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Does haemochromatosis predispose to coeliac disease? A study of 29,096 coeliac disease patients

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Abstract

Background and aim—Case reports suggest an association between hereditary haemochromatosis (HH) and coeliac disease (CD), but estimates of association are lacking. We estimated the association between HH and CD in a population-based study.

Materials and methods—Case-control study. We identified 29,096 individuals with biopsy-verified CD (equal to villous atrophy, Marsh stage III) through biopsy reports from all 28 pathology departments in Sweden. We then investigated the risk of a clinical diagnosis of HH in CD and in 144,522 controls matched for age, sex, county and calendar year. Conditional logistic regression was used to calculate odds ratios (ORs) for CD in patients with HH.

Results—HH was seen in 30 patients with CD and in 60 matched controls. HH was hence associated with an increased risk of CD (OR=2.30; 95%CI=1.53–3.25). Restricting HH to individuals with at least 2 records of HH, the OR for CD was 2.54 (95%CI=1.57–4.11), with a

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similar risk estimate when we only looked at HH diagnosed before CD (and matched date in controls) (OR=2.64; 95% CI=1.24–5.60).

Conclusion—HH seems to be associated with an increased risk of CD.

Keywords

autoimmunity; celiac; coeliac; hemochromatosis; haemochromatosis; inflammation

Introduction

Hereditary haemochromatosis (HH) is the most common iron overload syndrome, [1] and is associated with both excess mortality [2] and malignancy [3]. Longstanding iron-load can lead to bronze discolouration of the skin, diabetes, and liver cirrhosis. [1, 4] The etiological basis of HH is a mutation of the HFE protein. [5] While, the most common *HFE* mutation (C282Y homozygosity) occurs in about 0.5% of individuals from Northern Europe (or such ancestry), [6] most homozygotic individuals will not have clinical disease. [1] Factors that influence the phenotypic expression of C282Y include alcohol consumption and male gender. [7, 8]

Coeliac disease (CD) is an immune-mediated disease that occurs in about 1% of the Western population. It is characterized by small intestinal enteropathy. [9] CD can manifest through a number of blood disorders, [10] including anemia and immune thrombocytopenia. CD is also associated with lymphoproliferative disorders [11] and liver disease [12].

Several case reports suggest a link between HH and CD, [13–18] but none of these earlier studies have included non-CD controls and hence relative risks and odds ratios for CD and HH are lacking. The aim of this nationwide case-control study was to examine the association between HH and biopsy-verified CD.

Materials and methods

In this case-control study, we linked biopsy data on CD from all 28 Swedish pathology departments with inpatient and hospital outpatient data on HH, examining if individuals with HH were at increased risk of CD.

Exposure: Haemochromatosis

Haemochromatosis was defined as having a relevant international classification of disease (ICD) code in the Swedish Patient Register (*ICD7*: 289.23; *ICD8*: 273.20; *ICD9*: 275A; and *ICD10*: E83.1 during the years 1964 and 2009 (*study period*). The Swedish Patient Register started in 1964 (then only inpatient care), [19] and became nationwide in 1987. [19] Day-surgery was added in 1997, and hospital-based outpatient care in 2001.

In a validation of 562 patients, the positive predictive value of an HH diagnosis was 93%. [20] Although our study did not contain genetic data, an earlier genetic study in Sweden found that 92% of patients with clinical HH were positive for the C282Y mutation in the *HFE* gene. [21]

Outcome: Coeliac disease

We used data from computerized biopsy reports obtained from all 28 Swedish pathology departments to identify patients with VA (histopathology stage Marsh 3 and equal to CD in this study) [22]. Duodenal/jejunal biopsies originated from 1969–2008, but the data collection of this study took place 2006–08. Searches for relevant biopsy data were

performed by local IT personnel who provided data on personal identity number, [23] morphology (see appendix for a list of relevant morphology codes), topography (duodenum or jejunum), and date of biopsy.

Later validation of 114 randomly selected patients found that 108 (95%) of individuals with VA had CD. [24] On average, biopsy reports were based on 3 pieces of tissue [25] (likely to identify some 95% of all CD [26]). Patient chart data found that diarrhea (36%) and anemia (35%) were the most common symptoms at diagnosis. [24] Although we did not request positive CD serology for the diagnosis, a previous evaluation [24] found that 88% of patients with available data on serology were positive at time of biopsy.

We initially identified 351,403 small intestinal biopsy reports from 287,586 unique individuals. [24] Of these 29,148 individuals had VA and were defined as having CD.

