ORIGINAL ARTICLE

Persistent mucosal damage and risk of epilepsy in people with celiac disease

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Background and purpose: Celiac disease (CD) is associated with an increased risk of developing epilepsy, a risk that persists after CD diagnosis. A significant proportion of patients with CD have persistent villous atrophy (VA) on follow-up biopsy. The objective of this study was to determine whether persistent VA on follow-up biopsy affected long-term epilepsy risk and epilepsy-related hospital emergency admissions.

Methods: This was a nationwide cohort study. We identified all people in Sweden with histological evidence of CD who underwent a follow-up small intestinal biopsy (1969–2008). We compared those with persistent VA with those who showed histological improvement, assessing the development of epilepsy and related emergency hospital admissions (defined according to relevant International Classification of Diseases codes in the Swedish Patient Register). Cox regression analysis was used to assess outcome measures.

Results: Villous atrophy was present in 43% of 7590 people with CD who had a follow-up biopsy. The presence of persistent VA was significantly associated with a reduced risk of developing newly-diagnosed epilepsy (hazard ratio, 0.61; 95% confidence interval, 0.38–0.98). On stratified analysis, this effect was primarily amongst males (hazard ratio, 0.35; 95% confidence interval, 0.15–0.80). Among the 58 patients with CD with a prior diagnosis of epilepsy, those with persistent VA were less likely to visit an emergency department with epilepsy (hazard ratio, 0.37; 95% confidence interval, 0.09–1.09).

Conclusions: In a population-based study of individuals with CD, persisting VA on follow-up biopsy was associated with reduced future risk of developing epilepsy but did not influence emergency epilepsy-related hospital admissions. The mechanism as to why persistent VA confers this benefit requires further exploration.

Introduction

Celiac disease (CD) is an immune-mediated enteropathy that has a prevalence of 1% in Western populations [1,2]. It occurs in genetically susceptible individuals following exposure to dietary gluten. Strict adherence to a gluten-free diet (GFD) is the mainstay of treatment, which can reduce the risk of complications, such as lymphoma, osteoporosis and micronutrient deficiencies [3].

Neurological conditions, such as cerebellar ataxia [4], peripheral neuropathy [5] and headache [6], are all recognized extraintestinal manifestations associated with CD. Another important neurological disorder that has been examined is epilepsy. Previous work has shown large variability in the prevalence and incidence

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of epilepsy in CD (0–7.2%) [7–9], with our previous population-based study demonstrating a moderately increased risk [hazard ratio (HR), 1.42; 95% confidence interval (CI), 1.24–1.62] [10]. Potential underlying pathophysiological mechanisms for this association have been described previously in children in CD, epilepsy and cerebral calcifications syndrome; however, uncertainty exists about these mechanisms in adults [11].

Follow-up biopsy has emerged as a potentially important approach to risk-stratifying patients with CD with regards to long-term prognosis. The rates of persistent villous atrophy (VA) are variable in the literature, occurring in >30% of patients with CD in most series [12–14], with persisting VA inversely correlating with GFD adherence [13,15,16]. Although persistent VA does not impact overall mortality in CD, it may influence morbidity and be a factor explaining heterogeneity in previous epilepsy and CD studies [17]. Performing a follow-up biopsy was historically considered to be the gold standard to confirm healing after adoption of a GFD [18]. However, the practice has subsequently declined due to the availability of serology data, which normalize after elimination of dietary gluten [19]. This had led to recent guidelines no longer explicitly mandating a follow-up biopsy [2,20].

The study examines whether persistent VA, as compared with mucosal healing, is associated with an increased risk of developing newly diagnosed epilepsy among people with CD. In addition, we explore whether mucosal healing influences future epilepsy-related hospital emergency admissions in those with known epilepsy at the time of follow-up biopsy.

Methods

Identification of individuals with celiac disease

During the years 2006–2008 we queried all pathology departments in Sweden (n = 28) for reports of VA, as identified by SnoMed codes. Details regarding this database have been published previously [21]. In brief, VA was identified by Swedish pathologists and a prior validation study demonstrated that, among individuals identified via these histology codes, a clinical diagnosis of CD was present in 95%; alternative/comorbid diagnoses were rare (with inflammatory bowel disease, the most common comorbidity, present in 0.3% of 1534 manually reviewed patient records) [21].

The individuals in this analysis are those with CD who underwent more than one duodenal biopsy. They therefore represent a subset of all patients with CD who were included in our earlier study, which found an increased risk of epilepsy in CD [10]. We identified those people with CD who underwent follow-up biopsy between 6 months and 5 years after initial CD diagnosis. Those who had a modified Marsh histopathology score [22] of 3 were classified as having persistent VA, whereas those with a less severe score were classified as healed. As reported previously, among a subset of patients where serologic data were available, VA was more common among those with persistently elevated CD serologies (62%) compared with those with serologic normalization (21%) [17].

