Original Investigation

Risk of Neuropathy Among 28 232 Patients With Biopsy-Verified Celiac Disease

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IMPORTANCE Earlier research on celiac disease (CD) and neuropathy has been hampered by the use of inpatient data, low study power, and lack of neuropathic characteristics.

OBJECTIVE To examine the relative risk and absolute risk of developing neuropathy in a nationwide population-based sample of patients with biopsy-verified CD.

DESIGN, SETTING, AND PARTICIPANTS Between October 27, 2006, and February 12, 2008, we collected data on small-intestinal biopsies performed at Sweden's 28 pathology departments between June 16, 1969, and February 4, 2008. We compared the risk of neuropathy in 28 232 patients with CD (villous atrophy, Marsh 3) with that of 139 473 age- and sex-matched controls. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% CIs for neuropathy defined according to relevant *International Classification of Diseases* codes in the Swedish National Patient Register (consisting of both inpatient and outpatient data).

MAIN OUTCOMES AND MEASURES Neuropathy in patients with biopsy-verified CD.

RESULTS Celiac disease was associated with a 2.5-fold increased risk of later neuropathy (95% CI, 2.1-3.0; $P < .001$). We also found an increased risk (with results reported as HRs [95% CIs]) of chronic inflammatory demyelinating neuropathy (2.8; 1.6-5.1; $P = .001$), autonomic neuropathy (4.2; 1.4-12.3; $P = .009$), and mononeuritis multiplex (7.6; 1.8-32.4; $P = .006$), but no association between CD and acute inflammatory demyelinating polyneuropathy (0.8; 0.3-2.1; $P = .68$).

CONCLUSIONS AND RELEVANCE We found an increased risk of neuropathy in patients with CD. This statistically significant association in a population-based sample suggests that CD screening should be completed in patients with neuropathy.

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Celiac disease (CD) is an immune-mediated enteropathy occurring in genetically susceptible individuals as a result of sensitivity to gluten.[1] Celiac disease is common in the general population, with an estimated prevalence of 1%.[2] Neurologic extra-intestinal manifestations of CD have been described, with peripheral neuropathy and ataxia as the most frequently reported.[3,4] Peripheral neuropathy is also common in the general population, with an estimated prevalence of 2% to 7%; distal symmetric polyneuropathy is the most common subtype.[5-8]

The association between CD and neuropathy was first reported in 1966.[9] In that series of 16 patients with established CD and neurologic disorders, 10 had peripheral neuropathy. In a population-based study in Sweden, CD was associated with a 3-fold increased risk of polyneuropathy.[10] However, that study was limited to inpatients with CD and may therefore have overestimated the true risk for neuropathy. Few prevalence estimates of CD-associated neuropathy exist. A tertiary referral center in the United States evaluated patients with distal symmetric polyneuropathy and demonstrated the prevalence of CD to be between 2.5% and 8% compared with 1% in a retrospectively evaluated healthy population.[11] In another series from Finland, up to 23% of patients with established CD had neurophysiological evidence of a peripheral neuropathy.[12] One study from the United States reported that 39% of patients with CD had neuropathic symptoms.[13] Other investigators have studied the association between neuropathy and antibodies to gluten (in the presence or absence of CD). In one UK study, 34% of patients with idiopathic sensorimotor neuropathy had positive antigliadin antibodies.[14] Other investigators have questioned the association of peripheral neuropathy and CD.[15-17]

The objective of our study was to examine the relative risk and absolute risk of developing neuropathy in a nationwide population-based sample of patients with biopsy-verified CD.

Methods

Study Participants

We linked nationwide data on biopsy-verified CD from Swedish pathology registers to inpatient and hospital-based outpatient data on neuropathy obtained from the Swedish National Patient Register,[18] as well as to the Prescribed Drug Register.[19] Between October 27, 2006, and February 12, 2008, we collected data on small-intestinal biopsies performed between June 16, 1969, and February 4, 2008, at Sweden's 28 pathology departments. Data included location of biopsy (duodenum and jejunum), date of biopsy, morphologic codes, and personal identification number to allow for linkage with other registries.[20] Each individual with CD was matched on age, sex, calendar year, and county with up to 5 controls from the Swedish Total Population Registry. After removal of individuals with data irregularities, there remained 29 096 individuals with CD and 144 522 age- and sex-matched controls (these participants were identical to those in an earlier article on CD and mortality).[21] This study was approved by the Regional Ethical Review Board in Stockholm. Because this was a register-based study, no participant was contacted, and all data were anonymized prior to data analyses.

