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Original Article

Type 1 Diabetes, Celiac Disease, and Neuropathy—A Nationwide Cohort Study

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This project (2011/841-31/3) was approved by the Regional Ethical Review Board in Stockholm in 2011.

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Abstract

Objective:
Both type 1 diabetes (T1D) and celiac disease (CD) have been linked to an increased risk of neuropathy. This study examined the risk of neuropathy in patients with T1D compared with patients with both T1D and CD.

Methods:
In a nationwide population-based cohort, T1D was defined as having a diagnosis of diabetes between 1964 and 2009 recorded in the Swedish National Patient Register in individuals ≤30 years of age. CD was defined as having villous atrophy (Marsh histopathology stage III) on small intestinal biopsy. CD cases were identified through biopsies examined between 1969 and 2008 at any of Sweden's 28 pathology departments. Nine hundred fifty-eight patients had both T1D and CD and were matched for sex, age, and calendar period with 4590 controls who only had T1D. Through Cox regression analysis, with CD as the time-dependent covariate, we estimated the risk of neuropathy in T1D patients with CD.

Results:
Fifty-four individuals with T1D and CD had later neuropathy (expected: n = 42). This corresponded to an adjusted hazard ratio of 1.27 (95% confidence interval = 0.95–1.71) compared with those who had T1D alone. The hazard ratio was statistically significant in the first 5 years with CD (1.67; 95% confidence interval = 1.13–2.47) but decreased to neutrality thereafter. Risk estimates were similar in men and women, and did not differ by age at CD onset.

Conclusions:
CD does not seem to influence the risk of neuropathy in individuals with T1D, although a small excess risk cannot be ruled out.

Key Words: celiac disease, cohort studies, neuropathy, type 1 diabetes

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INTRODUCTION

Celiac disease (CD) is an immune-mediated chronic disease triggered by the ingestion of gluten.[1] It occurs in about 1%–2% of the general population.[2] An increased susceptibility to other immune-mediated diseases such as type 1 diabetes (T1D) has been well described.[3] The prevalence of biopsy-proven CD in T1D is approximately 6%.[4] Peripheral neuropathy is also associated with both CD and T1D.[5–8] Diabetes is the most common etiology of distal symmetric polyneuropathy.[9–11] The presenting symptoms commonly reported are a combination of numbness, pain, and tingling that generally starts in the feet and then spreads proximally up with a distribution in a stocking–glove pattern.[12] Symptoms generally begin insidiously and progress slowly.[13] As the neuropathy progresses, weakness may develop initially in toe extension.

Greater microvascular complications such as retinopathy, nephropathy, and neuropathy have been reported in CD patients with T1D.[5,14–18] T1D carries an increased risk of neuropathy with prevalence estimates of neuropathy in T1D as high as 10%–54%.[19–21] Consistent glycemic control reduces the incidence of distal symmetric polyneuropathy in patients with T1D.[22,23] CD is also associated with neuropathy and in one study of patients with neuropathy and gluten sensitivity, adherence to a gluten-free diet (GFD) was associated with improvement in the neuropathy.[24]

It is unclear, however, if T1D patients with CD have an increased risk of neuropathy

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compared with patients with T1D but no record of CD.

METHODS

We used nationwide biopsy data from Sweden's 28 pathology departments to identify CD cases. These data were then linked to the Swedish Patient Register containing both inpatient and hospital-based outpatient data to link CD, T1D, and neuropathy.[25] This register started in 1964 and added outpatient data in 2001.[26] This allowed us to calculate hazard ratios (HRs) for later neuropathy in patients with T1D according to CD status.

Type 1 Diabetes

T1D was ascertained using the data from the Swedish Patient Register.[26] T1D was defined according to relevant *International Classification of Disease* (*ICD*) codes (*ICD-7*: 260, *ICD-8*: 250, *ICD-9*: 250, and *ICD-10*: E10). Since the Swedish *ICD* system did not differentiate between T1D and type 2 diabetes until 1997, we also requested patients with T1D to have their first diabetes diagnosis at ≤30 years of age. Type 2 diabetes is rare before that age in Swedish individuals.[27] This definition of T1D has a 95% positive predictive value for insulin-dependent diabetes mellitus in Sweden.[28]