Identification of individuals with epilepsy and hospital emergency admissions

Epilepsy was defined according to relevant International Classification of Diseases (ICD) codes in the Swedish National Patient Register [23]; our definition of epilepsy did not include status epilepticus or febrile convulsions (ICD-7, 353 except for 353.2; ICD-8, 345 except for 345.2; ICD-9, 345 except for 345Q; ICD-10, G40). The Swedish National Patient Register includes inpatient diagnoses from parts of Sweden since 1964 (nationwide since 1987) as well as hospital-based outpatient care since 2001. Emergency hospital admissions for epilepsy were also defined using relevant ICD codes in the Swedish Patient Register for epilepsy but also including status epilepticus (ICD-8, 345.2; ICD-9, 345Q; ICD-10, G41) in patients with an earlier diagnosis of epilepsy.

Statistical considerations

We used Cox proportional hazard models to compare the risk of developing epilepsy among those with persistent VA versus those with mucosal healing on follow-up biopsy. In this analysis, the observation time (i.e. time at risk) started on the day of the follow-up biopsy and ended on the date of developing epilepsy, death, emigration or 31 December 2009, whichever occurred first. In this analysis we chose *a priori* the following covariates in the model: age at follow-up biopsy, gender, duration of CD at the time of follow-up biopsy, educational attainment (or in the case of children the highest educational attainment between the parents) and calendar period of follow-up biopsy.

As the risk of sequelae in CD (including mortality and morbidity) changes over time [24], we tested the proportional hazards by recalculating the association between VA and the development of epilepsy during the following three pre-specified time strata: <1 year, 1–5 years and >5 years after the patient's follow-up biopsy. We then performed stratified analysis by age, gender and calendar period of follow-up biopsy.

Analysis of epilepsy-related hospital emergency admissions was undertaken using Cox proportional hazard models. This analysis included all patients who were known to already have epilepsy at the time of follow-up biopsy. In addition to a Cox model measuring the risk of any emergency visit for epilepsy, we also assessed the association between persistent VA and the rate of emergency department visits among these individuals in the 5 years following their follow-up biopsy. For this latter model we calculated rate ratios using Poisson regression among patients with known epilepsy at the time of their follow-up biopsy who had at least 5 years of observation time after that date.

We used SAS version 9.3 (Cary, NC, USA) for statistical analyses. We report risk estimates as HR and corresponding 95% CI. All reported *P*-values are two-sided. This study was approved by the Research Ethics Committee of the Karolinska Institute on 14 June 2006. According to the board's decision no study participant was contacted as the study is strictly register-based [25].

Results

Characteristics of patients who underwent follow-up biopsy

Of 29 096 people with CD, 7648 (26%) underwent a follow-up biopsy between 6 months and 5 years after their initial CD diagnosis. A total of 58 of these individuals were known to have epilepsy at the time of follow-up biopsy, leaving a remainder of 7590 (Table 1). The median (interquartile range) age of CD diagnosis was 25 (3–51) years and the median (interquartile range) age of follow-up biopsy was 26.8 (5–52) years. Nearly half of the patients (45%) were less than 20 years of age at the time of follow-up biopsy. Most patients (63%) were female and 45% of patients had follow-up biopsy between 1 and 2 years after the CD diagnosis. A previous analysis of this cohort found that those patients with CD who had a follow-up biopsy differed slightly from those who did not; they were diagnosed with CD at a younger age (mean 28.4 vs. 33.4 years, $P < 0.0001$) and had a slightly greater female predominance (63% vs. 61%, $P = 0.0017$) [17].

Patients were followed up for a median (interquartile range) of 8.9 (5.4–14.1) years after follow-up biopsy. Most patients (53%) had a follow-up biopsy after the year 2000. Of the 7590 people who did not have epilepsy at the time follow-up biopsy, 3295 (43%) had persistent VA.

Risk of developing epilepsy

There were 75 new diagnoses of epilepsy during the observation period after follow-up biopsy. The mean/median (SD) time from follow-up biopsy to epilepsy diagnosis in these patients was 7.1/6.2 (5.5) years. Quantifications of the association between persistent VA and epilepsy stratified by gender, age and calendar period are shown in Table 2. Persistent VA was associated with a reduced risk of developing epilepsy (HR, 0.61; 95% CI, 0.38–0.98), as compared with those with mucosal healing. This effect was primarily among males (HR, 0.35; 95% CI, 0.15–0.80) and there was no significant association between persistent VA and epilepsy among females (HR, 0.85; 95% CI, 0.46–1.57). To test the robustness of our results, a sensitivity analysis was performed using patients who had at least two interactions with Swedish healthcare due to a diagnosis of epilepsy. This demonstrated similar results (HR, 0.57; 95% CI, 0.33–1.01), but findings were just short of statistical significance ($P = 0.0532$). The low number of events for 'partial' and 'generalized-other' epilepsy subtypes in our cohort precluded any analysis using epilepsy subtypes.

