4 % out of the 782 living patients. These patients were included in the study (Figure 2).

Table 8. Patients in studies I-IV and the main aim of the study

	Study group			Control group		
Study	Subjects Aim of the study	N (female)	Mean age (range)	Subjects	N (female)	Mean age (range)
I	Consecutive adult patients with coeliac disease How often are neurological symptoms the presenting feature in coeliac disease?	144		No reference group		
II	Consecutive adult patients with cerebellar ataxia of unknown origin Frequency of coeliac disease in patients with cerebellar ataxia of unknown origin?	44 (11)	58 (30-80)	Patients with alcohol-induced ataxia Historical, previously published prevalence studies	20 (2)	55 (30-74)
III	Consecutive adult epilepsy patients without known cause of epilepsy Frequency of coeliac disease in patients with epilepsy ?	199 (113)	40 (19-67)	Historical, previously published prevalence studies		
IV	Consecutive adult patients with coeliac disease on gluten-free diet Frequency and characteristics of neuromuscular findings in adult patients with coeliac disease?	26 (19)	51 (22-77)	Consecutive adult patients with gastroesophageal reflux disease	23 (7)	50 (18-73)

Fiqure 1. Design of study II.
Coeliac disease in patients with ataxia of unknown origin

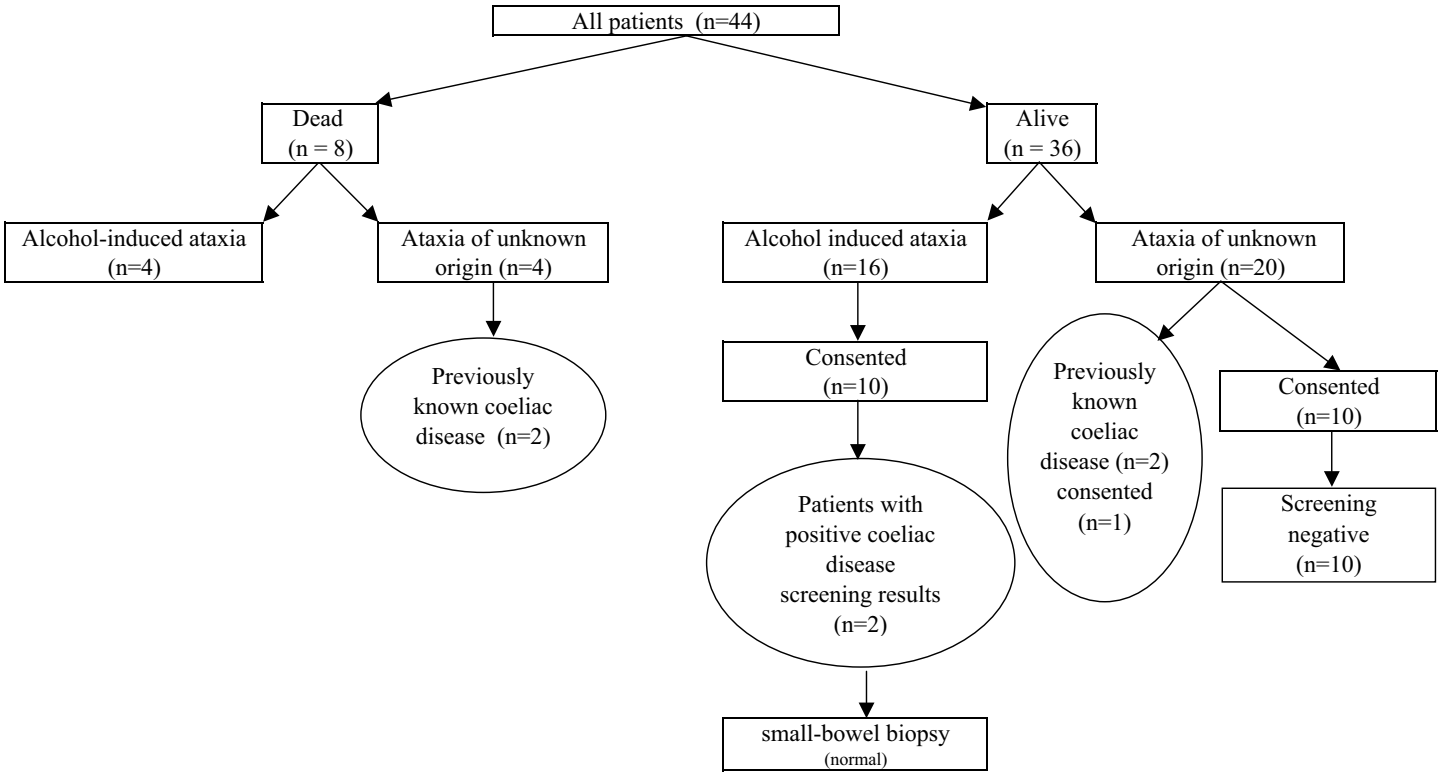
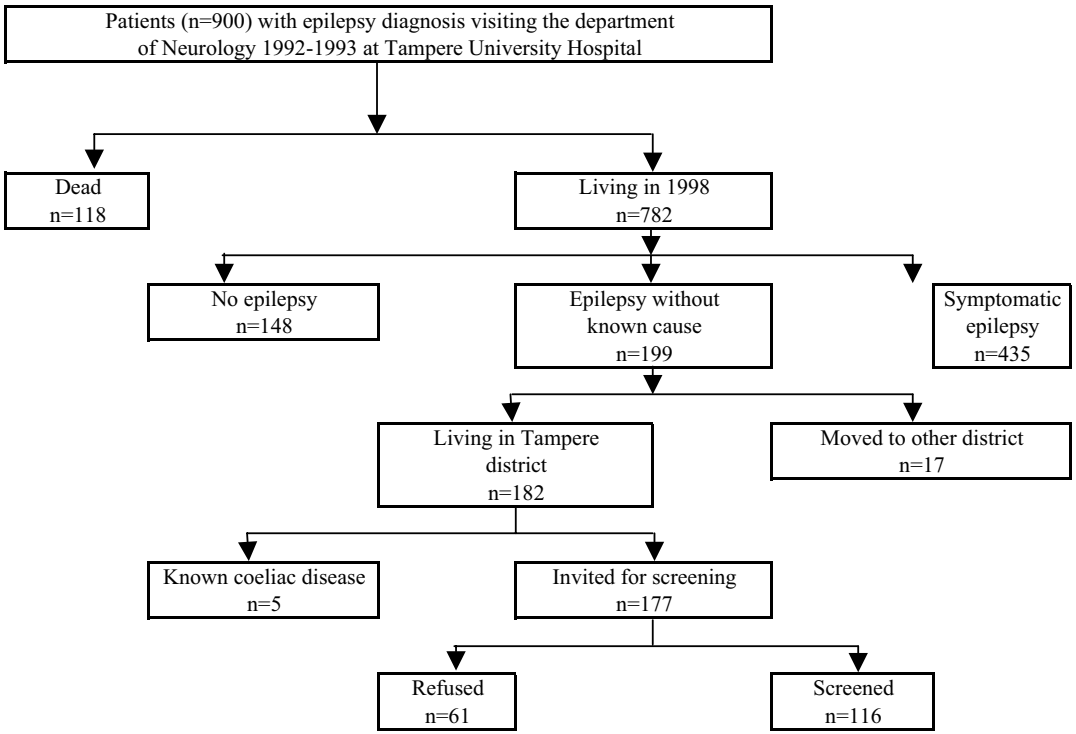


