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Hippocampal sclerosis in refractory temporal lobe epilepsy is associated with gluten sensitivity

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Abstract

Previously coeliac disease (CD) and gluten sensitivity (defined as the presence of anti-gliadin antibodies and positive immunogenetics) has been associated with cerebellar degeneration and epilepsy with occipital calcifications. Hippocampal sclerosis (HS) in temporal lobe epilepsy (TLE) is a potentially progressive disorder with unknown aetiology, and autoimmunity has been implicated in TLE+HS as one of the possible mechanism leading to HS. The purpose of this study is to analyze CD associated antibodies and gluten sensitivity in well characterized group of patients with refractory focal epilepsy.

We measured anti-gliadin, anti-tTG and anti-EMA and celiac type HLA (DQ2 and DQ8) in 48 consecutive patients with therapy resistant localisation-related epilepsy. The patients were categorised TLE+HS (N=16), TLE-HS (N=16) and extratemporal epilepsy (N=16) based on ictal eletro-clinical characteristics and high resolution MRI. Patients with suspected CD or gluten sensitivity underwent duodenal biopsies.

Seven patients were gluten sensitive, all of these patients had TLE+HS whereas none of the patients without HS were gluten sensitive ($p < 0.0002$). In duodenal biopsies three of the patients had histological evidence of CD and four had inflammatory changes consistent with early developing CD without villous atrophy. Four of the patients with gluten sensitivity had evidence of dual pathology (HS + another brain lesion) whereas none of the rest of patients did ($p < 0.0002$).

The present study demonstrates a previously unrecognized association between gluten sensitivity and TLE with hippocampal sclerosis. The association was very robust in this well characterised group of patients; thus gluten sensitivity should be added to the list of potential mechanism leading to intractable epilepsy and HS.

Introduction

Temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS) is probably the single most common form of human epilepsy, and the one most intensely studied (1). TLE with HS is a potentially progressive disorder characterised with anti-epileptic drug therapy resistance (2) with typical onset between ages 4 and 16 years (3). The aetiology of HS is unknown, although it is associated with initial precipitating incidents such as prolonged febrile seizures (4). The progression in TLE correlates with the number of tonic-clonic seizures, but the factors associated with progression of HS itself are largely unknown (2).

In celiac disease (CD) ingestion of gluten-containing grains (wheat, rye and barley) results in T cell mediated small bowel mucosal damage in genetically susceptible individuals. The disease is strongly associated with HLA DQ2, and practically all those negative for DQ2 carry DQ8 haplotype; 96-100% of CD patients share one of these haplotypes, compared to 30-40% in general population (5). According to recent studies the prevalence of celiac disease is 1% in general population (6). Evidence suggests that CD develops gradually from small bowel mucosal inflammation to crypt hyperplasia and subsequently to diagnostic villous atrophy, and the concept of gluten sensitivity has been suggested for genetically susceptible individuals, who have signs of early developing CD. Clinical manifestations of CD can be diverse ranging from diarrhoea and malabsorption of nutrients to atypical and extraintestinal symptoms (5).

Recently, gluten sensitivity has been associated with central nervous system pathology, most commonly in patients with cerebellar degeneration (7), where both humoral and cellular mechanisms have been implicated. Because most of the patients with gluten sensitivity and ataxia do not have the classical CD symptoms or small bowel mucosal atrophy, it has been concluded that intestinal pathology is not a prerequisite for developing cerebellar degeneration (8). Serum gluten-dependent antibodies against tissue transglutaminase (tTG), are highly sensitive and specific for CD (9). It is also known that tTG is expressed in the brain, and its expression is increased after

excitotoxic brain injuries (10). In addition, glutamic acid decarboxylase (GAD) has been proposed to act as the common antigen linking CD with neurological involvement (11).

Previous studies have provided conflicting data on the association between epilepsy and CD; an increased prevalence of CD associated antibodies in patients with epilepsy has been observed in some studies (12,13), whereas a recent study in patients with CD did not find significant difference in the prevalence of epilepsy compared with general population (14). Epilepsy is a heterogeneous group of disorders. Previous studies have been performed on unselected patients with epilepsy and have not properly addressed the syndromic variation in epilepsy, which might explain these conflicting results.