Table 1 Characteristics of patient cohort with celiac disease (CD) and follow-up biopsies, excluding those patients who had a diagnosis of epilepsy prior to their follow-up biopsy ($n = 7590$)

Characteristic	No. (%)
Age at follow-up biopsy (years) (mean/median/SD)	30.5/26.8/24.8
0–19	3390 (45)
20–39	1318 (17)
40–59	1670 (22)
≥60	1212 (16)
Male	2790 (37)
Female	4800 (63)
Interval between diagnosis and follow-up biopsy	
6 months to 1 year	2010 (26)
Between 1 and 2 years	3399 (45)
2–5 years	2181 (29)
Calendar period of follow-up biopsy	
1989 and before	719 (9)
1990–1999	2877 (38)
2000 and after	3994 (53)
Second biopsy result	
Mucosal healing	4295 (57)
Persistent villous atrophy	3295 (43)
Developed epilepsy	75 (1)

Mean/median/SD time between diagnosis of CD and follow-up biopsy: 1.7/1.3/1.0 years. Mean/median/SD follow-up time (to epilepsy diagnosis, death, emigration or 31 December 2009): 10.2/8.9/5.97 years. Of the 75 patients who developed a new diagnosis of epilepsy, the mean/median (SD) time from follow-up biopsy to epilepsy diagnosis was 7.1/6.2 (5.5) years.

On time-stratified analysis, the reduced risk of epilepsy was most pronounced in the first year after follow-up biopsy (HR, 0.36; 95% CI, 0.07–1.74), although this was not statistically significant. The point estimates for the subsequent time strata were similar to each other (1–5 years: HR, 0.66; >5 years: HR, 0.64). A test for heterogeneity did not find that these three risk estimates differed significantly between time strata ($P = 0.78$).

Persistent villous atrophy and epilepsy-related emergency hospital admissions

A total of 58 people with CD had an established diagnosis of epilepsy at the time of follow-up biopsy. Those with persistent VA were less likely to visit an emergency department with epilepsy-related problems, although this was not statistically significant (HR, 0.37; 95% CI, 0.09–1.09, $P = 0.1605$). When examining the rate of emergency department visits for epilepsy over a 5-year period, we identified 37 patients with a previous diagnosis of epilepsy who had 5 years of follow-up observation time. Among those with mucosal healing, the mean number of emergency visits over 5 years was 0.57 compared with 0.44 among those with persistent VA (rate ratio for those with persistent VA compared with those with healing, 0.51; 95% CI, 0.13–2.02).

Table 2 Association of persistent villous atrophy (VA) with epilepsy stratified by gender, age and year of celiac disease (CD) diagnosis

Stratum	No. of events	Adjusted HR[a] (95% CI)	*P*
Overall			
Mucosal healing	45	1.0	
Persistent VA	30	0.61 (0.38–0.98)	0.04
Gender			
Male			
Mucosal healing	22	1.0	
Persistent VA	8	0.35 (0.15–0.80)	0.01
Female			
Mucosal healing	23	1.0	
Persistent VA	22	0.85 (0.46–1.57)	0.2620
Age at follow-up biopsy (years)			
<20			
Mucosal healing	25	1.0	
Persistent VA	14	0.61 (0.30–1.25)	0.1745
20–39			
Mucosal healing	4	1.0	
Persistent VA	2	0.77 (0.14–4.36)	0.7669
40–59			
Mucosal healing	8	1.0	
Persistent VA	7	0.61 (0.21–1.80)	0.7934
≥60			
Mucosal healing	8	1.0	
Persistent VA	7	0.66 (0.23–1.87)	0.4362
Calendar year			
1989 and before			
Mucosal healing	6	1.0	
Persistent VA	5	0.29 (0.09–1.00)	0.0503
1990–1999			
Mucosal healing	21	1.0	
Persistent VA	19	0.66 (0.36–1.24)	0.1987
2000 and after			
Mucosal healing	18	1.0	
Persistent VA	6	0.75 (0.28–1.96)	0.5508

[a]Hazard ratios (HRs) are adjusted for patient age, gender, calendar period of diagnosis education and duration of CD at the time of follow-up biopsy. CI, confidence interval.