Figure 2. Flow chart of study III.

Patients with epilepsy investigated for the occurrence of coeliac disease



Methods

Clinical examination and laboratory tests

Clinical information was retrospectively collected from the medical records in studies I, II and III. All patients had had thorough neurological and laboratory examinations undertaken at the Department of Neurology to exclude the common causes for their neurological disorders. In studies II and IV the patients were invited to attend for a clinical neurological examination made by LL, and additional laboratory examinations if necessary. DNA analyses for GAA expansion in the X25 gene resulting in Friedreich's ataxia were made in all consenting ataxia patients (n=21).

Serological screening and diagnosis of coeliac disease

Serological screening for coeliac disease was carried out in studies II (n=21) and III (n=116). Serum gliadin antibodies (AGA) were investigated by enzyme-linked immunosorbent assay (ELISA) (Hill et al. 1991) and endomysial (EmA) antibodies were detected by an indirect immunofluorescence method, using human umbilical cord as antigen (Sulkanen et al. 1998a). IgA class reticulin antibodies (ARA) were detected by an indirect immunofluorescence method using a composite block of rat tissues (rat kidney, liver, stomach and heart) as antigen (Mäki et al. 1984). Serum tissue transglutaminase (tTG) antibodies were measured by ELISA test using antigen purified from guinea pig liver (Sulkanen 1998b). Subjects with positive screening results were referred for small-bowel biopsy. The revised diagnostic criteria of ESPGAN were applied in the diagnosis of coeliac disease (Walker-Smith et al. 1990).

Neuroradiological studies

In study III, all available brain computed tomography (CT) scans were systematically re-examined by one experienced neuroradiologist who was blinded to the diagnosis. The following parameters were recorded: the number and localisation of intracranial calcifications, and the severity and localisation of brain atrophy. Severity of brain atrophy was visually assessed as no atrophy, mild, moderate and severe atrophy. A number of patients also underwent magnetic resonance imaging (MRI) and information obtained was used to exclude patients with symptomatic epilepsy. In study II brain MRI was performed, if not previously done.

