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ORIGINAL PAPER

Sarcoidosis in Patients with Celiac Disease

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Abstract *Purpose* Several case reports and European studies have suggested an association between sarcoidosis and celiac disease; however, they have been inconsistent. We therefore analyzed a large cohort of celiac-disease patients to assess this association. *Methods* An anonymized database of patients with celiac disease was reviewed to determine the number of patients with sarcoidosis. Age- and gender-adjusted standardized morbidity ratios with corresponding 95% confidence intervals (CI) were calculated by comparing results to US-population-derived prevalence data. *Results* Ten patients were found to have a comorbid diagnosis of sarcoidosis, representing an age- and gender-adjusted standardized morbidity ratio of 36.8 (95% CI 26.7–50.9). *Conclusions* In this cohort of patients with celiac disease, there was a significantly increased risk of sarcoidosis when compared with the American white population. This further strengthens prior associations that have been made suggesting a shared mechanism behind the etiologies of celiac disease and sarcoidosis.

Keywords Celiac disease · Sarcoidosis · Prevalence · Etiology · Autoimmunity

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Introduction

Celiac disease is an autoimmune inflammatory disease of the small intestine induced by the ingestion of gluten, the storage protein of wheat, barley, and rye [1]. The disease was previously considered rare; however, serologic screening studies have shown that the disease has widespread occurrence, with a worldwide prevalence approaching 1% [2]. The clinical prevalence of the disease, however, is lower, as the diagnosis can be difficult in those patients who do not present with the classic symptom of diarrhea. Those with silent celiac disease may also present with occult manifestations of the disease, such as anemia, osteoporosis, ataxia, peripheral neuropathy, infertility, or dermatitis herpetiformis. Additionally, patients with celiac disease have an increased risk of developing malignancy and autoimmune disease, and thus present with other comorbid conditions [1]. Clinically, the diagnosis of celiac disease is made when patients in whom a small intestinal biopsy shows characteristic changes, such as intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy of different stages [3], show improvement in symptoms on a gluten-free diet.

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology characterized by the formation of non-caseating granulomas. It most commonly involves the lungs but can also affect the skin, eyes, gut, lymph nodes, and nervous system. Multiple causes of sarcoidosis have been proposed, with evidence to support genetic inheritance, infectious transmission, and shared exposures to certain environmental agents [4]. Its epidemiology is difficult to demonstrate, as many cases are asymptomatic, which is the reason that data from autopsy studies show a much higher prevalence [5]. Diagnostic criteria include clinical symptoms, radiological findings such as bilateral

hilar lymphadenopathy and/or diffuse pulmonary infiltrates or pulmonary fibrosis, histological evidence of noncaseating granulomas, and the exclusion of other granulomatous diseases [6, 7].

The association between celiac disease and sarcoidosis has been demonstrated in the literature through several case reports and studies examining patients with sarcoidosis. Certain class II haplotypes [8] and gastric autoimmunity [9, 10] have been implicated as linking factors. However, there has been no recent literature examining the converse relationship; thus, this study was done to determine the prevalence of sarcoidosis in patients with known celiac disease.

Methods

An anonymized database of patients with celiac disease seen at the Celiac Disease Center at the Columbia University Medical Center between 1981 and 2005 was reviewed. Clinical data had been entered into the database retrospectively for those seen prior to 1990 and prospectively since then. The database consisted of 978 Caucasian patients, ages ranging from 1 to 81 years at the time of diagnosis of celiac disease. Among these patients, 866 were identified as having small-intestinal biopsy-proven diagnoses of celiac disease and clinical or histological response to a gluten-free diet. The database of biopsy-proven celiac disease patients was then searched to identify patients with a comorbid diagnosis of sarcoidosis.

The expected incidence of sarcoidosis in the general US population was calculated for each gender- and 10-year age-specific stratum by specific incidence rates from data collected by Henke et al. in the Rochester population-based study [11]. Patient years at risk were calculated from the date sarcoidosis diagnosis to the date of celiac disease diagnosis or from the date of celiac disease diagnosis to the date of sarcoidosis diagnosis, whichever diagnosis was made first. Expected values for the number of sarcoidosis patients were weighted by the age-adjusted person years contributed by the patients in the data set [12]. Standardized morbidity ratios (SMR; ratio of observed to expected) and the corresponding 95% confidence intervals (CI) were calculated on the assumption that the observed incidence of sarcoidosis had a Poisson distribution.