Discussion

In this population-based database of people with CD who underwent a follow-up biopsy, there was a reduced risk of developing epilepsy among those with persistent VA compared with those with mucosal healing. This finding was primarily amongst males. No significant difference in emergency hospital admissions for epilepsy was identified in those with persistent VA.

These findings are in contrast to our original hypothesis. We had hypothesized that persistent VA would be associated with an increased risk of future epilepsy and would influence hospital admissions. This hypothesis was based on the observation that patients with CD develop epilepsy at a greater rate than would be expected in the general population [10]. It seemed plausible that the autoimmune reaction inherent to CD would also increase epilepsy risk, with intestinal permeability potentially influencing blood–brain barrier permeability, as has been reported in other neurological disorders [26,27]. However, our findings suggest that the mechanisms of mucosal injury and the chronic inflammation may be protective against developing epilepsy. Tumour necrosis factor (TNF)-alpha and the neuropeptide ghrelin are two inflammatory mediators in CD that could have influenced outcomes [28,29]. TNF-alpha is recognized to inhibit seizures in mice and ghrelin has been shown to have anticonvulsant properties, which could have conferred protection on those not achieving mucosal healing [30,31].

An alternative explanation is that a diagnosis of epilepsy is more frequently sought out and detected amongst those with mucosal healing, who better adhere to a GFD. It may be that individuals who follow physician's advice in this regard are more likely to seek medical attention for minor symptoms (including possible convulsions/epilepsy), when compared with non-adherent individuals (with persistent VA) who may defer consultations. Other factors may also have influenced outcomes. Previous work has shown that although adhering to a GFD can induce mucosal healing, it can lead to an increase in body weight

[32,33]. As weight change has been shown to influence other conditions, such as breast cancer and type 2 diabetes, it may be that the weight gain is adversely influencing neurological processes and inflammation [34–36].

Another possibility is that patients with persistent VA on a first follow-up biopsy may not reflect long-term mucosal healing rates. In a study of patients undergoing serial small intestinal biopsy, the prevalence of mucosal healing was greater at 5 years (66%) than at 3 years (34%), suggesting that some individuals gradually heal over subsequent years [15]. In this population-based study, the prevalence of persistent VA was similar among those whose follow-up biopsy was performed 1–2 and 2–5 years after diagnosis [37], suggesting that gradual mucosal healing is not a widespread phenomenon at least within this time frame. Another potential explanation is that patients undergoing follow-up biopsy may represent a healthier subset of patients with CD compared with those who did not undergo follow-up biopsy, which may have been deferred due to medical comorbidities. Supporting this notion is our previously reported finding that the overall mortality risk of individuals who underwent follow-up biopsy was slightly lower than that of those who did not have follow-up biopsy [17]. Although our study population had a large proportion of adults, the results were similar in both children and adult populations. These findings could suggest a shared underlying pathological mechanism between epilepsy and CD in both groups.

To our knowledge, this is the first study to investigate the risk of epilepsy according to follow-up histology in CD. This study has several strengths, including its population-based design and the independent ascertainment of cases from national health registers. The Swedish National Patient Register has been validated repeatedly, and the majority of diagnoses have a high positive predictive value (85–95%) [23]. Furthermore, CD was identified through biopsy records showing VA. During the study period, biopsy remained the gold standard for diagnosis in both children and adults, and ≥96% of all pediatricians and gastroenterologists in Sweden reported performing a small intestinal biopsy before diagnosis [21]. A patient chart review found that 95% of all samples with VA represented CD, a higher positive predictive value than physician-assigned diagnosis for CD in the Swedish National Patient register [38]. In addition, VA in Sweden is rarely explained by diagnoses other than CD (0.3% of individuals with VA had inflammatory bowel disease) [21]. Although positive CD serology was not included within the definition of CD, it has been demonstrated that 88% of those with available CD serology data have positive antibodies at the time of first biopsy [21].

This study is limited by a lack of data regarding several important risk factors for epilepsy, including previous head trauma, central nervous system infections and tumors [39]. Our ability to determine risk factors for both CD and epilepsy was limited to ascertainment of age, gender and histological outcomes. Therefore, we could not adjust for the previously highlighted risk factors that could have influenced our results. Our analysis of emergency department visits was limited by the small number of patients who developed epilepsy prior to follow-up biopsy, raising the possibility that we had insufficient power to detect whether healing is associated with this outcome.

In conclusion, this analysis of more than 7000 patients with CD undergoing follow-up biopsy found that persistent VA was associated with a significant reduction in subsequently developing epilepsy. Future work should investigate novel biomarkers of inflammation in CD that may impact epilepsy risk.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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