Neurophysiological studies

Neurophysiological studies were included in study IV. Electroneuromyography (ENMG) was carried out using a Keypoint ENMG device. As a rule, ENMG was performed on the left extremities. In addition, the right extremities were examined in patients with predominantly right-sided symptoms. Concentric needle electromyography (EMG) was performed on one distal (m. tibialis anterior) and one proximal (m. biceps brachii) muscle. The EMG was considered abnormal if fibrillation or positive sharp waves, or both, were present in more than one location within the muscle. In addition, the muscles were studied quantitatively by the multi-motor unit potential (MUP) analysis method. The number of outliers was noted as well as the mean amplitude and duration of the MUPs, which were compared to reference values provided by the manufacturer. The results were considered abnormal if the number of outliers exceeded three or the mean values were outside the normal range. Nerve conduction studies were carried out in motor (left median, ulnar, and peroneal) and sensory nerves (left median, ulnar, radial and sural). All studies were performed with surface electrodes using standard techniques with the exception of the median and ulnar digital nerves, which were measured antidromically. The hands and feet were warmed up to at least 30°C before all conduction velocity measurements. The left peroneal motor conduction measurements, the left sural and radial sensory measurements and F-waves of all motor nerves were utilised. The results were

compared to age- and height-corrected reference values provided by the manufacturer.

Vibration thresholds were measured from carpal and tarsal areas using the method of limits. In addition, vibration thresholds from the index fingers and big toes were studied by the Bio-Thesiometer. Thermal thresholds (heat, cold and heat-pain thresholds) were assessed by a skilled technician using Somedic Thermotest equipment. Tactile thresholds were assessed with Semmes-Weinstein monofilaments in dermatomes L3 and S1.

Statistical analysis

Data were expressed as means or frequencies with 95% confidence interval as indicated. Contingency tables with θ^2-test or Fisher's exact test were used for statistical comparisons of frequency data when appropriate. Mann-Whitney U-test and unpaired t-test were used to analyse continuous data.

Ethical considerations

All the study protocols were approved by the Ethical Committee of Tampere University Hospital. Written informed consent was obtained from all patients.

Results

Neurological symptoms as the presenting feature of coeliac disease (Study I)

Out of 144 patients with coeliac disease detected in the period 1995-1997, 10 (7%) were initially examined by neurologists, and referred to the department of gastroenterology because serologic tests or malabsorption raised a suspicion of coeliac disease (Table 9). Four patients had neuromuscular disorders and six suffered mainly from CNS symptoms. Extensive clinical and laboratory investigations failed to reveal a specific aetiology for their neurological symptoms.

Table 9. Coeliac disease patients presenting with neurological symptoms (Study I)

Case no	1	2	3	4	5	6	7	8	9	10
Age	58	died, 51	52	57	58	64	72	35	57	died, 56
Sex	female	male	male	male	female	female	male	male	female	female
Neurological symptoms	neuropathy	neuropathy	neuropathy	myopathy	memory imp cereb.atr.	memory imp	ataxia	epilepsy	tremor	parkinsonism
Duration of symptoms	6 months	9 months	29 years	6 months	few years	few years	10 years	months	4 years	4 months
Time of neurological dg	Feb/95	Feb/96	1966	Aug/96	Nov/94	April/96	1995	1992	April/95	Aug/91
Time of coeliac disease dg	March/95	Feb/96	Feb/96	Aug/96	Aug/95	Oct/96	April/96	June/96	Aug/95	Feb/95
Delay in diagnosis of coeliac disease	?	over 5 years	?	years	?	?	?	years	years	?
GI-symptoms	no	yes	no	yes	no	no	no	yes	yes	no
Hb (g/l)	151	85	171	132	128	130	141	131	137	130
Vitamin B_{12}	normal	low	normal	normal	low	normal	low	normal	-	-
E-folate	-	low	normal	low	normal	low	low	normal	-	-
Screening	glia+,retic+	glia+,retic+	glia+,retic+	glia +	-	retic +	glia+,retic+	glia+,retic+	retic +	retic +
Biopsy finding	sva	sva,lymphoma	sva	sva	sva	sva	sva	sva	sva	sva
Outcome of neurological symptoms	relieved	progressed	no change	relieved	no change	no change	no change	cured	no change	no change
Gluten-free diet	yes	yes	yes	yes	yes	yes	yes	yes	yes	no

GI-symptoms = gastrointestinal symptoms (diarrhoea, abdominal pain, vomiting, weight loss)

E-folate, reference values > 280 nmol/l

Vitamin B_{12} reference values > 170 pmol/l

glia+ = positive antigliadin antibody test

retic+ = positive antireticulin antibody test

sva = subtotal villous atrophy

cereb.atr. = cerebellar atrophy

memory imp = memory impairment

Frequency of coeliac disease in patients with cerebellar syndrome
(Study II)

Frequency of coeliac disease

Of 44 patients with ataxia of unknown origin, eight were deceased, 15 refused to participate in the study and 21 underwent clinical and laboratory examinations and serological screening for coeliac disease (Figure 1). A thorough interview, review of the patient files and exclusion of other causes indicated that heavy alcohol consumption was a probable cause of cerebellar disease in 20 cases. Coeliac disease had not previously been detected in any of these patients with heavy alcohol consumption; serological screening for coeliac disease in 10 of them revealed AGA and anti-tTG antibodies in two. However, their small-bowel mucosa was normal. Laboratory and genetic tests, cerebrospinal fluid (CSF) analyses and MRI studies screening for common causes of cerebellar ataxia revealed no specific aetiology in 24 patients with non-alcohol related ataxia. Coeliac disease had previously been diagnosed in four; serological screening for coeliac disease was negative in 10 additionally screened patients.