Results

Of the 866 biopsy-proven celiac-disease patients in the database, 566 were women and 300 were men; all were Caucasian. Most were residents of the northeastern USA, and more specifically, the New York/New Jersey area. Ten patients (six females, four males) were found to have biopsy-proven sarcoidosis (Table 1). The age- and gender-adjusted standardized morbidity ratio of sarcoidosis in patients with celiac disease was 36.8 (95% CI of 26.7–50.9). In females, the SMR was 27.5 (95% CI of 18.9–40.0); in males, the SMR was 67.7 (95% CI of 53.3–85.9). These ratios were calculated using population-based data from Rochester, MN, USA, which revealed an age- and gender-adjusted incidence rate of 6.1 per 100,000 person years in the US white population [11]. Although that paper is from 1985, the populations being compared were more similar than the majority of alternative populations that have been studied [13–15].

Sarcoidosis was the initial diagnosis in seven patients, with the diagnosis being made a mean of 15.9 years earlier than for celiac disease (Tables 2 and 3). Nine patients had lung involvement by sarcoidosis, either alone or together with joint, skin, eye, bowel, and/or nasopharyngeal involvement (Table 2). Initial patient presentation varied depending on which organs were involved. Of note, patient 8 was the most severely ill. She was initially diagnosed with sarcoidosis of the liver and primary biliary cirrhosis at the age of 50, underwent liver transplantation at the age of 65, and was found to have lung involvement of sarcoidosis on transbronchial biopsy during her hospitalization for transplantation. She then presented with abdominal pain at the age of 75 and had a repeat endoscopic biopsy during which she was noted to have small intestinal granulomas in addition to villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, consistent with both sarcoidosis and celiac disease. With the exception of this patient, all

Table 1 Standardized morbidity ratios

Gender	Number of celiac-disease patients	Observed number of sarcoid cases	Expected number of sarcoid cases[a]	SMR	95% CI
Female	566	6	0.218117	27.5	18.9–40.0
Male	300	4	0.059116	67.7	53.3–85.9
Total	866	10	0.271570	36.8	26.7–50.9

SMR standardized morbidity ratio (observed/expected number of cases of sarcoidosis based on population data); *95% CI* 95% confidence interval

[a] Calculated based on incidence rates from data collected by Henke et al. in a population-based study from Rochester, MN, USA [11]

Table 2 Characteristics of sarcoidosis

Patient	Gender	Age at diagnosis (years)	Organs of involvement proven by biopsy	Presenting symptoms
1	F	57	Lung	Lower extremity edema, found to have hilar lymphadenopathy on chest X-ray
2	F	25	Lung, joints	Arthritis
3	F	27	Lung	Dyspnea
4	M	38	Lung, skin	Prolonged respiratory illness, found to have hilar lymphadenopathy on chest X-ray
5	F	27	Lung, nasopharynx, colon	Epistaxis
6	F	40	Lung, eyes	Eye complaints (nodule on sclera)
7	M	61	Lung	Dyspnea, cough
8	F	50	Lung, liver, small bowel	Dyspnea
9	M	35	Lung, joints	Fever and arthritis
10	M	33	Skin, joints	Erythema nodosum

other patients had duodenal biopsies that were diagnostic of celiac disease only (intraepithelial lymphocytosis, crypt hyperplasia, or various degrees of villous atrophy) and not consistent with intestinal sarcoidosis (intestinal granulomas).

Celiac disease diagnosis was made for a variety of presenting symptoms (Table 3). Three patients presented with the classic symptom of diarrhea, another three patients had abdominal pain without diarrhea, two were detected upon screening when family members were diagnosed, and the remainder presented with anemia and osteoporosis. Duodenal biopsy demonstrated total villous atrophy in five patients, partial villous atrophy in four, and intraepithelial lymphocytosis in one.

Discussion

Prior studies examining the relationship between celiac disease and sarcoidosis have been inconsistent. In 2004, Rutherford et al., in a study based out of western Ireland, showed an increased prevalence of biopsy-proven celiac disease in patients with sarcoidosis (4% prevalence compared with 0.33% in the general population, a 12-fold increase) [9]. In contrast, a Swedish study by Papadopoulos et al. in 1999 found an increased frequency of gliadin antibodies but no actual increase in the diagnosis of celiac disease in patients with sarcoidosis [8]. Similarly, in 1988, McCormick et al. discovered elevated levels of gliadin antibodies in Irish patients with sarcoidosis but were not able to diagnose celiac disease by biopsy in a significant number of patients [10]. Despite these studies, there have been several case reports of patients with both diagnoses [16–18].

The results of our study demonstrate a clear association between celiac disease and sarcoidosis. The major limitation of this study is that the center in which the patients were seen is a large, university-associated referral site. This may have resulted in a bias of sicker patients, which may have served to exaggerate the observed association.