Celiac Disease

We defined CD as villous atrophy (Marsh stage 3) according to biopsy reports. Having a positive CD serologic test result was not a prerequisite for the diagnosis of CD, but in 81 patients with available data, 71 (88%) had a positive serologic test result at the time of biopsy. Additional details on the data collection, including validation data on CD, have been published previously.[22] Each biopsy report was based on an average of 3 tissue specimens.

Neuropathy

We defined neuropathy according to relevant *International Classification of Diseases* (*ICD*) codes in the Swedish National Patient Register (eAppendix in the Supplement).[18] The Patient Register started in 1964 and was used nationwide beginning in 1987. It contains diagnoses from *ICD-7* through *ICD-10* (the latter was introduced in 1997). Until 2000, the Patient Register was limited to inpatient care, but since 2001 it also contains hospital-based outpatient care.

Other Covariates

The government agency Statistics Sweden contributed data on the following potential confounding factors: country of birth (Nordic vs not Nordic), educational level, and socioeconomic status. We divided education into 4 prespecified groups (≤9 years of primary school, 2 years of high school, 3-4 years of high school, and college or university), while socioeconomic status was divided into 6 groups (according to the European Socioeconomic Classification).[23] We lacked data on educational level in 1109 individuals with CD (3.9%) and on socioeconomic status in 8585 individuals with CD (30.4%). We fitted these individuals into separate categories for the statistical analyses. We identified patients with type 1 diabetes mellitus, autoimmune thyroid disease, rheumatic disorders (rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome), vitamin deficiencies (vitamins A, B, C, D, E, and K), and pernicious anemia using the Patient Register.[18] Finally, we used medical diagnoses (including psychiatric disorders and liver disorders) as a proxy for high alcohol consumption, which has been linked to neuropathy.[24] Relevant *ICD* codes for these diseases, including alcohol-associated disorders, are in the eAppendix in the Supplement.

Statistical Analysis

We used internally stratified Cox proportional hazards regression to estimate hazard ratios (HRs) for neuropathy. This statistical approach is similar to a conditional logistic regression since individuals with CD are compared only with their matched controls (one stratum at a time) before a summary HR is calculated. We tested the proportional hazards assumption using log minus log curves (eFigure in the Supplement). The attributable risk percentage (the proportion of all neuropathy in patients with CD that could be explained by the underlying CD) was estimated by the formula 1-1/HR.

We began follow-up time at the first biopsy for CD diagnosis in patients with CD and at the same time in the matched controls. Follow-up ended at first neuropathy diagnosis up to December 31, 2009, emigration, or death, whichever occurred first.

In prior defined analyses, we examined the risk of neuropathy according to time since CD diagnosis and calculated HRs stratified by sex, age at CD diagnosis, and calendar period. In separate analyses, we then adjusted for country of birth, educational level, socioeconomic status, type 1 diabetes, type 2 diabetes, autoimmune thyroid disease, vitamin deficiencies, pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, and disorders indicating high alcohol consumption (see eAppendix in the Supplement for definitions).

We also examined CD and the risk of neuropathy corroborated by evidence of medications used for neuropathy (eAppendix in the Supplement). This analysis was restricted to individuals with a follow-up beyond July 1, 2005, as the Swedish Prescribed Drug Register was started on that date.

Finally, to examine the temporal association between CD and neuropathy, we also calculated the odds ratios (ORs) for having a neuropathy prior to the first biopsy for CD diagnosis. For this analysis, we used conditional logistic regression comparing each individual with CD with his or her matched control. This analysis was based on 29 096 individuals with CD and 144 522 controls.

We used SPSS, version 22 (SPSS Inc), to calculate statistics. $P < .05$ was considered statistically significant.

Results

Restricting our main analyses to individuals without a prior neuropathy diagnosis (at time of biopsy for CD diagnosis and corresponding date in matched controls), our data included 28 232 individuals with CD and 139 473 matched controls.

Most study participants were females (**Table 1**). A total of 41.7% of the patients with CD were diagnosed in childhood (Table 1), with a median age at diagnosis of 29 years (range, 0-95 years). Patients were followed up for a median of 10 years.