We have earlier described a variety of immunological alterations (GAD autoimmunity, antiphospholipid antibodies, cytokine gene polymorphisms) in epileptic patients, which were concentrated in the group of patients with refractory localization-related epilepsy (15,16,17). Recently it was also suggested that there is a possible association between such refractory epilepsy and the presence of HLA DQ2 (18). This prompted us to study whether patients suffering from refractory epilepsy have signs of CD and gluten sensitivity. First, we categorized refractory epilepsy according to the topographic type of the seizures and the presence of HS in magnetic resonance (MR) imaging. Secondly, CD associated autoantibodies (anti-gliadin, anti-tTG and anti-EMA) and the presence of celiac type HLA, DQ2 and DQ8, were determined in patients; the patients with suspected CD or gluten sensitivity underwent duodenal biopsy.

Materials and Methods

Patients

Forty-eight unselected consecutive patients with therapy resistant localization-related epilepsy (defined as >1 seizures/month despite prior treatment with at least two antiepileptic drugs) attending the outpatient clinic of department of neurology at Tampere University Hospital (TAUH) were

included in the study. The enrolment of the study patients was done without a priori knowledge on the presence or absence of concomitant autoimmune diseases. The study was approved by the ethics committee of TAUH, the patients gave their informed consent.

Table 1 Patient characteristics

	TLE+HS n=16	TLE-HS n=16	ETL n=16
Sex, F/M	10/6	7/9	6/10
Mean age, years (range)	42(24-60)	43(17-63)	44(17-64)
Mean duration of epilepsy, years (range)	27(12-47)	29(10-61)	33(3-45)
Mean seizure frequency/month (range)	3 (1-10)	3 (1-25)	6 (1-30)

TLE+HS = temporal lobe epilepsy with hippocampal sclerosis

TLE-HS = temporal lobe epilepsy without hippocampal sclerosis

ETL = extratemporal epilepsy

The patients were classified (Table 1) to three different groups: temporal lobe epilepsy with hippocampal sclerosis (TLE+HS), temporal lobe epilepsy without hippocampal sclerosis (TLE-HS) and extra-temporal epilepsy (ETL) based on ictal eletro-clinical characteristics and MRI findings.

The topographic diagnosis was done according to ictal video-EEG recordings in 41 out of 48 patients; in seven patients without ictal recordings the classification was based on seizure semiology, interictal EEG and localizing MRI findings. The classification of patients with video-EEG proven multifocal epilepsy was based on presence of temporal lobe seizures; if the patient had temporal lobe seizures the patient was classified to TLE+HS or TLE-HS depending on the presence of HS, in the absence of temporal lobe seizures the patient was classified to ETL-group.

All patients were taking antiepileptic medication: 13 were currently on monotherapy and 35 on polytherapy. Evaluation of available clinical data on the patients revealed that three patients had concomitant autoimmune disorders [systemic lupus erythematosus (ETL) , Sjögrens syndrome

(TLE-HS), Henoch Schönlein syndrome (TLE+HS), N=1 each]. One patient had a prior diagnosis of CD. None of the epilepsy patients had type 1 diabetes mellitus.

MR imaging

Forty-six of 48 patients had high resolution MRI performed, in two patients only CT scans were available (one patient died in breast cancer, the other was resuscitated from cardiac arrest and transferred to a nursing home).

All 46 patients who underwent a diagnostic brain MRI examination on a 1.5 Tesla machine (General Electric Signa Easyvision, Wisconsin, USA). The MRI protocol included a sagittal T1-weighted localizer series, axial T1-, T2 turbo spin echo (TSE)- and fluid attenuated inversion recovery (FLAIR)-weighted sequences and coronal or sagittal T1 weighted inversion recovery (IRPREP) sequences. IRPREP series were undertaken to analyse the pathological lesions in the area of amygdohippocampal complex and in addition to detect small anomalies associated with migration disorders. In cases with suspicion of occult arteriovenous malformations (AVM), an additional T2 weighted gradient echo sequence was taken. In addition in most of the examinations an additional Gadolinium-DTPA enhanced axial T1 sequence was performed. In our study brain MRI served the purpose of both diagnosis and preoperative evaluation for epilepsy surgery.