The calculated frequency of coeliac disease was 9.1% (CI 95% 2.5-21.7%) (4/44) in all patients and 16.7% (CI 95% 4.7-37.4 %) (4/24) in patients with ataxia of unknown origin and alcohol abuse excluded.

Clinical characteristics and findings in patients with ataxia

There were no significant differences in mean age at ataxia onset between patients with alcohol-related ataxia and those with ataxia of unknown origin. The clinical features of the cerebellar syndrome were similar in both groups. Most patients had

mainly truncal and gait ataxia with no or mild limb ataxia. Clinical signs of polyneuropathy were more common in patients with alcohol-related cerebellar disease than in those with ataxia of unknown origin. All except one showed cerebellar atrophy on CT or MRI.

Four patients with ataxia of unknown origin had coeliac disease. The diagnosis of coeliac disease was established after the onset of ataxia in all four. All had balance disturbances as a first symptom and one had concomitant memory decline; all also suffered from peripheral neuropathy. Two coeliac disease patients had a cerebellar syndrome with signs of truncal and gait ataxia. Two other patients were sisters who had a combination of progressive spinocerebellar disease, epilepsy and coeliac disease. Both died in status epilepticus.

Frequency of coeliac disease in patients with epilepsy (Study III)

Frequency of coeliac disease

Altogether five patients (2.5%, CI 95% 0.8–5.8%) out of 199 with cryptogenic epilepsy had previously diagnosed coeliac disease. Seventeen had moved away and 61 refused screening. Six out of the 116 remaining patients tested had positive antibodies and histological examination of the small-bowel mucosa was carried out (Figure 2). One of these six patients showed signs of probable coeliac disease in its early stage in histopathological examination of the small intestine. She was the only one with high positive tTG antibodies. The biopsy showed mucosal inflammation and crypt hyperplasia compatible with incipient coeliac disease; no atrophy was found, and the diagnostic ESPGAN criteria were thus not fulfilled. Subsequently this patient developed classic coeliac disease with small-bowel villous atrophy (unpublished observation). Hence the prevalence of coeliac disease in our patients at the time of the study was 2.5% (CI 95% 0.8-5.8%) (5/199) and later 3.0% (CI 95% 1.1 –6.4%) (6/199).

Characteristics of epilepsy in association with coeliac disease

There were no statistically significant differences between patients with or without coeliac disease in mean age at onset of epilepsy or duration of epilepsy. In patients with coeliac disease, the epilepsy type was partial in two cases, generalised in one and unclassified in two; none had occipital seizures. There were no significant differences in the estimated seizure frequency between patients with or without coeliac disease.

Neuroradiological findings in epilepsy patients

CT scans were available for 130 patients; intracranial calcifications were found in 11 (8.5%). Localisation of calcifications was basal ganglia (n=3), falx (n=3), tentorium (n=2), cerebellar (n=1), occipital (n=1) and bilateral occipital (n=1). All 11 patients with epilepsy and intracerebral calcifications had negative screening results for coeliac disease. Supratentorial brain atrophy was found in 37 patients, of whom 18 had mild and 19 moderate atrophy. Four (80 %) patients with definite coeliac disease had supratentorial atrophy compared with 33 (26 %) out of 125 patients without coeliac disease (Fisher's exact p=0.023). There was no statistically significant difference in the frequency of cerebellar atrophy (2/5 vs. 14/125) between patients with or without coeliac disease.

Frequency of neuropathy in coeliac disease patients (Study IV)

Frequency of neuropathy and clinical findings in patients with coeliac disease

Altogether six out of 26 (23.1 %) patients with coeliac disease and one (4.3 %) with reflux disease yielded findings of neuropathy in quantitative EMG with increased

amplitude or duration of MUPs. The findings were more prominent in distal than proximal muscles in five out of the six coeliac patients. None of the subjects had fibrillations or positive sharp waves in EMG. The clinical data and results of patients with neuropathy are summarised in Table 10. All conduction velocities and amplitudes of the action potentials as well as F-latencies were within reference values in each coeliac and control patient.

Neuropathy was mainly distal, sensorimotor axonal neuropathy in all six coeliac and one reflux patient. Three coeliac patients had clinically symptomatic neuropathy, whereas three coeliac and the reflux patient had subclinical neuropathy. Seven (27%) coeliac disease patients and five (22%) controls had a possible predisposing factor for neuropathy; the difference was not statistically significant. Two of the coeliac patients yielding neuropathy findings also had some other predisposing factor to neuropathy (Table 11).

Quantitative somatosensory findings

Heat-pain and tactile thresholds in both upper and lower extremities were significantly higher in patients with coeliac disease than in control subjects. There were no significant differences in heat, cold, or vibration thresholds between the groups (Table 12).

Myographic findings

Two coeliac patients (7.7%) showed reduced amplitudes and duration of MUPs suggestive of myopathy in quantitative EMG. Muscle biopsy was not performed, as the patients did not show muscle weakness or wasting in clinical examination.