Future Risk of Any Neuropathy

During follow-up, we identified 198 individuals with CD with a later diagnosis of neuropathy (0.7%) vs 359 controls (0.3%) with a later diagnosis of neuropathy. The absolute risks of neuropathy were 64 per 100 000 and 15 per 100 000 person-years, respectively, for patients with CD and matched controls. This absolute risk corresponded to an HR of 2.5 (95% CI, 2.1-3.0; $P < .001$). Adjusting for educational level, socioeconomic status, country of birth, type 1 diabetes, type 2 diabetes, autoimmune thyroid disease, rheumatologic diseases, pernicious anemia, vitamin deficiencies, and alcoholic disorders had only a marginal effect on the risk estimate (HR, 2.3; 95% CI, 1.9-2.7).

Risk estimates for neuropathy were highest in the first year after diagnosis of CD (HR, 4.4; 95% CI, 2.6-7.4; $P < .001$), but there was also a significantly increased risk of neuropathy after the first year of follow-up (HR, 2.4; 95% CI, 2.0-2.9; $P < .001$). The incidence rates of neuropathy in patients with CD are given in **Table 2** and correspond to a cumulative incidence of 3.7 new neuropathy cases in 1000 individuals with CD followed up for 5 years.

Overall, there were no differences between men and women in the risk of neuropathy in patients with CD ($P = .68$ for interaction) or according to the calendar period ($P = .50$ for interaction) (**Table 3**). Age at diagnosis also did not influence the risk estimates for any neuropathy in patients with CD ($P = .68$ for interaction).

Additional Analyses

Age did not influence the risk of neuropathy in patients with CD (HR, 2.5; 95% CI, 2.1-3.0). When we restricted our outcome to neuropathy in individuals with a record of neuropathy-associated medication (see eAppendix in the Supplement for a complete list) in the Swedish Prescribed Drug Registry, the association between CD and neuropathy remained (HR, 2.7; 95% CI, 1.8-4.0).

Subtypes of Neuropathy

The vast majority of cases with neuropathy were nonspecified neuropathy. Among other neuropathies, we found an increased risk of chronic inflammatory demyelinating neuropathy, autonomic neuropathy, and mononeuritis multiplex but no association with acute inflammatory demyelinating neuropathy (**Table 4**). Although sensory ganglionopathy is the second most common type of neuropathy reported in patients with CD, there is no corresponding *ICD* code to complete a subanalysis.[25] In addition, in 10 patients who had a diagnosis

Table 1. Characteristics of Participants

Characteristic	Value[a]	
	Matched Controls	Celiac Disease
Total	139 473	28 232
Age at study entry, y		
0-19	58 647 (42.0)	11 763 (41.7)
20-39	25 366 (18.2)	5118 (18.1)
40-59	30 366 (21.8)	6159 (21.8)
≥60	25 094 (18.0)	5192 (18.4)
Sex		
Female	86 327 (61.9)	17 431 (61.7)
Male	53 146 (38.1)	10 801 (38.3)
Calendar period		
1989 and earlier	20 183 (14.5)	4071 (14.4)
1990-1999	58 191 (41.7)	11 782 (41.7)
2000 and later	61 099 (43.8)	12 379 (43.8)
Year of diagnosis, median (range)	1998 (1969-2008)	1998 (1969-2008)
Follow-up, median (range), y	10 (0-41)	10 (0-41)
Nordic country of birth	131 596 (94.4)	27 318 (96.8)
Any neuropathy	359 (0.3)	198 (0.7)
Comorbidity		
Type 1 diabetes mellitus	575 (0.4)	914 (3.2)
Alcohol use	3615 (2.6)	762 (2.7)

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Table 2. Risk of Neuropathy in Patients With Celiac Disease According to Follow-up

Follow-up	HR (95% CI)[a]	Observed, No.	Expected, No.	Person-years	Incidence Rate[b]	Excess Risk[b]	Attributable Percentage
All, y	2.5 (2.1-3.0)	198	78	308 979	64	39	60
<1 y	4.4 (2.6-7.4)	25	6	27 871	90	69	77
1-5 y	2.8 (2.1-3.7)	71	26	103 290	69	44	64
>5 y	2.2 (1.7-2.7)	102	47	177 818	57	31	54
Beyond 1 y of follow-up	2.4 (2.0-2.9)	173	73	281 108	62	36	58

Abbreviation: HR, hazard ratio.

[a] $P < .001$ for all.

[b] Neuropathy cases per 100 000 person-years. Due to rounding of data, total numbers and percentages may deviate from the total (or from 100%).