Hippocampal sclerosis was defined by the following criteria: 1) hippocampal atrophy demonstrated with coronal T1- weighted images 2) increased signal intensity within the hippocampus on T2-weighted spinecho images 3) decreased T1- weighted signal intensity and 4) disruption of the internal structure of the hippocampus (19,20). The presence or absence of general brain atrophy and cerebellar atrophy was also evaluated. When present, the degree of atrophy was qualitatively evaluated and graded to classes of mild, moderate or severe.

There were 16 patients with TLE+HS, three of which had MRI evidence of dual pathology (two vascular lesions and one ganglioglioma). Eight of these patients were operated with one patient

having neuropathological findings compatible with cortical dysplasia without MRI evidence of cortical dysplasia. Thus there were altogether four patients with dual pathology.

In patients with TLE without HS (N=16) the following MRI-findings were observed (N=1 each): cortical dysplasia, arachnoid cyst, hamartoma, dysembryoplastic neuroepithelial tumor, posttraumatic scar, vascular lesion. One patient with cryptogenic TLE was previously operated with corresponding MRI findings, another patient with cryptogenic TLE was subsequently operated as well as one patient with post-traumatic lesion. Six patients with TLE did not have any MRI pathology. Two patients had only CT scans performed.

In patients with ETL (N=16) three patients had MRI results compatible with vascular lesions, two patients had evidence of posttraumatic lesions, one patient had a vascular malformation, and seven patients did not present any abnormalities.

Controls

71 consecutive healthy blood donors served as controls for antibody measurements.

Celiac disease serology

Serum IgA-class endomysial antibodies (EmA) were investigated by an indirect immunofluorescence method using human umbilical cord as substrate; a dilution of 1:≥5 was considered positive (9). Assessment of serum IgA-class tissue transglutaminase antibodies (tTG-ab) were measured using the commercial kit Quanta Lite tTG ELISA (INOVA Diagnostics, Inc., San Diego, CA, USA) according to the manufacturer's instructions. The antibody concentrations were expressed in arbitrary units (AU), that is, percentages of the positive reference serum, and values > 20 AU were considered positive. Serum IgA and IgG-class antigliadin (AGA) antibodies were measured according to standard enzyme immunoassay with a crude gliadin (Sigma G3375) as

antigen (21). The lower limit of positivity for IgA-class AGA was 0.2 EU/ml and for IgG-class 10 EU/ml.

Genotyping

All the patients were genotyped for HLA-DQB1*02 and *0302 alleles using the DELFIA[®] Coeliac Disease Hybridization Assay (PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) according to the manufacturer's instructions. The method relies on lanthanide chelate labels and time-resolved fluorescence detection (22).

Small bowel biopsy

Upper gastrointestinal endoscopy was offered to patients having antibody positivity and relevant genetics to obtain five forceps biopsy specimen from the distal part of duodenum. Three biopsy specimen were processed, stained with hematoxylin-eosin and studied under light microscopy and histologically classified into normal, mild partial, severe partial and subtotal villous atrophy with crypt hyperplasia. To study signs of small bowel mucosal inflammation and early developing celiac disease, two biopsy specimen were freshly embedded in optimal cutting temperature compound (OCT, Tissue-Tek, Miles Inc, Elkhart, IN, USA), snap-frozen in liquid nitrogen and stored at -70 C° until used. Immunohistochemical studies using the avidin-biotin immunoperoxidase system were carried out on 5µm-thick frozen sections. CD3⁺ intraepithelial lymphocytes (IELs) were stained with monoclonal antibody Leu-4 (Becton Dickinson, San Jose, CA, USA) and the numbers of positively stained IELs were counted and expressed as cells per millimetre epithelium, as previously described (23). Small bowel mucosal HLA DR expression was examined by staining frozen biopsy specimen with monoclonal antibody HLA DR (Becton Dickinson) in a dilution of 1:1500. The expression was considered enhanced when strong in the villous epithelium or present in crypts.