Celiac Disease

CD was defined as having duodenal/jejunal villous atrophy (VA, Marsh stage 3 on small intestine biopsy) at any of Sweden's 28 pathology departments.[29] Although the collection of biopsy report data took place between 2006 and 2008, the biopsies had been performed between 1969 and 2008. In Sweden, small intestinal biopsy was the preferred method of CD diagnosis throughout the study period.[25] Additional details on the data collection have been published elsewhere,[30] and a patient chart validation of 114 individuals with VA found that 108 had CD, that is, a positive predictive value of 95%. On average, pathologists had access to 3 biopsy specimens to diagnose VA.[30]

Neuropathy

Neuropathy was defined according to relevant *International Classification of Disease* (*ICD*) codes in the Swedish Patient Register: *ICD-7* (260.40; 364; and 366.29); *ICD-8* (250.05, 354); *ICD-9* (250F, 337A, 337B, 354F, 356D, 356E, and 357); *ICD-10* (E10.4, G58.7, G60-63, and G90.0).

Study Population

Through the Swedish National Board of Health and Welfare, we identified 42,806 individuals with T1D. Of these, the identity of 42,578 (99%) could be confirmed by the government agency Statistics Sweden. Of these individuals, 960 had both CD and T1D and were matched on age, sex, and calendar period with 4608 controls who only had T1D (5 controls per CD patient).[18] Individuals with CD could have been diagnosed with this disease before or after T1D, but only follow-up time when they had been diagnosed with both diseases was assigned to the CD+T1D group.

Individuals with neuropathy before the first T1D diagnosis (or corresponding date in matched controls) were excluded from all prospective analyses. This meant that this study was based on 958 individuals with T1D and CD and 4590 controls with T1D without CD ("T1D only").

Statistical Analyses

Through Cox regression, we estimated HRs for neuropathy according to CD status in patients with T1D. CD was modeled as a time-dependent variable. Follow-up time started on the date of the first T1D diagnosis and ended with a diagnosis of neuropathy, death, emigration, or end of study period (December 31, 2009), whichever happened first. All analyses were adjusted for sex, calendar year at T1D diagnosis (1964–1975, 1976–1987, 1988–1999, and 2000–2009), and age at T1D diagnosis (0–9, 10–19, and 20–30 years). We chose to divide age at T1D onset in these categories because Swedish children rarely enter puberty before the age of 10 years.[31] We calculated incidence rates through dividing the number of incident

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neuropathies with person-years at risk. Furthermore, we examined the interaction between CD and sex, age, and calendar period with regards to the risk of neuropathy.

Sensitivity Analyses

We performed 3 sets of sensitivity analyses (for numbers, see Table 1). Initially, we excluded individuals with a record of oral antidiabetic medication in the Prescribed Drug Register according to relevant anatomical therapeutic chemical codes (A10B and A10X) because such patients may suffer from type 2 diabetes despite an *ICD* code consistent with insulin-dependent diabetes. In a second sensitivity analysis, we excluded women with potential gestational diabetes [women who had their first T1D diagnosis during pregnancy (0–9 months before delivery)]. Pregnancy data were obtained from the Swedish Medical Birth Registry.[32] In a third sensitivity analyses, we restricted our analysis to individuals with an inpatient diagnosis of T1D. We also examined the risk of neuropathy excluding individuals born in the Nordic countries, as both incidence and prevalence of CD[33] and T1D[34] vary by geographic region. Finally, we studied the risk of neuropathy in T1D according to lifetime CD status (ie whether patients with T1D and CD had more neuropathy before or after CD than T1D-only patients).

Ethics

This project (2011/841-31/3) was approved on June 15, 2011 by the Ethics Review board, Stockholm, Sweden. The Ethics Review Board determined that no informed consent was needed because of the strict registry-based study design.[35]

RESULTS

The median age at T1D onset was 9 years (range 0–30 years) in both patients with

TABLE 1. Characteristics of the Study Participants

	Type 1 Diabetes	Type 1 Diabetes and Celiac Disease
Total	4590	958
Age at T1D diagnosis (median, range), yrs	9 (0–30)	9 (0–30)
Age at T1D diagnosis, %		
0–9	2649 (57.7)	565 (59.0)
10–19	1286 (28.0)	261 (27.2)
20–30	655 (14.3)	132 (13.8)
Age at the end of study (median, range)	23 (2–71)	22 (4–72)
Entry year (median, range)	1997 (1964–2009)	1996 (1964–2009)
Follow-up* (median, range), yrs	13 (0–47)	13 (0–47)
Age at CD diagnosis (median, range), yrs		12 (1–63)
Females, %	2502 (54.5)	527 (55.0)
Males, %	2088 (45.5)	431 (45.0)
Calendar year		
1964–1975	479 (10.4)	102 (10.6)
1976–1987	745 (16.2)	153 (16.0)
1988–1999	1607 (35.0)	344 (35.9)
2000–2009	1759 (38.3)	359 (37.5)
Nordic country of birth	4453 (97.4)	951 (99.3)
Gestational diabetes	93 (2.0)	14 (1.5)
Oral antidiabetic medication	138 (3.0)	19 (2.0)

