Original Investigation

A Nationwide Study of the Association Between Celiac Disease and the Risk of Autistic Spectrum Disorders

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IMPORTANCE Most case reports suggest an association between autistic spectrum disorders (ASDs) and celiac disease (CD) or positive CD serologic test results, but larger studies are contradictory.

OBJECTIVE To examine the association between ASDs and CD according to small intestinal histopathologic findings.

DESIGN AND SETTING Nationwide case-control study in Sweden.

MAIN OUTCOMES AND MEASURES Through 28 Swedish biopsy registers, we collected data about 26 995 individuals with CD (equal to villous atrophy, Marsh stage 3), 12 304 individuals with inflammation (Marsh stages 1-2), and 3719 individuals with normal mucosa (Marsh stage 0) but positive CD serologic test results (IgA/IgG gliadin, endomysium, or tissue transglutaminase) and compared them with 213 208 age- and sex-matched controls. Conditional logistic regression estimated odds ratios (ORs) for having a prior diagnosis of an ASD according to the Swedish National Patient Register. In another analysis, we used the Cox proportional hazards regression model to estimate hazard ratios (HRs) for future ASDs in individuals undergoing small intestinal biopsy.

RESULTS A prior ASD was not associated with CD (OR, 0.93; 95% CI, 0.51-1.68) or inflammation (OR 1.03; 95% CI, 0.40-2.64) but was associated with a markedly increased risk of having a normal mucosa but a positive CD serologic test result (OR, 4.57; 95% CI, 1.58-13.22). Restricting our data to individuals without a diagnosis of an ASD at the time of biopsy, CD (HR, 1.39; 95% CI, 1.13-1.71) and inflammation (HR, 2.01; 95% CI, 1.29-3.13) were both associated with moderate excess risks of later ASDs, whereas the HR for later ASDs in individuals with normal mucosa but positive CD serologic test results was 3.09 (95% CI, 1.99-4.80).

CONCLUSIONS AND RELEVANCE Although this study found no association between CD or inflammation and earlier ASDs, there was a markedly increased risk of ASDs in individuals with normal mucosa but a positive CD serologic test result.

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Autism or autistic spectrum disorder (ASD) is a complex developmental disorder characterized by the triad of symptoms of impaired social interaction, impaired communication, and repetitive behaviors. Previously, ASD was estimated to occur in fewer than 1 per 1000 individuals,[1] but increasing disease awareness, new diagnostic criteria, and a potentially true increase in ASD incidence have led some to suggest that more than 1% of the population of US children have some kind of ASD.[2] Typically apparent before age 3 years, ASDs include infantile autism, Åsperger syndrome, and pervasive development disorders (atypical autism).[3] Many children with ASDs have feeding symptoms from infancy.[3]

Although there is a strong genetic component in ASDs[4,5] (siblings of individuals with ASDs are at a highly increased risk of having an ASD themselves),[6] no single mutation has been identified that can explain more than a small percentage of all disorders, and emerging research has linked various determinants, including an array of toxicant exposures with subsequent ASDs.[7,8] The fact that not only pregnancy-related and neonatal adverse events[9] but also intrauterine exposure to certain teratogenic drugs may increase the risk of ASDs[10] strongly suggests that ASD begins early in life. We have recently demonstrated a link between parental autoimmunity and ASDs.[11]

Celiac disease (CD) is an immune-mediated disorder that occurs in 1% to 2% of the Western population.[12] It is triggered by gluten exposure in genetically susceptible individuals.[12] Individuals with CD usually have small intestinal villous atrophy (VA) and inflammation, but in the past years it has be-

come evident that some individuals with CD or CD-related disorders have only minor, if any, mucosal changes.[12] Most individuals with CD test serologically positive not only for endomysium and tissue transglutaminase antibodies but also for the less CD-specific antigliadin antibodies.[13] Celiac disease is associated with substantial comorbidity, including neurologic and psychiatric disorders.[14]

Several case reports[15,16] suggest a positive association between ASD and CD, but more systematic research findings[17-20] have been contradictory and widely challenged, with most studies[18-20] indicating no association between the diseases. Still, the negative studies[18-20] were underpowered to demonstrate a positive relation between ASD and CD. Furthermore, although 2 studies[18,20] detected individuals with ASD and positive CD serologic test results, none of the studies was designed to examine the association between ASD and CD without VA. The objective of this study was to examine the association between ASD and CD in individuals grouped by their small intestinal histopathologic findings at biopsy: (1) VA (equal to CD), (2) inflammation without VA, or (3) normal mucosa but a positive CD serologic test result.