Table 3. Risk of Neuropathy in Patients With Celiac Disease

Follow-up	HR (95% CI)	*P* Value	Observed	Expected	Person-years	Incidence Rate[a]	Excess Risk[a]	Attributable Percentage
Age, y								
<20	2.0 (1.0-3.9)	.06	11	6	145 064	8	4	49
20-39	2.6 (1.6-4.3)	<.001	24	9	55 275	43	27	62
40-59	2.5 (1.9-3.3)	<.001	81	32	68 683	118	71	61
≥60	2.6 (2.0-3.4)	<.001	82	31	39 956	205	127	62
Sex								
Male	2.5 (2.0-3.2)	<.001	99	39	116 993	85	51	60
Female	2.5 (2.0-3.3)	<.001	99	39	191 986	52	31	61
Calendar period								
1989 and earlier	2.7 (1.9-3.8)	<.001	54	20	82 189	66	41	70
1990-1999	2.6 (2.0-3.4)	<.001	89	34	153 515	58	36	62
2000 and later	2.3 (1.7-3.1)	<.001	55	24	73 274	75	42	59

Abbreviation: HR, hazard ratio.

[a] Neuropathy cases per 100 000 person-years.

Table 4. Types of Neuropathy

Follow-up	HR (95% CI)	*P* Value	Observed	Expected	Person-years	Incidence Rate[a]	Excess Risk[a]	Attributable Percentage
AIDP	0.8 (0.3-2.1)	.68	5	6	308 979	2	0	−22
CIDP	2.8 (1.6-5.1)	.001	17	6	308 979	6	4	65
Autonomic neuropathy	4.2 (1.4-12.3)	.009	6	1	308 979	2	1	76
Mononeuritis multiplex	7.6 (1.8-32.4)	.006	4	1	308 979	1	1	87

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; HR, hazard ratio.

[a] Neuropathy cases per 100 000 person-years.

of idiopathic neuropathy after CD diagnosis, the coefficients did not converge in our Cox proportional hazards regression model and, hence, we were unable to calculate an HR for idiopathic neuropathy.

Prior Neuropathy and CD

In a separate logistic regression based on 29 096 individuals with CD and 144 522 matched controls (same study base as in an earlier study[21]), we found a positive association between any neuropathy and CD before diagnosis of CD (odds ratio, 1.8; 95% CI, 1.4-2.2; $P < .001$).

Discussion

In this nationwide population-based sample, CD was associated in adjusted analyses with a 2.5-fold increased risk of neuropathy. There was also a bidirectional association between CD and neuropathy since patients with neuropathy were also at increased risk of future CD.

Our risk estimate of CD and the risk of future neuropathy was lower than that reported in an earlier population-based study from Sweden.[10] In that study, the HR for the risk of later neuropathy was 3.2 in the adjusted analysis; hospital discharge diagnoses were used, which may have increased risk estimates.[26] The diagnosis of neuropathy was further validated by demonstrating that individuals with CD were also at increased risk of having 2 later discharge diagnoses of polyneuropathy.[10] This same sample did not find a statistically significant association between CD and later multiple sclerosis, hereditary ataxia, myasthenia gravis, and other neurodegenerative diseases, such as Parkinson disease and Alzheimer disease. The Swedish National Patient Register does not contain data on diagnostic procedures, such as electromyography. We further validated our diagnoses of neuropathy with the addition of independent drug prescription data, which increased the specificity of our outcome, demonstrating that the HR remained at approximately 2.5.

Major strengths of this study are the nationwide population-based design and high statistical power. Other strengths include the validated CD diagnosis and biopsy registers. At least 90% of patients with suspected CD in Sweden undergo biopsy performed by adult and pediatric gastroenterologists before diagnosis.[22] For validation of the CD diagnosis, 114 patient medical records were examined for diagnosis of villous atrophy; 108 (94.7%) of these patients had CD.[22] In Sweden, villous atrophy is almost exclusively caused by CD, which was determined by manual review of more than 1500 biopsy reports.[22]

Given the autoimmune nature of CD, our data reinforce the potential role of immunologic mechanisms for the develop-

ment of neuropathy.[4,27] Neuropathy has been linked to several other autoimmune disorders.[8] Based on earlier research, we adjusted for 5 such disorders (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome) that are associated with CD, with little influence on our risk estimate. We also eliminated all cases of diabetes and still found a significant risk estimate between CD and later neuropathy.