Age was rounded to the nearest year.
Includes patients with a CD diagnosis before or after first T1D diagnosis.
*Follow-up time until death, emigration or December 31, 2009, whichever occurred first.

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CD and those without. The median age at first CD diagnosis was 12 years (range 1–63 years). Slightly more than half of the study participants were female, with 38% diagnosed with T1D in the year 2000 or later. The median age at onset of neuropathy was 33 years (range 4–66 years) in patients with T1D and CD and similar in patients with T1D only (34 years; range 3–66 years).

CD and Future Neuropathy

During follow-up, some 54 individuals with T1D and CD developed neuropathy (expected: n = 42). The corresponding HR (1.27) just failed to reach statistical significance (adjusted 95% confidence interval [CI] = 0.95–1.71) (Table 2). The absolute risk of neuropathy was 603/100,000 person-years in T1D+CD patients versus 473/100,000 in T1D-only patients. The highest risk estimate for neuropathy was seen in the first 5 years after CD diagnosis (HR = 1.67; 95% CI = 1.13–2.47), and thereafter the HRs decreased and CD was no risk factor for neuropathy among patients with T1D (Table 2, and Kaplan–Meier curve in the **Appendix**, **Supplemental Digital Content 1**, http://links.lww.com/JCND/A13). As can be seen from Table 3, the absolute risk of neuropathy was strongly age dependent. Individuals in this study were followed for a median period of 13 years, and this means that individuals aged 0–9 years at T1D onset were younger at the end of follow-up (with a lower percentage having neuropathy), than individuals diagnosed with T1D between 20 and 30 years (older at the end of follow-up). However, the influence of CD did not differ with age at T1D although the HR for neuropathy attained statistical significance in one of the age groups (T1D onset between 10 and 19 years of age) (Table 3). The relative risk of neuropathy did not differ by calendar period of T1D. The absolute risk of neuropathy was highest in patients diagnosed with T1D in the first calendar period (1964–1975).

Sensitivity Analyses

The relative risk of neuropathy did not change when we restricted our cohort to individuals without a record of oral antidiabetic medication (HR = 1.27; 95% CI = 0.95–1.71). HRs were all between 1.26 and 1.28 when we excluded individuals with gestational diabetes, those without a record of inpatient care for T1D, and those born outside the Nordic countries. Neither did the HR change when we examined the risk of neuropathy in T1D and also included undiagnosed CD (ie neuropathy occurring after T1D onset but before CD diagnosis) (Data not shown).

DISCUSSION

Peripheral neuropathy in T1D is associated with poor glycemic control, but additionally, risk of neuropathy is associated, with male sex, hypertension, and cigarette use.[36] Increased triglycerides are associated with progression of neuropathy, independent of glycemic control.[37] In this study, we asked

TABLE 2. Risk of Neuropathy According to Time With Celiac Disease Among Patients With Type 1 Diabetes

Subgroup, yrs	Observed Events	Expected Events*	HR; 95% CI Adjusted	*P*	Absolute Risk/100,000 PYAR	Excess Risk/100,000 PYAR
Overall	54	42	1.27; 0.95–1.71	0.105	603	130
0 to <5	25	15	1.67; 1.13–2.47	0.010	636	256
5 to <10	16	13	1.22; 0.73–2.02	0.446	581	104
≥10	13	18	0.74; 0.39–1.40	0.351	585	−207

PYAR, person-years at risk.
*Due to rounding the numbers do not add up.