Methods

Autism Spectrum Disorders

Autism spectrum disorder was defined as having a relevant *International Classification of Diseases, Ninth Revision (ICD-9)* or *International Statistical Classification of Diseases, 10th Revision (ICD-10)* code (international classification of disease code in the Swedish National Patient Register; see the eAppendix in the Supplement). The Swedish National Patient Register was started in 1964, becoming nationwide in 1987. Since 2001, it has also included hospital-based outpatient care. In Sweden, physicians examine all 4-year-old children as part of the national child health surveillance system. When an ASD is suspected at this mandatory screening or earlier by parents or during infant care, the child is referred to a child psychiatrist specialist unit. The validity of the registry-based diagnosis is high. Two of the authors (A.R. and C.M.H.) recently conducted a medical record review by ascertainment of a random sample of cases (n = 88) with ASDs that appear in the Swedish National Patient Register and implemented a validation protocol developed by the Centers for Disease Control and Prevention.[21] In 83 of 88 patients (94.3%) the presence of *DSM-IV* autism was substantiated according to medical record reviews, identical to findings from Denmark.[22]

This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institutet on June 14, 2006. The board did not require individual informed consent because data were strictly register based.

CD, Inflammation, and Normal Mucosa

We searched computerized biopsy registers at Sweden's 28 pathology departments and obtained data on personal identity number,[23] date of biopsy, and morphologic findings (see eAppendix in the Supplement for a list of histopathologic codes according to the Swedish SnoMed system) in all individuals undergoing a duodenal or jejunal biopsy. Celiac disease was defined as having VA (equivalent to Marsh stage 3, see eTable 1 in the Supplement).[24] We also collected data on individuals with a lesser degree of mucosal damage, such as inflammation without VA (equivalent to Marsh stages 1-2)[24] and normal mucosa (Marsh stage 0).[24] In total, we identified 287 586 unique individuals who had undergone a biopsy (29 148 with VA, 13 446 with inflammation, and 244 992 with normal mucosa) (Figure).[25] Data about normal specimens from biopsies performed at 10 university hospitals (n = 121 952) were then sent for matching with CD serologic test results at the 8 biochemistry departments responsible for the same catchment area as the university hospitals. Thus, we were able to identify 3736 individuals with normal mucosa but positive IgA/IgG gliadin, endomysium, or tissue transglutaminase antibodies at the time of biopsy (≤180 days before biopsy until ≤30 days after biopsy).[26] A detailed description of the data collection procedure has been published elsewhere.[25,26] We then excluded individuals with data irregularities (Figure) and those undergoing a biopsy (or enrolling in the study) before January 1, 1987, because only then could a patient be diagnosed as having an ASD according to our definitions. In all, this study included 26 995 individuals with CD, 12 304 individuals with inflammation but no VA, and 3719 individuals with normal mucosa but a positive CD serologic test result. Of these 3719 individuals, 359 had positive IgA endomysium or IgA tissue transglutaminase test results, whereas 3360 had positive IgA gliadin or positive IgG antibodies against endomysium, transglutaminase, or gliadin (see eAppendix in the Supplement for detailed information).