Controls

The government agency Statistics Sweden matched each individual with CD with up to 5 controls for age, gender, county, and calendar year. Controls were identified from the Total Population Register and only individuals *without* a prior small intestinal biopsy were eligible. Hence, controls were not obtained from biopsy registers.

Finally we excluded 29 individuals whose biopsy may have originated from the ileum and 23 for whom there were data irregularities. Similarly controls with data irregularities were removed. The remaining 29,096 individuals with CD and 144,522 matched controls made up our study base, and were identical to the participants in our study on mortality in CD. [27].

Statistics

Odds ratios (ORs) were calculated through conditional logistic regression, and in the main analysis we examined HH and the risk of CD. As ORs can represent a bidirectional relationship we have chosen to present the association as risk of CD in patients with HH.

All analyses were carried out stratumwise, this means that each individual with CD was only compared to his/her matched controls and only then did we calculate an overall OR. This statistical approach eliminated the effect of gender, age, county and calendar year on our ORs. In the main analysis we included all cases of HH, independently of if they were diagnosed before or after CD. The argument for doing so is that the genetic origin of HH means that HH has been present since birth, (although it is often clinically expressed and discovered only later in life), and HH was the exposure of ours study even if sometimes *diagnosed* after CD.

Pre-defined subanalyses included stratifications for gender, and calendar period at CD diagnosis (-1989, 1990–99; 2000–). In separate analyses we also adjusted for country of birth (Nordic vs. not Nordic) and education according to four a priori-defined categories. [28] About 4% of individuals lacked data on education and were therefore fitted into a separate fifth category in the multivariate analysis (CD: n=1152 (4.0%), and controls: n=5153 (3.6%)). Due to small numbers we did not stratify for age category.

We performed three sensitivity analyses. In the first one, we examined the association between having at least two records of HH and CD. In a second analysis we restricted HH to those individuals who had a *recorded* HH diagnosis before CD. In this second analysis we also examined the risk of CD according to time since first diagnosis of HH (<1, 1–4.99, and 5 years after HH). Finally we excluded individuals with a cancer diagnosis within 1 year before or after first HH diagnosis since patients with cancer may undergo extensive investigations leading up to a diagnosis of haemochromatosis.

Univariate comparisons were analysed using either Mann-Whitney U-test (non-parametric distributions), or or Chi-2/Fisher's exact test (proportions).

SPSS 20 (SPSS, Inc. Chicago, IL, USA) was used for all analyses. We regarded ORs with 95% confidence intervals as statistically significant.

Ethics

The current study was approved by the Ethics Review board of Stockholm, Sweden, which deemed that no individual informed consent was required since data were strictly register-based.

Results

About 40% of CD patients were diagnosed in childhood (Table 1). The majority of study participants entered the study from 1990 and onwards since we based our coeliac biopsy data on computerized registers. The majority of study participants were female (Table 1). This study was based on 30 cases with CD and HH vs. 60 controls with HH.

Characterization of patients with HH

The median age at first HH diagnosis was 61 years in patients with CD and 57 years in controls (Mann-Whitney U-test: $p=0.067$). Three individuals with CD had an HH diagnosis before the age of 40 years (16, 27, 31 years), compared to twelve controls (3, 15, 19, 27, 31, 34, 35, 37, 39, 39, 39, 39 years).

Alcohol-related disease was seen in 4 (13%) individuals with CD and HH vs. 4 (7%) of controls with HH. None of the HH individuals had a record of cardiomyopathy.

Some form of cancer was diagnosed in 20 HH patients (CD: 7 (23%); controls: 13 (22%)). Four of these had their cancer diagnosis within 1 year before or after first HH diagnosis, all of them were controls. Liver cancer was seen in 2 CD individuals with HH but in no control. Of individuals with HH, 2 CD patients and 1 control had a diagnosis of lymphoproliferative cancer. No HH patient had a record of either thalassemia or porphyria.

Liver biopsy had been performed in 8/30 (27%) CD patients with HH vs. in 6/60 (10%) controls with HH. This difference was not statistically significant ($p=0.062$, Fisher's exact test). Liver cirrhosis was seen in 1 patient with CD+HH and in 3 controls with HH. Three patients with CD+HH had undergone a colonoscopy before CD diagnosis (10%) compared with 1 control with HH (1.6%; $p=0.11$, Fisher's exact test).

HH and CD

HH was associated with an increased risk of CD (OR=2.30; 95%CI=1.53–3.45; based on 30 cases with CD and HH vs. 60 controls with HH). Adjusting for education and country of birth did not influence the risk estimate (OR=2.26; 95%CI=1.50–3.40).