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TABLE 3. Subgroup Analyses

Subgroup	Observed Events	Expected Events	HR; 95% CI Adjusted	*P*	Absolute Risk/ 100,000 PYAR	Excess Risk/ 100,000 PYAR
Sex						
Female	31	25	1.24; 0.84–1.82	0.280	603	116
Male	23	18	1.31; 0.83–2.06	0.243	603	142
Age at T1D diagnosis, yrs						
0–9	20	19	1.07; 0.66–1.73	0.785	363	23
10–19	18	11	1.70; 1.01–2.83	0.047	802	327
20–30	16	13	1.27; 0.74–2.18	0.383	1336	285
Calendar period						
1964–1975	21	14	1.47; 0.91–2.37	0.117	2234	710
1976–1987	17	12	1.38; 0.82–2.32	0.228	896	246
1988–1999	11	11	0.97; 0.51–1.84	0.916	287	−10
2000–2009	5	4	1.12; 0.43–2.94	0.811	218	24

Neuropathy in T1D. Influence of CD.
PYAR, person-years at risk.

whether CD increased the risk of neuropathy in T1D.

In this nationwide population-based study, CD does not seem to influence the risk of neuropathy in individuals with T1D. The higher HR in the first 5 years of follow-up (HR = 1.67) compared with the HR after more than 5 years suggests that surveillance bias just after CD diagnosis may have played a role, but we cannot exclude that increased inflammation just before CD diagnosis [and up until the GFD has had an effect on the mucosa] might trigger the development of neuropathy. The Swedish Patient Register also included hospital data until 2001. Neuropathy is mostly managed and diagnosed in the outpatient setting, and it is possible that some patients with neuropathy were not identified leading to the overall low relative risk of neuropathy in individuals with T1D and CD compared with those with T1D only.

The overall relative risk of neuropathy was low in individuals with both T1D and CD compared with those with only T1D (+27%). This nonsignificant risk increase corresponded to about 1 extra case per 1000 person-years of follow-up. We conclude that if CD plays a role for neuropathy development in patients with T1D, its absolute importance is only minor and seems to decrease with time since CD diagnosis. Hence, although there may be reasons to screen patients with for CD due to a metabolic or nutritional reasons,[5,18,38] the risk of neuropathy is not sufficiently excessive to warrant CD screening.

A previous retrospective analysis of biopsy-proven CD in 1000 T1D hospital-based cases demonstrated a higher prevalence of neuropathy although this was not statistically significant.[5] This same series demonstrated a statistically significant increased prevalence of other microvascular complications such as retinopathy and nephropathy in T1D with CD versus T1D without CD. The subjects in this study with CD and T1D were placed on a GFD and after 1 year of follow-up, there was no significant reported improvement of the neuropathy.

The prevalence of positive tissue transglutaminase antibodies which are associated with CD was examined in patients with T1D with and without autonomic neuropathy.[39] The autonomic neuropathy was assessed by

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cardiac reflex testing and gastric scintigraphy. No difference in the prevalence of positive tissue transglutaminase antibodies was found between T1D patients with and without autonomic neuropathy. Only 1 individual in this study had biopsy-confirmed CD.

This is the first study to assess the effect of neuropathy in T1D patients with CD. Major strengths of this study are the nationwide population-based design, validated CD diagnoses based on biopsy registers, and validated T1D diagnoses based on *ICD* codes and age stratification.[28,30] The association between neuropathy and CD has been established in the Swedish population independent of diabetes.[7] However, the lack of electrophysiological data and additional confirmatory tests makes standardization of neuropathies difficult. Nonetheless, patients were followed for a median of 13 years and *ICD* codes in the Swedish National Patient Register have high positive predictive values. Through the unique personal identity number assigned to all Swedish residents, patients cannot be lost to follow-up.[40]

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. Another limitation is our lack of data on alcohol and smoking which may influence the risk of neuropathy.[41,42] However, *ICD* codes in general have a high positive predictive value in the Swedish National Patient Register.[26]

Future studies examining the association between neuropathy in T1D and CD should include electrophysiological studies, serum evaluations, previous drug histories, and other confirmatory tests. Data on adherence to a GFD should also be included because adherence to a GFD in CD is associated with protection against other autoimmune diseases.[43,44] It is possible that adherence to a GFD in T1D may reduce the risk of microvascular complications. It was beyond this study to determine the influence of undiagnosed CD on the risk of neuropathy in patients with T1D, although the similar risk for neuropathy in our sensitivity analysis that included exposure time when CD was undiagnosed suggests that undiagnosed CD is not a major risk factor for neuropathy in T1D.

In conclusion, this study found no increased risk of neuropathy in patients with T1D and CD as opposed to a reference population with T1D and no record of CD.

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