Table 10. Clinical data and neurophysiological findings in seven patients with neuropathy (Study IV)

	1	2	3	4	5	6	7
Disease	Coeliac disease	Coeliac disease	Coeliac disease	Coeliac disease	Coeliac disease	Coeliac disease	Reflux disease
Time from diagnosis, years	3	2	3	4	2	3	6
Sex	male	female	female	female	female	male	male
Age	70	56	77	65	60	67	54
Possible predisposing factor	no	no	no	no	Graves` disease	alcohol	no
Clinical/subclinical neuropathy	clinical	clinical	subclinical	subclinical	subclinical	clinical	clinical
Motor nerve conduction							
Median nerve (elbow - wrist)							
Amplitude, mV	3.4	2.1	3.3	8.2	3.9	3.4	3.7
Velocity, m/s	54	53	49	54	64	52	56
Ulnar nerve (elbow - wrist)							
Amplitude, mV	8.3	6.2	7.5	8.6	11	6.9	6.5
Velocity, m/s	55	66	63	64	66	49	64
Peroneal nerve (knee - ankle)							
Amplitude, mV	3.2	3.2	3.2	4.6	4.5	6.6	8.2
Velocity, m/s	37	42	44	48	46	42	46
Sensory nerve conduction							
Median nerve (wrist - digit 2)							
Amplitude, µV	6.1	45	4.8	38	28	8.5	24
Velocity, m/s	54	56	48	58	67	50	58
Ulnar nerve (wrist - digit 5)							
Amplitude, µV	3.5	21	5.8	31	23	11	19
Velocity, m/s	59	54	40	58	54	56	61
Sural nerve (calf - ankle)							
Amplitude, µV	2.7	4.4	7.3	4.7	8.2	12	4.4
Velocity, m/s	48	54	45	47	54	42	64

	1	2	3	4	5	6	7
Disease	Coeliac disease	Coeliac disease	Coeliac disease	Coeliac disease	Coeliac disease	Coeliac disease	Reflux disease
EMG findings							
Tibialis anterior							
Mean amplitude (SD)	4*	1.5	1.2	1.6	0.2	1.1	1.3
Duration of MUPs (SD)	3.6*	2.5*	2.9*	3.9*	3.4*	0	2
Number of outliers	A9*, D3*	A1, D3*	A1, D7*	A2, D3*	A0, D1	A0, D0l	A3*, D2
Biceps brachii							
Mean amplitude (SD)	0.3	2.3	1.8	0.6	0	2.7*	0.6
Duration of MUPs (SD)	0.2	1.8	-0.7	1.2	1.5	0.1	0
Number of outliers	A0, D1	A0, D0	A1, D0	A0, D1	A0, D5*	A0, D0	A0, D2
Heat pain threshold (°C)							
Left thenar	54.4	47.1	44.7	50.5	49.4	48.1	49.2
Left foot	49.4	48.3	47.3	47.0	47.5	46.6	45.3
Tactile threshold (as10log of force, milligrams, compressing skin)							
Left leg							
Dermatome L3	3.84	4.74*	5.07*	3.84	4.08	4.17	2.44
Dermatome S1	3.84	4.56	4.31	4.08	4.08	4.08	4.56

All conduction measurements were within normal limits
A= High amplitude of MUPs
D= long duration of MUPs
*=abnormal value

Table 11. Demographic data (Study IV)

	Coeliac patients			Reflux patients		
	Female	Male	All	Female	Male	All
Number of patients	19	7	26	7	16	23
Mean age (years)	51	50	51	52	49	50
Range (years)	25-77	22-70	22-77	31-66	18-73	18-73
Factor predisposing to neuropathy						
Alcoholism	1	1	2 (7.7%)	0	2	2 (8.7%)
Malignancy	1	0	1 (3.8%)	0	0	0
Rheumatic disease	2	0	2 (7.7%)	0	1	1 (4.3%)
Thyroid disease	2	0	2 (7.7%)	2	0	2 (8.7%)
No known predisposing factor	13	6	19 (73%) #	5	13	18 (78.3%)#
All	19	7	26 (100%)	7	16	23 (100%)

p= n.s.

Table 12. Quantitative sensory thresholds in patients with coeliac disease and controls (Study IV)

	Coeliac patients n=26 mean (SD)	Controls n=23 mean (SD)	p
Heat threshold (°C)			
Left thenar	1.7 (0.8)	1.7 (1.0)	0.8895
Left foot	5.1 (3.4)	6.0 (3.4)	0.3760
Cold threshold (°C)			
Left thenar	1.0 (0.3)	0.9 (0.3)	0.3269
Left foot	1.3 (0.8)	1.8 (1.8)	0.2573
Heat-pain threshold (°C)			
Left thenar	46.9 (4.5)	44.5 (3.5)	0.0454
Left foot	46.1 (2.9)	42.9 (3.2)	0.0005
Vibration threshold (deviation from mean)			
Left wrist	0.3 (0.2)	0.4 (0.2)	0.4451
Left ancle	2.9 (8.8)	1.7 (1.5)	0.5889
Tactile treshold (as 10log of force, milligrams, compressing skin)			
Left leg			
Dermatome L3	3.9 (0.7)	2.1 (0.7)	<0.001
Dermatome S1	4.1 (0.7)	2.9 (0.8)	<0.001

Discussion

Methodological considerations

There have been some selection bias in the study. It was conducted in a tertiary referral centre, and epilepsy patients were selected cases, either newly diagnosed or treatment-resistant. A further factor increasing the selection bias was the relatively high refusal rate; only 58% of living ataxia patients and 66 % of epilepsy patients consented to participate. The frequency of coeliac disease may thus be an underestimation in these patients, at least in ataxia patients, in whom coeliac disease was commonly asymptomatic.