We did not require a positive CD serologic test result for the diagnosis of CD, and data about positive CD serologic test results were only collected in a subsample of individuals with CD (n = 3388 with positive serologic test results) and inflammation (n = 141). However, a patient medical record validation found that 88% of individuals with available data about CD serologic testing had positive test results at the time of biopsy.[25] This same evaluation found that the positive predictive value of VA for CD was 95% (108 of 114).[25]
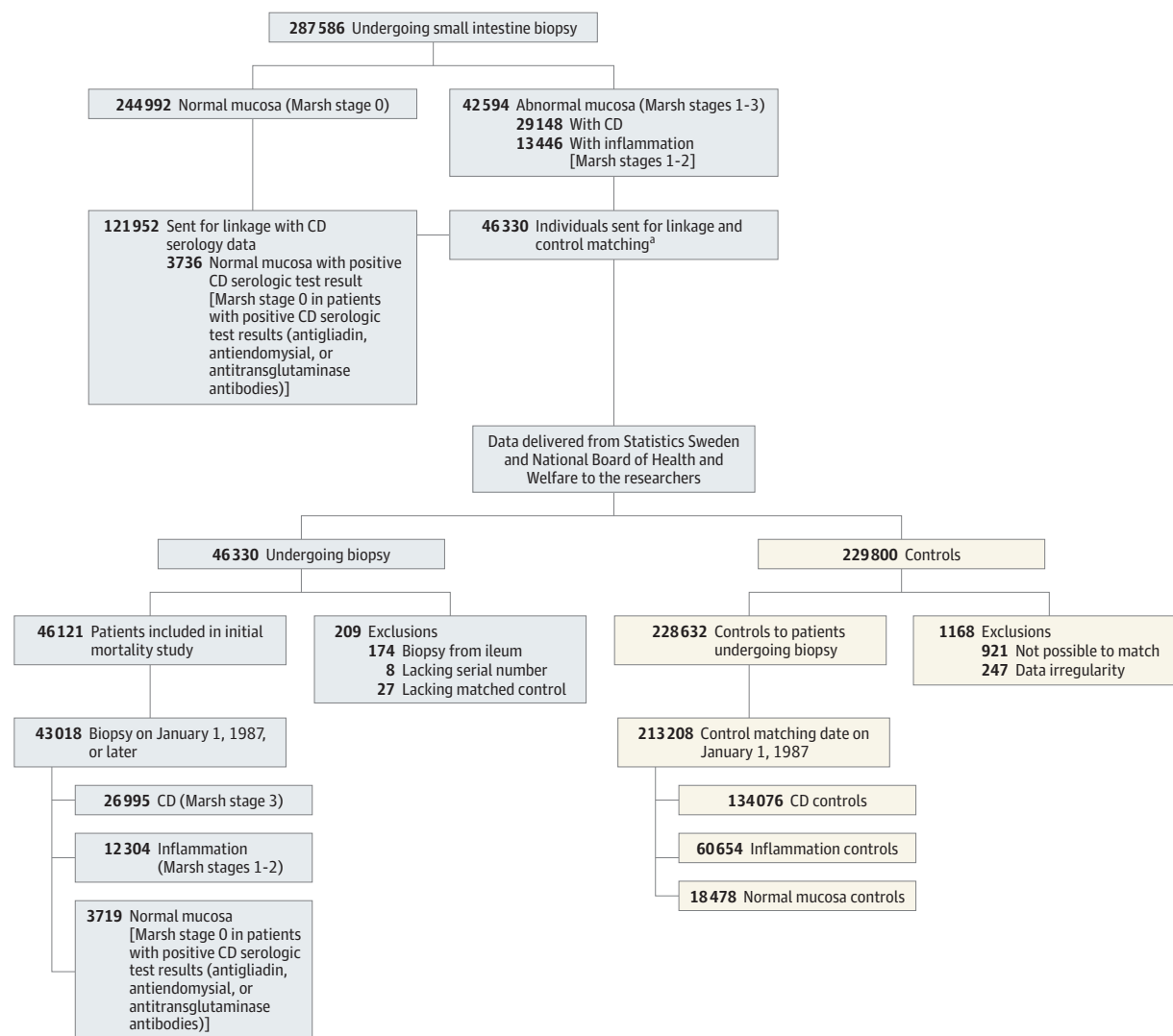
Controls

For each patient undergoing biopsy, the government agency Statistics Sweden (responsible for producing official statistics) identified up to 5 controls from the total population register matched for sex, age, county, and calendar year. Controls were only selected from among individuals without a previous record of small intestinal biopsy. Finally, for arguments given above, we only kept controls enrolling in the study in 1987 or later. In all, this study was based on 213 208 controls (CD controls, 134 076; inflammation, 60 654; and normal mucosa but a positive CD serologic test result, 18 478). We did not have data about CD serologic status in controls.