Risk estimates were similar in men and women and did not differ according to calendar period (Table 2).

Restricting our analyses to individuals with at least 2 records of HH, the overall OR was 2.54 (OR=1.57–4.11) (22 CD patients and 39 controls had at least two records of HH). Additional data from stratified analyses are presented in Table 3.

Restricting HH to individuals diagnosed before CD and date of matching in controls, we identified 24 HH cases (CD: 9, and controls: 15). This corresponded to an OR of 2.64

(95%CI=1.24–5.60). Due to limited power we could only calculate ORs for certain strata. This subanalysis showed a higher OR for CD in *females* with HH (Table 3).

Patients with HH (either gender) were at increased risk of a later CD diagnosis both in the first year after HH diagnosis (OR=2.26; 95%CI=0.62–8.26), in years 1–4.99 after HH diagnosis (OR=1.99; 95%CI=0.57–6.98) and beyond 5 years after first HH diagnosis (OR=5.13; 95%CI=1.26–2.96). Excluding the four individuals with first cancer diagnosed within 1 year of first HH, the OR for CD was 2.43 (95%CI=1.61–3.66).

Excluding the three individuals (one with CD, and two controls) where HH had been diagnosed before the age of 20 years did not influence the OR (OR=2.30; 95%CI=1.52–3.49).

Post-hoc analyses

Of the 30 cases with both CD and HH, 21 were first diagnosed with CD (and then HH). Hence, 1 in every 1400 CD patients was diagnosed with later HH during an average follow-up of 11 years.

Discussion

This nationwide case-control study suggests that patients with HH are at a 2-fold increased risk of CD.

Main findings

This study included 30 cases with both CD and HH. That is more than the total reported number of CD-HH cases in the literature until this date. [13–18]

In one of our sensitivity analyses we found a higher OR for CD in females with HH. However, we urge caution when interpreting those data since they were based on very few cases. In contrast we found no interaction between HH and gender with regards to CD in our main analysis (here the OR was actually 2.44 in males and 2.14 in women), or when we restricted our analysis to individuals with at least 2 records of HH.

Earlier validation has found that some 93% of individuals with a diagnosis of haemochromatosis have HH. [20] In order to reduce potential misclassification further, we performed a separate analysis where we excluded individuals with a diagnosis of cancer 1 year before or after first HH diagnosis. This resulted in a marginally higher OR for CD. None of the HH individuals had a record of either thalassemia, or porphyria. In the current study the prevalence of HH was 41.5/100,000 controls (60/144,522), which is similar to that in our larger study on mortality in HH (HH prevalence = 40/100,000). [2]

It is important to note however that our prevalence data cannot be compared with Norwegian data presented by Asberg et al. [29] In that study, the authors screened a limited population for phenotypic HH through blood samples (individuals with high serum transferrin saturation in two tests and high serum ferritin were clinically evaluated for HH), while our study was based on data obtained through routine health care. Testing for transferrin saturation and ferritin is not routine in patients attending hospital for most disorders, and will not be undertaken in healthy individuals without healthcare contact.

Besides, although our study period included 1964–2009, the Swedish inpatient register became nationwide only in 1987. The latter is not an issue when estimating strengths of associations between diseases, but we urge caution when interpreting the absolute risks of HH in our study.

Potential explanations

More than 95% of individuals with CD are either DQ2+ or DQ8+. [30] Of note DQ2 is situated on the short arm of chromosome 6, near the *HFE* locus (e.g. mutation through C282Y homozygosity). While earlier research on C282Y prevalence in CD has been contradictory, [31] at least one large study has found a significant higher prevalence of *HFE* mutations in CD patients than in controls. [32] Shared genetic susceptibility may have contributed to the positive association seen in this study. Unfortunately we had no data on HLA in study participants.

We did not have access to dietary data, more than that an earlier patient chart validation of a random subset of CD patients in this study found indications of low adherence to a gluten-free diet in 17%. [24] CD is also associated with increased levels of transaminases, [33] and it is possible that investigation of liver disease in some cases have resulted in a HH diagnosis. That said the association is less likely to be due to surveillance bias. We did not note any particularly increased risk of CD in the first year after HH diagnosis (OR=2.26). Finally, iron overload per se seems to influence the immune system, such as increasing the levels of NF- κ B. [34] NF- κ B is also activated in the small intestine in patients with CD. [35]