Negative crypt and only slight to moderate villous epithelium expression was considered negative (23).

Diagnosis of gluten sensitivity and celiac disease

The definition of gluten sensitivity has been widely used especially in the context of neurological disorders such as gluten ataxia (11). In this paper gluten sensitivity was defined as the presence of positive serum IgA-class EMA, tTG-ab or AGA together with positive celiac type HLA, HLA DQ2 or DQ8. Patients found to have small bowel severe partial or subtotal villous atrophy with crypt hyperplasia, and evincing subsequent clinical, serological or histological recovery on gluten-free diet, were considered to have celiac disease (24). Increased density of epithelial CD3+ IELs and enhanced mucosal HLA-DR expression in apparently normal small bowel mucosa were indicative for early developing celiac disease (23). To determine the true prevalence of celiac disease/gluten sensitivity in patients suffering from therapy resistant focal epilepsy we added together previously diagnosed celiac disease patients and the new screen-detected cases.

Statistical analysis

Fisher's Exact Test were used for analysis of statistical significance. P-values are two-sided.

Results

Seven patients with epilepsy had gluten sensitivity, all of these patients had TLE+HS, none of the patients with TLE-HS or with ETL were gluten sensitive ($p < 0.0002$). All patients with gluten sensitivity had a long duration of medically refractory epilepsy (range 14-46 years) with MRI evidence of HS, one patient was previously and three other patients were subsequently operated with standard temporal lobe surgery. Four of the patients with gluten sensitivity had evidence of

dual pathology whereas none of the rest of patients did ($p < 0.0002$). In two of these patients there were precipitating incidents such as encephalitis and prolonged febrile convulsion. Two of the operated patients are currently seizure free and two other operated have still rare (1-3/year) seizures. Three patients with medical treatment only have persistent frequent seizures. Altogether eleven out of 48 patients with therapy resistant localization-related epilepsy (table 2) tested positive for either Ig-A or Ig-G class antigliadin antibodies or both compared with eleven out of 71 controls ($p = \text{NS}$). Three out of 48 patients had anti-tTG and EMA antibodies, whereas none of the controls had such antibodies ($p = 0.06$). Seven out of 11 antigliadin positive patients had TLE, two had frontal lobe epilepsy and two parietal lobe epilepsy. Three out of sixteen patients with TLE+HS but none of the patients with TLE-HS or ETL had CD ($p = 0.03$).

Table 2 The frequency of immunological findings in different patient groups with epilepsy

Type of epilepsy	N	AGA-IgG/A	HLA DQ2/8	tTG/EmA	Gluten sensitivity	Celiac disease
TLE+HS	16	7	7	3	7	3
TLE-HS	16	0	6	0	0	0
ETL	16	4	3	0	0	0
Controls	71	11	NA	0	NA	0

TLE+HS = temporal lobe epilepsy with hippocampal sclerosis
TLE-HS = temporal lobe epilepsy without hippocampal sclerosis
ETL = extratemporal epilepsy
AGA = IgA and IgG-class antigliadin antibodies
tTG = IgA-class tissue transglutaminase antibodies
EmA = IgA-class endomysial antibodies
NA= not available

General brain atrophy and cerebellar atrophy

None of the seven patients with gluten sensitivity had clinical signs suggestive of ataxia, whereas six had MRI evidence of mild or moderate cerebellar degeneration. Five of these patients had either

mild or moderate general brain atrophy. Both general and cerebellar atrophy were frequently found in patients with epilepsy without gluten sensitivity as well. Mild or moderate cerebellar atrophy was present in 28 and three patients had severe atrophy. Mild or moderate general brain atrophy was found in 26 patients.