Statistical Analyses

We used 2 statistical approaches to examine the relationship between ASDs and CD.

Figure. Flowchart of Study Participants

CD indicates celiac disease.
[a] The subgroup of 3736 is part of this 46 330 individuals.

Case-Control Study

In our main analyses, we calculated odds ratios (ORs) using logistic regression conditional on age, sex, county, and calendar year (analyses performed stratum-wise). In the analyses, we examined the proportion of individuals with a prior diagnosis of an ASD among those undergoing biopsy. The calculated ORs equal the risk of future CD, inflammation, or normal mucosa with positive CD serologic test results in individuals with a diagnosis of an ASD.

In separate analyses, we restricted ASDs to individuals (1) with a diagnosis before the age of 10 years; (2) with an inpatient record of an ASD; (3) with an outpatient record of an ASD; (4) with at least 2 records of an ASD, of which at least 1 occurred before small intestinal biopsy (and corresponding date in matched controls); (5) with an ASD according to a narrower definition corresponding to "infantile autism" (*ICD-9* code 299A

and *ICD-10* code F840); and (6) when only looking at study participants born in 1987 or later since only these individuals were at risk of having a recorded diagnosis of ASD throughout their entire life (*ICD-9* began in 1987).

In individuals with CD and their controls, we also estimated the association with ASDs according to age, sex, and calendar period of CD diagnosis. We calculated the risk of having a biopsy specimen with CD according to time since first diagnosis with ASD (first year, beyond first years). To determine whether the association between ASD and CD was influenced by country of birth (Nordic vs not Nordic) or education (4 predefined categories), we added these 2 variables as covariates in one analysis. If the individual had no education, we used the highest available parental education. We also adjusted for intrauterine growth retardation in individuals with available birth data from the Swedish Medical Birth Register (individuals with

Table 1. Prior ASDs and Small Intestine Histopathologic Findings

	Odds Ratio (95% CI)						
Subgroup	Any	Diagnosed as Having ASD at <10 Years of Age	Inpatient Diagnosis[a]	Outpatient Diagnosis[b]	At Least 2 Records[c]	Narrow Definition[d]	Study Participants Born on Jan 1, 1987, or Later
CD	0.93 (0.51-1.68)	1.06 (0.48-2.31)	0.90 (0.36-2.27)	0.91 (0.46-1.80)	1.15 (0.60-2.21)	0.79 (0.32-1.98)	1.07 (0.53-2.13)
Inflammation	1.03 (0.40-2.64)	1.50 (0.46-13.64)	0.93 (0.28-3.11)	1.14 (0.34-3.87)	1.52 (0.58-4.02)	1.44 (0.42-4.98)	1.24 (0.27-5.68)
Normal mucosa but positive CD serologic test result[e]	4.57 (1.58-13.22)	5.59 (1.27-24.56)	5.00 (1.25-19.99)	2.82 (0.72-11.03)	3.14 (0.94-10.51)	4.72 (1.25-17.86)	7.05 (1.80-27.53)[f]

Abbreviations: ASD, autistic spectrum disorder; CD, celiac disease.

[a] The patient had at least one diagnosis of ASD as an inpatient. This need not be his/her first diagnosis of autism.

[b] The patient had at least one diagnosis of ASD as an outpatient. This need not be his/her first diagnosis of autism.

[c] At least one diagnosis of autism had to be recorded before biopsy.

[d] See text for definition.

[e] Includes positive test results for IgA/IgG antigliadin, endomysium, and transglutaminase antibodies 180 days or less before biopsy and 30 days or less after biopsy.

[f] Three of 785 with normal mucosa but a positive CD serologic test result vs 2 of 3925 controls had an earlier diagnosis of ASD.