Estimates of the incidence and prevalence of sarcoidosis vary widely, because up to 90% of cases may be asymptomatic and thus difficult to detect and diagnose [19]. Even when patients do present with respiratory symptoms,

Table 3 Characteristics of celiac disease

Patient	Gender	Age at diagnosis (years)	Biopsy[a]	Presenting symptom
1	F	56	PVA	Diarrhea
2	F	42	PVA	Diarrhea
3	F	44	IEL	Abdominal pain
4	M	56	PVA	Familial screening after mother and son diagnosed
5	F	31	TVA	Familial screening after daughter diagnosed
6	F	40	TVA	Osteoporosis
7	M	60	PVA	Abdominal pain
8	F	75	TVA	Abdominal pain
9	M	47	TVA	Iron-deficiency anemia
10	M	51	TVA	Diarrhea

TVA total villous atrophy, *PVA* partial villous atrophy, *IEL* intraepithelial lymphocytosis

[a] Pathologic finding on duodenal biopsy (highest degree of involvement shown)

clinicians may attribute the symptoms to other more common alternative diagnoses, such as asthma. This difficulty in diagnosis may contribute to the observed lower prevalence of sarcoidosis in population-based data when compared with autopsy data [20]. In contrast, patients who are already being followed in the health care system for chronic medical problems such as celiac disease or sarcoidosis may be diagnosed with a second occult disease with increased frequency. This may contribute to the higher prevalence found in this study. On the other hand, celiac disease is considered to be markedly underdiagnosed in the USA, which serves to reduce the association, further enhancing the significance of our findings.

Despite this bias, there is a clear association between the two diseases beyond increased detection. There is evidence suggesting that both sarcoidosis and celiac disease may be the result of defective antigen processing. Genetically, sarcoidosis is a complex disease with varying gene polymorphisms determining susceptibility and phenotype. In particular, the class II haplotype, HLA-DR3/HLA-DQ2, has been shown to be increased in several cohorts with sarcoidosis, and has also been linked to other autoimmune disorders [21]. Interestingly, susceptibility to celiac disease is linked to HLA-DQ2, which in northern Europeans is linked to HLA-DR3 [22]. Defective handling of a common antigen is a plausible explanation for the increased prevalence of sarcoidosis in celiac disease patients, but it is also possible that the effects of one disease enhances the expression of HLA class II molecules, thus increasing the susceptibility to the second disease.

Another shared mechanism to consider is autoimmunity. Celiac disease is considered to be a unique autoimmune disease because the environmental precipitant is known [1]. It has been well documented that celiac disease occurs in association with many other autoimmune disorders [23], such as type I diabetes [24], Sjögren's syndrome [25], thyroid disease [26], primary biliary cirrhosis [27], and Addison's disease [28]. There have also been studies showing that patients with pulmonary sarcoidosis appear to have a heightened cellular immune response, mediated by helper T lymphocyte activity and a heightened humoral response with reactivity toward multiple antigens, including self-antigens [29]. Sarcoidosis, though not proven to be autoimmune in nature, has been associated with autoimmune thyroid disease [30] and autoimmune polyglandular syndromes [31–33], presumably by this mechanism. The association demonstrated between sarcoidosis and celiac disease in our study further advocates for autoimmunity as an etiologic factor of sarcoidosis.

It is important to note the association between celiac disease and sarcoidosis for clinical reasons as well. There are well-known complications of the continued exposure to gluten in celiac-disease patients, such as osteoporosis, infertility, and malignancy [34]. Additionally, there is data to suggest that the prevalence of comorbid autoimmune diseases may be related to the duration of gluten exposure [35]. Furthermore, diabetes- and thyroid-related serum antibodies can disappear when children with celiac disease maintain a gluten-free diet, highlighting the etiological link between celiac disease and autoimmune diseases [36]. It is unclear, among our patients, whether the presence of celiac disease or the treatment of it may have influenced the course of sarcoidosis. Although most of the patients in this study were diagnosed with sarcoidosis before celiac disease, being aware of the association between these diseases is important for the earlier diagnosis of celiac disease in patients with known sarcoidosis. The earlier initiation of a gluten-free diet could help prevent long-term sequelae of the disease.

In this cohort of biopsy-proven celiac-disease patients, there was a significantly increased prevalence of sarcoidosis compared with the general US population. The mechanisms behind this association have yet to be elucidated, but several have been proposed, lending evidence toward the etiology of sarcoidosis. The impact of sarcoidosis in celiac-disease patients on the course and interaction of both illnesses needs to be assessed in future studies.

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