Duodenal biopsies (table 3)

Table 3 Characteristics of TLE patients with gluten sensitivity

Patient no.	Age	Sex	Duration of epilepsy	AGA	tTG/EmA	HLA	Duodenal biopsy	Expression of HLA-DR	MRI findings	Neuropathological findings (temporal lobectomy)
1	31	F	31	IgA,IgG	positive	DQ2	CD*	ND	HS+dp	ND
2	47	M	31	IgA,IgG	positive	DQ2	CD	enhanced	HS	HS
3	46	M	22	IgA	positive	DQ2	CD	enhanced	HS+dp	HS+ ganglioglioma
4	32	M	24	IgA	negative	DQ2	lymphocytic infiltration	enhanced	HS	HS+cortical dysplasia
5	25	F	14	IgA	negative	DQ8	lymphocytic infiltration	enhanced	HS+dp	ND
6	45	M	26	IgA	negative	DQ8	lymphocytic infiltration	enhanced	HS	HS
7	60	M	46	IgA	negative	DQ8	normal	enhanced	HS	ND

AGA = IgA and IgG-class antigliadin antibodies
tTG = IgA-class tissue transglutaminase antibodies
EmA = IgA-class endomysial antibodies
CD= celiac disease
HS= hippocampal sclerosis
dp= dual pathology
ND= not done

*patient with previously diagnosed CD

All the patients with gluten sensitivity underwent duodenal biopsy except the one with a prior diagnosis of biopsy proven CD. This patient did not adhere to gluten-free diet, and tested positive for all CD associated antibodies. In subsequent duodenal biopsies the two other patients who tested positive for anti-tTG and EMA antibodies had following findings:1.) One had normal bowel histologic characteristic in the first biopsy, but immunohistochemical findings suggested potential CD, he also suffered from malabsorption related problems (iron deficiency anemia, osteopenia). During the follow-up the patient developed severe partial villus atrophy with crypt hyperplasia in a subsequent biopsy and was diagnosed to have CD. 2.)The other

patient had severe villus atrophy with crypt hyperplasia compatible of CD. Furthermore, all four patients with gluten sensitivity but normal small bowel villous morphology were found to have enhanced intestinal mucosal HLA DR expression, and three of them had in addition increased density of CD3+ IELs (table 3). None of the patients with gluten sensitivity without CD did not have any GI or malabsorption symptoms, two out of three patients with CD did not have any GI or malabsorption symptoms.

Discussion

The present study demonstrates a previously unrecognized association between gluten sensitivity, celiac disease and temporal lobe epilepsy with hippocampal sclerosis. When comparing three epileptic groups, gluten sensitive patients were exclusively concentrated in the TLE+HS group, and none of the HS-negative patients were gluten sensitive. Even though the sample size of the epilepsy population was not large, the patients were very extensively studied and the categorization of the patients was based on ictal recordings and high resolution MRI findings. The statistical significance between gluten sensitivity and HS was robust underlying the strength of the association. With the exception of one case, patients with previously unrecognized CD were diagnosed by the procedures of our study.

Evidence suggests that gluten sensitivity/ celiac disease clearly exist beyond small bowel mucosal villous atrophy (25). Even if AGA is regarded unspecific for classic small bowel lesion that defines celiac disease (26), it has been useful in detecting diverse neurological manifestations of gluten sensitivity (8). Gluten sensitivity has been implicated in cerebellar degeneration (11), where there is emerging data addressing the epidemiology, pathogenetic mechanisms and genetic background of gluten sensitivity and cerebellar degeneration. Interestingly, the findings in the duodenal biopsies from patients with gluten ataxia are similar to our patients with gluten sensitivity and TLE+HS; inflammatory changes are consistent with early developing CD without villus atrophy (27). Furthermore, the presence of class IgA tTG deposits were recently