CD, 11 647; controls, 56 440) because this exposure is associated with an increased risk of both ASD[9] and CD.[27]

Cohort Study

To further examine the temporal relationship between CD and ASD, we used Cox proportional hazards regression to estimate hazard ratios (HRs) for ASD in the future in individuals undergoing small intestinal biopsy. Also using the Cox proportional hazards regression model, we compared each individual with CD only with his or her matched control (that is the analysis performed within each stratum, thereby eliminating the influence of sex, age, county, and calendar year), and our HR was the result of all these stratum-specific HRs. We restricted our analyses to individuals without a previous record of ASD and those who were biopsied in 1987 or later (when *ICD-9* was introduced and ASD could be diagnosed). Furthermore, we excluded individuals who belonged to strata in which earlier exclusion meant that there were either no index cases (those with biopsy) or controls. Hence, the cohort analyses were based on 26 981 individuals with CD, 12 299 with inflammation but not VA, and 3713 with normal mucosa but a positive CD serologic test result. These 3 groups were compared with 213 055 matched controls. We used SPSS statistical software, version 20 (SPSS Inc), to analyze all the data. *P*< .05 (2-tailed) was considered statistically significant.

Results

Background Data

Approximately half the study participants underwent biopsy in 2000 or later (47.9% of individuals had been diagnosed as having CD since 2000). Most were females (eTable 2 in the Supplement). Approximately 40% of individuals had CD diagnosed in childhood. Controls were matched for age, sex, and calendar year; thus, their distribution was identical to that of the individuals undergoing biopsy (eTable 2 and eTable 3 in the Supplement).

Conditional Logistic Regression: Prior ASD

Having a prior diagnosis of an ASD was not associated with CD (OR, 0.93; 95% CI, 0.51-1.68) or inflammation (OR, 1.03; 95% CI,

0.40-2.64) but with a highly increased risk of having a normal mucosa but a positive CD serologic test result (OR, 4.57; 95% CI, 1.58-13.22) (**Table 1**). The number of individuals with ASDs is given in eTable 2 in the Supplement. Six individuals with normal mucosa but a positive CD serologic test result had an earlier diagnosis of an ASD. These individuals were positive for different antibodies (IgA gliadin, 3; IgG gliadin, 2; and IgA endomysium,: 1). Adjusting for intrauterine growth retardation (adjusted OR, 1.04; 95% CI, 0.56-1.95) and educational level or country of birth (data not shown) did not influence the risk estimate for CD.

Sensitivity analyses produced ORs similar to those listed above (Table 1), with the exception of a slightly lower OR for normal mucosa and a positive CD serologic test result in individuals with at least 2 records of ASD (OR, 3.14; 95% CI, 0.94-10.51) and a slightly higher OR in the same patient group when we restricted study participants to those born in 1987 or later (OR, 7.05; 95% CI, 1.80-27.53) (Table 1).

No individual who was diagnosed as having CD from age 40 years or older had a record of earlier ASD. With this exception and our finding of a nonsignificantly lower OR for CD in females with ASD, no differences in ORs were found based on age, sex, or calendar year (eTable 4 in the Supplement).

In a post hoc analysis, we estimated the OR for earlier ASD in patients with VA (here classified as CD) who also had positive CD serologic test results. We found no association between serologically positive VA and earlier ASD (OR, 1.47; 95% CI, 0.52-4.15). None of the 141 individuals with inflammation and positive CD serologic test results had an earlier diagnosis of ASD; hence, no risk estimate could be calculated for that association.

In a second post hoc analysis we calculated the OR for earlier ASD in individuals who either had VA (here classified as CD) or positive IgA tissue transglutaminase–endomysium test results at the time of biopsy. This combined group was not associated with earlier ASD (OR, 1.21; 95% CI, 0.74-1.97).

Cohort Study: Future ASDs

Individuals with CD and inflammation had a 1.5- to 2-fold increased risk of having a later diagnosis of ASD (**Table 2**),

Table 2. Small Intestine Biopsy and Risk of Later ASDs (Overall and According to Time Since Biopsy)

Subgroup	Observed vs Expected ASDs[a]	Hazard Ratio (95% CI)		
		Overall[a]	First Year	Beyond First Year
CD	113 vs 81	1.39 (1.13-1.71)	1.44 (0.48-4.28)	1.39 (1.12-1.71)
Inflammation	25 vs 12	2.01 (1.29-3.13)	3.20 (0.84-12.18)	1.91 (1.19-3.06)
Normal mucosa but positive CD serologic test result	26 vs 8	3.09 (1.99-4.80)	7.05 (1.31-37.87)	2.95 (1.87-4.65)

Abbreviations: ASD, autism spectrum disorder; CD, celiac disease.