The other main source of concern is related to its retrospective nature. In study III, we focused on cases with cryptogenic or idiopathic epilepsy, but this distinction is indefinite, because many cases with cryptogenic epilepsy in fact prove to be symptomatic cases when investigated well enough (Kilpatrick et al. 1991, Resta et al. 1994). Also the retrospective approach produces many difficulties in epilepsy classification. Therefore, we could not exclude all symptomatic cases and this epilepsy group may represent a particularly heterogeneous group of patients. Moreover, there was no control group in studies I-III.

Ataxia patients had late-onset ataxia and there was no evident aetiology for the condition. Dominant ataxias were excluded with a negative family history and Friedreich's ataxia with DNA analyses for GAA repeat of the Frataxin gene. However, there have been studies in which a genetic basis has been found in up to 20% of apparently idiopathic ataxia cases (Futamura et al. 1998, Schols et al. 2000).

Serum tTG antibodies together with AGA, EmA and ARA were used in screening tests for coeliac disease. The sensitivity of the tTGA test has been 95% and the

specificity 94%. The other additional tests may increase the sensitivity to find new cases of coeliac disease, and, it is thus probable that we have recognised most coeliac patients with these tests. One disadvantage was that HLA typing was not used in the studies. With HLA typing we might have identified patients running an increased risk of coeliac disease and possibly cases with latent and potential coeliac disease.

Neurological disorders in association with coeliac disease

The findings here imply that neurological symptoms are not only coincidental in association with coeliac disease, they may even be the presenting feature in 7% of all new cases of coeliac disease. Coeliac disease was over represented in patients with epilepsy and ataxia of unknown origin. Signs of neuropathy were found in 23% of patients with well-treated coeliac disease. These findings are in line with previous studies (Cronin et al. 1998, Hadjivassiliou et al. 1996, 1997, 1998, Pellechia et al. 1999).

The prevalence of coeliac disease was increased (2.5 %) in epilepsy. However, the increase was only moderate as compared to results of recent population screening studies, where the prevalence has been as high as 0.8% to 1.2% (Table 2). The association between coeliac disease and epilepsy has been disputed (Table 6). Recently, Cronin and associates (1998) reported the frequency of coeliac to be higher in adult epilepsy patients (2.3 %) than in pregnant women (0.4 %). The present study provides further evidence of an association between coeliac disease and epilepsy. Most patients had abdominal symptoms indicating coeliac disease, and screening of 116 asymptomatic patients revealed only one probable case of coeliac disease. Although this patient did not yet fulfil the criteria for definite coeliac disease, she subsequently developed the disease. Thus the prevalence of coeliac disease in our epilepsy population may be as high as 3.0 % (six out of 199 patients). The problem with most studies concerning associations between epilepsy and coeliac disease is the inadequate characterisation of epilepsy syndromes. In this study the epilepsy type was partial in two cases, generalised in one and unclassified in two; none had occipital seizures. In a study by Labate and colleagues (2001), coeliac disease was associated with partial epilepsy with occipital paroxysms. In this epilepsy type, the frequency of

coeliac disease was as high as 8%. However, the series comprised only 25 patients. So far, there is no evidence of a particular epilepsy type, which might be associated with coeliac disease (Cronin et al. 1998, Fois et al 1994).

Sammaritano and colleagues (1985) first proposed a new syndrome consisting of coeliac disease, epilepsy and intracranial calcifications, although a group under Visakorpi (1970) had described a single patient 15 years earlier. Since then, many studies, particularly in Italy, have confirmed the existence of this syndrome, especially in paediatric series (Table 7). However, we did not find any patient with the syndrome in our hospital-based patient material. Re-evaluation of 130 CT scans from two-thirds of our epilepsy patients revealed only one single patient with bilateral occipital calcifications. This notwithstanding she was screening negative. The present results agree with those of Cronin and associates (1998), suggesting that the syndrome involving coeliac disease, epilepsy and intracranial occipital calcifications is rare in adults and does not explain the association between coeliac disease and epilepsy.