demonstrated both in jejunal tissue and in the brain of patients with gluten ataxia without an enteropathy (28). In the present study the definition of gluten sensitivity included AGA positivity and classical celiac type HLA. However in cerebellar degeneration patients with AGA positivity without the presence of HLA DQ2/8 have been described and in future studies also this group of patients would be interesting to address in patients with epilepsy. Majority of our patients with gluten sensitivity had MRI evidence of mild or moderate cerebellar or general brain atrophy without clear clinical signs of ataxia. However, in this respect these patients did not differ from epileptic patients without gluten sensitivity. In addition, many of our patients have previously used phenytoin, a drug generally known to cause cerebellar atrophy. Furthermore, cerebellar atrophy has been reported previously in 26% of patients with TLE (29). Lack of volumetric MRI analysis and variable duration of epilepsy in our patients may have had an impact in our findings. In future studies these issues should be systematically addressed. Earlier studies addressing the association between epilepsy and CD have not presented consistent MRI data.

There are several studies suggesting that autoimmunity is involved in refractory localization-related epilepsy, especially in TLE+HS patients (30). Increased prevalence of anti-GluR3 antibodies (31) and anti-GAD antibodies (15) have been observed in refractory TLE. Cytokine gene polymorphism of the interleukin-1 β gene associated with heightened immune response (e.g, the presence of the allele 2 of the -511 region) was observed in Japanese TLE+HS population (32).

In the present study the frequencies of HLA DQ2 and DQ8 were unevenly distributed among epileptic patients, in TLE-HS and ETL groups the frequencies of HLA DQ2 and DQ8 are comparable to general population in Finland. In TLE+HS group 44% of the patients are positive for the CD associated genes. The weakness of our study is the lack of information of HLA data on controls making us unable to provide the prevalence of gluten sensitivity in the normal population. The frequencies of HLA alleles were previously studied in 65 patients with TLE+HS, the risk ratio for DQ2 was 16 compared with that of general population (18). There is also recent

data reporting that genetic susceptibility to both type 1 diabetes and coeliac disease share common alleles, which suggest that common biologic mechanism, such as autoimmunity-related tissue damage and intolerance to dietary antigens may be etiologic features of both diseases (33).

However, in our study none of the epilepsy patients had type 1 diabetes.

The pathogenetic significance of increased gluten sensitivity in TLE+HS patients is not known. In cerebellar degeneration the proposed mechanisms include anti-gliadin antibodies that crossreact with epitopes on Purkinje cells, even though cell-mediated mechanisms have also been implicated (34). Other possible mechanisms involve GAD as an autoantigen mediating the CNS pathology and gluten sensitivity (11), interestingly GAD autoimmunity has been also implicated in therapy resistant epilepsy (15). On the other hand tissue transglutaminase is expressed in the brain, and its expression is increased in association with acute and chronic neurodegeneration especially in the context of excitotoxic neuronal injury (10).

The etiopathogenesis of HS is not well understood; currently it is regarded as a progressive disorder in which various mechanisms modifying pathological plasticity are involved (2). Autoimmunity is one of the proposed pathways in development of HS. The pathogenetic substrate of the possible association between gluten sensitivity and HS are currently unknown, however, similar mechanisms as in cerebellar degeneration may also be involved in the development of HS. Our findings open a possibility for prevention of progression of HS in TLE. In CD gluten free diet (GFD) produces clinical and symptomatic improvement and also decreases the possibility of developing complications of CFD such as lymphoma and osteoporosis (5). Gluten ataxia responds to GFD even in the absence of an enteropathy (35). In the epileptic syndrome with occipital calcifications the chances of seizure control after GFD seem to be significantly inversely related to the duration of epilepsy before GFD and to the age at the beginning of GFD (36). Thus in temporal lobe epilepsy GFD should most probably to be initiated early in the course of epilepsy to be

effective, our patients had a long duration of epilepsy with established HS where GFD is very unlikely to be effective.

In conclusion, in the present study we have provided robust evidence of an association between HS and gluten sensitivity. In future studies the mechanisms of this association should be addressed. Also measurement of antigliadin, anti-tTG and EMA-antibodies as well as the presence of DQ2 and DQ8 should be performed in patients with TLE and HS. The patients with antibody positivity and relevant genetics should be offered a chance of duodenal biopsy.

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