[a] Hazard ratios estimated through Cox proportional hazards regression model.

whereas the highest HRs for ASD were seen in individuals with normal mucosa but a positive CD serologic test result (Table 2).

Discussion

This study found no association between CD and ASD before diagnosis of CD and only a weak relation thereafter. In contrast, we found a strong association between having normal mucosa but a positive CD serologic test result and ASD both before and after biopsy.

Comparison With Earlier Literature

To our knowledge, the first large case series with autistic individuals undergoing investigation for CD was reported in 1973.[28] In that study, 18 children with ASD were examined, of which 7 had a history of gastrointestinal symptoms.[28] Three children underwent small intestinal biopsy, but none of these children had VA.[28] In a second study, 8 autistic children with steatorrhea and alleged behavioral improvements on gluten restriction underwent biopsy, but the researchers did not identify any patient with CD.[29]

Two larger studies have investigated the association between CD and ASDs. In the first study, Pavone et al[18] evaluated 120 individuals with CD from Catania, Italy. Parents were asked to answer 16 *DSM-III-R* questions relating to their child's behavior.[18] The researchers concluded that the prevalence of ASDs was not elevated in those with CD. The same researchers tested 11 of 22 children with infantile autism in the same hospital for antigliadin and endomysium antibodies. Although 2 children were serologically positive, both had normal small intestinal mucosa. In a second study, Batista et al[20] examined 211 individuals with biopsy-proven CD for ASDs. Two of these 211 children had an ASD, resulting in a prevalence of ASDs of 0.95% (95% CI, 0.11%-3.82%). Of 147 individuals with a diagnosed ASD, 6 tested positive for antigliadin or transglutaminase antibodies, but all tested negative for the more CD-specific endomysium antibodies. In contrast, Barcia et al[17] reported that 5 of 150 individuals with ASD had both serologic and histopathologic findings of CD (*P* = .01).

Our data are consistent with earlier research in that we found no convincing evidence that CD is associated with ASD[18-20] except for a small excess risk noted after CD diagnosis. A possible explanation for the excess risk of ASD after CD diagnosis is surveillance bias. We found a strong association (OR >4) between positive serologic test results (with normal mucosa) and a later ASD. These individuals may have nonceliac gluten sensitivity[12] for which a gluten-free diet can be

beneficial.[30] Markers of gluten sensitivity have been linked to other neurologic[31] or psychiatric[32] disorders, such as schizophrenia.[33,34] Many antibody-positive patients are negative for HLA DQ2/8,[35] suggesting that the response to gliadin in psychiatric and neurologic disease[33] may be typical of nonceliac gluten sensitivity rather than CD. Sensitivity-related illnesses are increasing,[36] and effects from gluten may be mediated by a number of mechanisms.

Part of the positive association between positive serologic test results and ASD could also be due to an increased likelihood of serologic testing for CD in children because with ASDs increased serologic testing, more individuals with true CD should also have been diagnosed as having CD. The association between serologically positive CD and an earlier ASD was neutral, although this analysis was limited in power.

The role of gluten and a gluten-free diet in individuals with an ASD is under debate. One study reported that a gluten-free diet in 15 children with ASDs had no effect; however, after the trial, parents of 9 of the children wanted to continue with the diet because they thought their autistic children had improved.[37,38] A Cochrane review found only a small effect of gluten- and casein-free diets on ASD,[39] whereas a later randomized, single-blind study reported that dietary intervention with a gluten- and casein-free diet had a beneficial effect in some children with ASD.[40]

This study has some limitations, including the fact that we did not have data about symptoms in individuals with ASDs. If these individuals have more gastrointestinal tract symptoms because of disorders other than CD, that could result in surveillance bias. Awareness of the potential effect of dietary interventions in ASD may also have led to more testing for CD. However, as stated previously, this should have resulted in a higher OR for all 3 pathology groups and not just for having a positive serologic test result with normal mucosa.