To our knowledge, this is the first analysis to examine CD and the development of various types of neuropathy. In this analysis, there were positive risk estimates between CD and later chronic inflammatory demyelinating neuropathy, autonomic neuropathy, and mononeuritis multiplex. Asymmetric forms of neuropathy, such as mononeuritis multiplex and autonomic neuropathy, have previously been reported in association with CD.[28,29] A tertiary referral center treated 5 patients with CD with intravenous immunoglobulin for suspected multifocal sensorimotor polyneuropathy, but there are no other reports of chronic inflammatory demyelinating neuropathy related to CD.[11] Although isolated case reports have reported an association between CD and acute inflammatory demyelinating neuropathy,[30,31] we did not find an association between CD and later acute inflammatory demyelinating neuropathy.

Part of the increased risk of neuropathy may be owing to surveillance bias. The highest risk for future neuropathy was just after diagnosis of CD (Table 2). Physicians may be more prone to investigate patients with CD for neuropathy, thereby contributing to the excess risk of neuropathy seen in patients with CD in our study. However, there was a consistent excess risk of neuropathy beyond 5 years after a diagnosis of CD (excess risk was 31 per 100 000 person-years more than 5 years after diagnosis). One questionnaire study also suggested an ongoing risk of neuropathy more than 5 years after diagnosis.[13] This ongoing risk after more than 1 year suggests that a CD diagnosis does not protect the patient from the development of neuropathic symptoms. Some evidence suggests that strict adherence to a gluten-free diet (the only treatment for CD) may protect against the new development of autoimmune diseases and may prevent the progression of neuropathy.[32,33] However, we do not have information as to the degree of dietary adherence among individuals diagnosed with CD.

We did not have enough statistical power to examine the association between CD and multifocal motor neuropathy, which has been previously reported in association with CD.[34] Small fiber neuropathy also has been demonstrated in association with CD, with diagnostic support provided by skin biopsy.[35] We were unable to assess this association as there was no *ICD* code for this diagnosis during the data collection interval. Another limitation is our lack of data on hospital-administered chemotherapy treatment, which may induce neuropathy.

Guidelines for the initial evaluation of distal symmetric polyneuropathy recommend an evaluation for diabetes with tests for fasting glucose levels, glucose tolerance, and vitamin B_{12} levels, as well as serum protein electrophoresis.[8,36] In our analysis, the influence of vitamin deficiencies did not significantly affect our risk estimate. Vitamin B_{12} deficiency has been found to be associated with CD both before and after diagnosis and with neuropathy, suggesting that the association may be nutritional.[8,9,37,38] Malabsorption of nutrients, such as iron, copper, calcium, and vitamins B_1, B_2, B_3, B_6, D, and E, have also been reported in patients with CD.[39-41] However, nutritional deficiencies have not always been found in patients with neuropathy and CD. In one series of 18 patients with neuropathy and biopsy-verified CD, all 18 patients had normal vitamin B_{12} levels and normal copper levels or mild hypercupremia.[42] In another series of patients with neuropathy and CD, all 20 patients had normal vitamin B_{12} levels and, in the 16 patients tested, all had normal B_1, B_6, and vitamin E levels.[11]

We observed an increased risk for neuropathy both before and after diagnosis of CD. There is a possibility that some patients with CD had received a nondocumented diagnosis of neuropathy before receiving a biopsy-verified diagnosis of CD and then, owing to their neuropathy, the patients were evaluated for CD. These data may also suggest that the 2 diseases may share risk factors or a common underlying etiology for the development of neuropathy, such as a potential role of immunologic mechanisms. The association between CD and different types of neuropathy suggests that there may be specific underlying mechanisms that may lead to the predominance of one type of neuropathy compared with others. Without knowledge of the electrophysiological features and additional confirmatory tests, we cannot adequately confirm or standardize the classification of neuropathies in this study. However, *ICD* codes in general have a high positive predictive value in the Swedish National Patient Register.[18] Nonetheless, future studies examining the association between CD and neuropathy should include electrophysiological studies, thorough serum evaluations, prior drug histories, and skin biopsies to evaluate for small fiber neuropathy.

Conclusions

We found an increased risk of neuropathy in patients with CD that persists after CD diagnosis. Although absolute risks for neuropathy are low, CD is a potentially treatable condition with a young age of onset. Our findings suggest that screening could be beneficial in patients with neuropathy.

ARTICLE INFORMATION

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