Retrieving additional data on HH patients from the Swedish Patient Register, we found that alcohol-related diseases were more frequent in CD patients with HH than in controls with HH (although the difference was not statistically significant). In one of our earlier studies, we found that CD is associated with severe liver disease (HR for liver cirrhosis/fibrosis: HR=2.23; and for fatty liver: 6.06). [12] Two of the CD patients with HH in the current study developed liver cancer, and this is consistent with our earlier study showing that HH patients are at a highly increased risk of liver cancer (standardized incidence ratio=21). [3]

Limitations and merits

We used biopsy registers to ascertain CD. More than 96% of all paediatricians and gastroenterologists in Sweden perform a biopsy before CD diagnosis. Biopsy data will therefore have high sensitivity for *diagnosed* CD. Since we did not screen the Swedish population for CD we were unable to examine the association between HH and undiagnosed CD, and we cannot rule out an even stronger association between HH and *undiagnosed* CD. The positive predictive value for CD of 95% in biopsy registers with VA, [24] is actually higher than a physician-assigned diagnosis of CD in the National Patient Register. [36] When two researchers independently examined more than 1500 biopsy reports with VA or inflammation, non-CD diagnoses were rare in VA (IBD made up 0.3% of all VA and was thereby the most common non-CD diagnosis). [24] Another potential limitation is that we cannot rule out that a small proportion of individuals with true VA in our study was misclassified as Marsh I or II due to poor quality of biopsy specimen, and therefore not included in this study.

Our study did not have access to laboratory data such as levels of transferrin saturation and serum ferritin. Neither did we have data on liver enzymes, phlebotomy treatment or *HFE* mutations. This being a register-based study we were not allowed to contact patients and we could not perform either liver biopsy or imaging (such as Fibroscan) to determine liver status. We did not have any data on phenotype in HH patients. Hence, we do not know if the association seen in this study is valid for patients with atypical HH phenotype or individuals diagnosed through HH screening. Neither can we rule out that part of the excess risk for HH is due to surveillance bias, since patients with CD may have their ferritin estimated more often than general population controls.

In conclusion this case-control study based on more than 29,000 patients with CD found an increased risk of CD in patients with HH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CD	Coeliac disease
CI	Confidence Interval
HH	Hereditary haemochromatosis
HR	Hazard Ratio
VA	Villous atrophy

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Table 1

Characteristics of study participants

	Coeliac disease	Matched controls
<i>Total</i>	<i>29,096</i>	<i>144,522</i>
Age * 0–19 years (%)	11,802 (40.6)	58,852 (40.7)
Females (%)	18,005 (61.9)	89,544 (62.0)
Males (%)	11,091 (38.1)	54,978 (38.0)
Age * 0–19 years (%)	11,802 (40.6)	58,852 (40.7)
Calendar year *		
-1989	4,105 (14.1)	20,378 (14.1)
1990–99	12,059 (41.4)	59,874 (41.4)
2000–	12,932 (44.4)	64,270 (44.5)

* At time of coeliac disease diagnosis

Table 2

Hereditary hemochromatosis and risk of Coeliac disease, stratified analyses.

Subgroup	HH, N (%)		OR; 95% CI	P-value
	Coeliac disease	Controls		
<i>Sex</i> [*]				
Males	17	32	2.44; 1.41–4.22	0.001
Females	13	28	2.14; 1.16–3.94	0.015
<i>Calendar period</i> ^{*#}				
-1989	5	9	2.57; 0.91–7.25	0.075
1990–1999	13	25	2.42; 1.29–4.56	0.006
2000–2008	12	26	2.10; 1.12–3.95	0.021

HH, Hereditary hemochromatosis

^{*} Interaction tests: Sex: p=0.754; Age: p=0.039; Calendar period: p=0.702.

[#] At time of coeliac disease diagnosis

Table 3

Hemochromatosis and risk of later Coeliac disease, subanalyses.

Subgroup	2 records of HH	HH diagnosed before CD
	OR; 95% CI	OR; 95% CI
Overall	2.54; 1.57–4.11	2.64; 1.24–5.60
<i>Sex</i>		
Males	2.89; 1.60–5.24	1.58; 0.54–4.69 [*]
Females	2.03; 0.89–4.63	5.13; 1.78–14.73 ^{*#}
<i>Calendar period</i> [*]		
-1989	4.23; 0.98–18.25	NC (no control with HH)
1990–1999	2.93; 1.45–5.91	2.38; 0.47–12.05
2000–2008	1.95; 0.90–4.21	2.06; 0.78–5.47

NC, Not calculated due to lack of HH cases in either patients with CD or controls.

^{*} An interaction analysis found that the ORs were statistically significantly different between males and females (p=0.002).[#] The OR 5.13 was based on 5 cases with HH in 18,005 CD women vs. 3 HH cases in 89,544 control women.