Previous studies have established that cerebral atrophy may be found in up to 29% of patients with late-onset epilepsy (De la Sayette et al. 1987) and cerebellar atrophy in 26% in patients with intractable temporal lobe epilepsy (Sandok et al. 2000). Also, investigators have previously hypothesised that there may exist a syndrome consisting of late-onset epilepsy and diffuse brain atrophy of unknown origin (Regesta and Tanganelli 1992). It is probable that this syndrome has a heterogeneous aetiology. Brain atrophy and epilepsy may be signs of a progressive neurodegenerative disease or, on the other hand, brain atrophy and epilepsy may share a common aetiological factor including coeliac disease. However, it has been shown that patients with coeliac disease have an increased frequency of cerebellar atrophy, but the occurrence of cerebral cortical atrophy is more anecdotal (Ghezzi et al. 1997, Hadjivassiliou et al. 1998). In this present study supratentorial brain atrophy was found in up to 28% of epilepsy patients. In patients with epilepsy and coeliac disease supratentorial brain atrophy was found in up to 80 % compared with 26 % in patients without coeliac disease. Cerebellar atrophy was found in 40% in patients with coeliac disease compared with 11% without coeliac disease; especially the frequency of supratentorial brain atrophy was increased in patients with epilepsy and coeliac disease. From these results it may be concluded that screening for coeliac

disease would seem warranted in patients with epilepsy of unknown aetiology. This is particularly important in cases where there is co-existent cerebral atrophy of unknown origin, even though the causal relationship between coeliac disease and epilepsy remains speculative.

The frequency of coeliac disease in patients with ataxia of unknown aetiology was high, 16.7% in this study. In previous studies there has been discrepancy (Table 5); the patient series have been small, altogether 211 cases with idiopathic ataxia were documented and 9 cases (4.3%) with coeliac disease were found. The frequency of coeliac disease is increased compared to recent prevalence studies. This supports the hypothesis whereby the association is not coincidental; ataxia and coeliac disease may share pathogenetic mechanisms.

The clinical features of coeliac disease-associated ataxia did not differ from those of other late-onset ataxias, again in line with previous studies (Hadjivassiliou et al. 1998, Pellechia et al. 1999). The first symptom was ataxic gait in most patients and gastrointestinal symptoms were rare. As cerebellar ataxia in association with coeliac disease shows no characteristic clinical features as compared to other late-onset ataxias, coeliac disease should be considered in all patients with ataxia of unknown origin.

An association of neuromuscular disorders with coeliac disease has occasionally been described over time (Bannerji and Hurwiz 1971, Cooke et al. 1966, Hadjivassiliou et al. 1997). The estimated frequency of neuropathy in population studies has been 1-4% (Beghi et al. 1988, Beghi et al. 1998). In the present study 23.1 % of coeliac patients yielded findings of neuropathy, although in half of the cases it was subclinical. Moreover, all our four patients with coeliac disease and cerebellar disease also had peripheral neuropathy. By comparison, the frequency of neuropathy in scleroderma has been reported to be 34%, clinical neuropathy in 15.6% and subclinical in 18.8% (Hietaharju et al. 1993). In patients with newly diagnosed non-insulin-dependent diabetes 8.3% had definite or probable polyneuropathy compared with 2.1% among the control subjects (Partanen 1995), a frequency comparable to that in a control group in the present study. The frequency of neuropathy in patients with well-treated coeliac disease seems thus comparable to that in patients with newly diagnosed non-insulin-dependent diabetes mellitus.

The characteristic features of peripheral nervous system involvement in coeliac disease have also been unclear. Our results suggest that polyneuropathy associated with coeliac disease is of axonal type and affects both motor and sensory fibres. In one patient, small-fibre neuropathy was the presenting feature of coeliac disease. Increases of heat-pain and touch thresholds in coeliac disease patients compared to controls provide further evidence that peripheral nerve fibres are affected in coeliac disease.

The relationship between GFD and the occurrence and progression of neuropathy, ataxia or epilepsy in coeliac disease patients was not investigated here; all patients in the coeliac disease group were on GFD and clinically in remission. In previous studies neurological symptoms have sometimes developed or progressed (Ambrosetto et al. 1992, Muller et al. 1996, Ghezzi et al. 1997) while patients have been on GFD, while in some cases neurological symptoms have resolved after GFD has been instituted (Cernibori et al. 1995, Gobbi et al. 1992 a, Pellechia et al. 1999b). In some cases coeliac disease has been refractory and this may explain why neurological symptoms have developed despite strict GFD (Muller et al 1996, Ghezzi et al. 1997). However, it is reasonable to adopt a strict diet and follow-up of dietary compliance to prevent or slow down or perhaps reverse the progression of the neurological disorders associated with coeliac disease.

Possible pathogenic mechanisms of the neurological manifestations associated with coeliac disease

The classical symptoms of coeliac disease are nowadays rare. In some cases, however, malabsorption of vitamins and trace elements is the relevant cause of neurological symptoms. Although coeliac disease may be silent and overt malabsorption is rare, subclinical metabolic disturbances remain a possibility (Dahele and Ghosh 2001). In studies II - IV, dietary compliance was good and laboratory studies revealed no malabsorption, so it is probable that other mechanisms are involved in the pathogenesis of the neurological manifestations.