Concurrently, impaired communication in autistic individuals may lead to difficulties in communicating gastrointestinal tract symptoms but could also make physicians hesitant to perform a biopsy before a CD diagnosis in individuals with ASDs. A major strength of our study is our use of several patient groups in which the high risk for positive serologic test results in those with normal mucosa indicates that the lack of association with CD is unlikely to be due to physicians refusing to perform small intestinal biopsies.

We used nationwide registers to ascertain ASDs. Although the prevalence of ASDs in our study is lower than in smaller data sets in which individuals are screened for ASDs, our prevalence of ASDs (either before or after study enrollment) in our reference population (controls) was nevertheless 2.8 of 1000 (606 divided

by 213 208), which is consistent with American register-based data on ASD prevalence (0.6-4.6 of 1000).[41]

Another shortcoming is that we lacked data on gluten-free diet. A gluten-free diet usually results in negative CD serologic test results and a lower probability of undergoing small intestinal biopsy. Hence, if a large number of autistic individuals were already receiving a gluten-free diet already when being investigated for CD, that could underestimate the association with CD. However, the strong positive association between ASD and positive serologic test results makes such an explanation unlikely. Antibody levels will usually decrease before the mucosa heals in persons on a gluten-free diet.[42]

At the same time, we cannot rule out that the moderate excess risk for ASDs seen in individuals with diagnosed CD (HR, 1.49) may be restricted to individuals with CD and poor adherence, although we believe surveillance bias is a more likely explanation. In a validation of a random subset of individuals with CD, 17% had evidence of poor dietary adherence.[25]

Another limitation is that we did not have access to data about family history and could not adjust for parental autoimmunity. We have previously found that parental autoimmunity is a risk factor for ASDs. However, different patterns of parental autoimmunity are unlikely to explain the highly increased risk of positive serologic test results and normal mucosa, as well as a largely neutral risk for CD. Finally, we did not have data about serologic testing in all individuals with CD and inflammation.

Apart from the different comparison groups, the main strength of our study is its statistical power. This study included more individuals with both CD and ASDs than all previous studies (12 before CD diagnosis and 127 after, for a total of 139). The heightened power allowed us to calculate narrow CIs and to test the association with positive CD serologic test results in various sensitivity analyses. We also had data about several potential confounders, including country of birth, educational level, and, in a subset of individuals, intrauterine growth retardation. Adjustment for these variables had little effect on the risk estimates.

Other advantages include the high sensitivity and specificity of VA as proof of diagnosed CD. More than 95% of Swedish gastroenterologists and pediatricians perform a biopsy before CD diagnosis,[25] and Swedish pathologists classify 90% of all slides with VA correctly.[25]

Another strength is our long follow-up. This study was based on data about ASDs recorded in the Swedish National Patient Register for a period of more than 20 years.

Potential Mechanisms

Given that ASD is linked to early brain development, the reason for the positive association with positive CD serologic test results is not self-evident. Because most individuals with positive CD serologic test results are likely to have the same HLA as CD patients with VA (in which little association with ASD was seen), shared genetics is unlikely to explain our findings. Instead, we speculate that the positive association between ASDs and serologic test results positive for CD observed in this study may be due to increased mucosal permeability noted in some individuals with early CD[43,44] or individuals with elevated levels of more nonspecific antigliadin antibodies.[45]

A recent Italian study[46] found a significantly higher intestinal permeability in patients with ASDs and their first-degree relatives compared with healthy controls. However, the di Magistris et al[46] study also found that patients with ASDs who avoided gluten and casein had lower intestinal permeability compared with those consuming gluten and casein. A high intestinal permeability may allow an increased absorption of short peptides that trigger the immune system, leading to ASDs. We cannot, however, explain the different pattern in individuals with CD compared with those with normal mucosa but a positive CD serologic test result. Unfortunately, we had no information on antibodies to other food antigens that could perhaps shed light on whether this is a broad sensitization. In conclusion, we found weak evidence of a link between ASDs and CD but a strong association between ASDs and positive CD serologic test results in individuals with normal mucosa.

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