Immunological and genetic mechanisms have been implicated as a possible explanation for the development of neurological complications in coeliac disease. Recent studies have shown positive coeliac-type serology without villous atrophy in patients with cerebellar syndrome. Bushara and associates (2001) found 27% of patients with sporadic and 37% of these with autosomal dominant ataxia to be AGA-positive, but to have normal small-bowel mucosal structure. Bürk and colleagues (2001) showed that 11.5% of patients with sporadic ataxia had a positive serology for coeliac disease and 70% of them were found to have the HLA DQB1*0201 haplotype, while small-bowel biopsy indicated coeliac disease in only 10% of them. Patients with gliadin antibodies and the HLA-DQ alleles DQA1*0501 or DQB1*0201 seem thus to be susceptible to coeliac disease, which may present itself with neurological manifestations before the appearance of mucosal atrophy. Recent studies have suggested that AGA might be neurotoxic (Chinnery et al. 1997). It is also possible that some patients may be prone to the development of autoantibodies, possibly due to the immunogenetic predisposition. In a recent study, a group under Hadjivassiliou (2002) showed that patients with gluten ataxia have antibodies against Purkinje cells. AGA cross-reacted with epitopes on Purkinje cells, but the reactivity against Purkinje cells could not be abolished with the absorption of AGA.

One possibility for the occurrence of neurological symptoms in association with coeliac disease is an immune reaction against a shared epitope expressed in the small intestine and in nerve or muscle cells. One such tissue factor may be tissue transglutaminase (tTG), the main autoantigen in coeliac disease. It is normally synthesised by many cell types but is usually retained in intracellular compartments. Upon wounding it can be released from cells, where it is thought to aid in tissue repair by cross-linking extracellular proteins. In active coeliac disease, the expression of tTG is increased. The deamidating activity of tTG seems to generate gliadin peptides which bind to DQ2 to be recognised by disease-specific intestinal T cells (Dieterich et al. 1998, Fasano 2001, Godkin and Jewell 1998, Sollid et al. 1997). It has been suggested that antibodies against tissue transglutaminase may play a direct role in the pathogenesis of coeliac disease. TTG has recently also been implicated in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease. Further, it may contribute to apoptotic cell death and the formation of expanded CAG repeats (Miller and Johnson 1995, Johnson et al. 1997, Cooper et al. 1997 and 2002,

Benzinger et al. 1998, Zhang et al. 1998, Zemaitaitis et al. 2000, Lesort et al. 2000 and 2002, Chun et al. 2001, Facchiano et al. 2001, Citron et al. 2002).

There are only a few reports of neuropathological findings in patients with coeliac disease. Hadjivassiliou and colleagues (1998) have reported two cases with necropsy findings. The neuropathological findings indicate that an inflammatory process may result in neural tissue damage. However, neuropathological examination in one of our coeliac disease patients with ataxia of unknown origin revealed degenerative changes without signs of inflammation, similarly to the coeliac disease case described by Hadjivassiliou and colleagues (1998); in their patient degeneration of the posterior columns of the spinal cord was observed without inflammation of the central nervous system, and it is thus possible that apoptotic mechanisms of cell death are in some cases involved.

Clinical impact of the study and future prospects

Neurological symptoms associated with coeliac disease may be long-standing and may occur without overt gastrointestinal signs. It is widely accepted that coeliac disease is underdiagnosed and may be clinically silent despite manifest mucosal lesion. Our study confirms the previous evidence that coeliac disease is common in patients with neurological symptoms of unknown origin and may present with neurological symptoms. Even though we found no new cases by screening, serologic screening is expected to be more effective in areas where the prevalence of coeliac disease is low, i.e. where the disease remains underdiagnosed. It is important that neurologists bear in mind this association between neurological symptoms and coeliac disease. Screening for coeliac disease is warranted if the aetiology of epilepsy, ataxia or neuropathy remains unknown.

In future, the value of GFD in patients with neurological disorders and gluten sensitivity should be assessed. It is possible that GFD might prevent progression of neurological symptoms or even restore function. Also, the diagnostic criteria for coeliac disease should be re-evaluated. Coeliac disease is not restricted to the small intestine. The current diagnostic criteria do not work in clinical practice, because the disease can manifest itself in neurological disorders while the small-bowel mucosa is

still normal. Such cases might be found with serological screening tests and HLA typing. It is conceivable that some complications of coeliac disease might be prevented with early case finding and the institution of GFD in these gluten-sensitive patients.

Summary

I. Neurological symptoms may be the presenting feature in coeliac disease. Seven % of coeliac disease patients were initially examined by neurologists.

II. The frequency of coeliac disease is increased in patients with ataxia of unknown origin. The calculated frequency of coeliac disease was as high as 16.7% in such patients.

III. An association between coeliac disease and epilepsy is common. Altogether five (2.5%) out of 199 patients with cryptogenic epilepsy had coeliac disease. The syndrome with coeliac disease, epilepsy and intracranial occipital calcifications is rare in adults. We did not find this syndrome in any of 130 patients with epilepsy.

IV. Neuromuscular disorders are common even in patients with well-treated coeliac disease. Altogether 23.1 % of coeliac disease patients yielded findings of axonal neuropathy in quantitative EMG.

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