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Uveitis as a Manifestation of Celiac Disease: A Population-Based Study

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Abstract

Introduction: The prevalence of celiac disease (CD) in the United States population has been estimated to be 0.71%, or 1 in 141, with the prevalence in first- and second-degree relatives of those affected being 4.55% and 2.59% respectively. Due to the multitude of ways in which this disease may initially present, it is important to screen for CD to avoid the potential consequences of inadequately managed disease. Many ophthalmic conditions have also been implicated as extraintestinal manifestations of CD, including uveitis. Despite several studies and case reports suggesting a positive correlation between CD and uveitis, there has yet to be a nationwide study in the United States quantifying this relationship. Therefore, the aim of this study is to conduct a large-scale multi-center population-based study to assess whether there is a statistically significant increased risk of uveitis in individuals with celiac disease.

Methods: A validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States consisting of data accumulated from 1999 to September 2022 was utilized to construct this study. We excluded patients with a history of autoimmune diseases, cataract surgery, or any type of eye infection. We included a subgroup of patients with a diagnosis of "uveitis" for further analysis. The risk of developing uveitis was calculated using a univariate logistic regression. A multivariate analysis was also done to account for confounding variables including African American ethnicity, male gender, sexually transmitted diseases, and celiac disease.

Results: 70,632,440 patients were screened and a cohort of 46,895,750 individuals was selected for the final analysis after accounting for inclusion and exclusion criteria were met. The incidence of uveitis in patients with celiac disease in the past 3 years was 280 per 100,000 people. The prevalence of uveitis in the US population from 1999 to September 2022 was 150 per 100,000 people (0.15%). In order to adjust for confounding variables, a multivariate regression analysis was performed and showed an increased risk of being African-American (OR: 3.20%; 95% CI: 3.14-3.26) and male (OR: 1.13%; 95% CI: 1.12-1.16); and having a diagnosis of celiac disease (OR: 3.80%; 95% CI: 3.35-4.28) and sexually transmitted diseases (OR: 4.12%; 95% CI: 3.96-4.29) in patients with uveitis.

Discussion: Recent population-based studies demonstrated that the prevalence of CD in the United States is much greater than previously thought, such that a trend of underdiagnoses is suspected to have occurred for several years. Many newly diagnosed uveitis cases, 48%, have been classified as idiopathic uveitis even after a complete workup was done. Several studies have been published in which a correlation between uveitis and CD is reported. The findings of this study further emphasize the importance of a thorough workup to evaluate for an underlying inflammatory process prior to diagnosing uveitis as idiopathic.

Conclusion: In conclusion, we established that patients with celiac disease are at increased risk of developing uveitis after excluding and controlling for any confounding variables. In further studies, it could be interesting to investigate the impact of gluten-free diet in patients with celiac disease on the risk of developing uveitis.

Keywords: Autoimmune disease, Celiac disease, Uveitis

Introduction

Celiac disease (CD) is an enteropathy primarily affecting the small intestine of those genetically predisposed to intestinal inflammation precipitated by the ingestion of gluten. The prevalence of CD in the United States population has been estimated to be 0.71%, or 1 in 141, with the prevalence in first- and second-degree relatives of those affected being 4.55% and 2.59% respectively [1,2]. Individuals with genetic or autoimmune disorders such as type I diabetes mellitus and trisomy 21 demonstrate a predisposition to CD, with a higher prevalence disease burden than the general population [2].

Due to the multitude of ways in which this disease may initially present, it is important to screen for CD to avoid the potential consequences of inadequately managed disease. Manifestations of CD are broadly categorized as being either gastrointestinal (e.g., abdominal pain, diarrhea) or extraintestinal (e.g., iron deficiency anemia, osteopenia). Many ophthalmic conditions have also been implicated as extraintestinal manifestations of CD, including uveitis. Uveitis refers to inflammation in the uveal layer of the eye. This disease process can be further classified by etiology: idiopathic, infectious, or non-infectious. The most common etiology is idiopathic.

Uveitis is one of the leading causes of legal blindness, with 30,000 cases reported in the United States annually [4]. Three epidemiological studies conducted in the United States showed an incidence of 17.4-52.4/100,000 person-years and an annual prevalence of 57.5-115.3/100,000 persons [4,5,6]. Despite several studies and case reports suggesting a positive correlation between CD and uveitis, there has yet to be a nationwide study in the United States quantifying this relationship. Therefore, the aim of this study is to conduct a large-scale multi-center population-based study to assess whether there is a statistically significant increased risk of uveitis in individuals with celiac disease.

Methods

Database

Explorys Inc., Cleveland, OH, USA is a validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States consisting of data accumulated from 1999 to September 2022. It was developed and has been prospectively maintained by IBM Corporation, Watson Health [7]. It includes electronic health records (EHR) from greater than 60 million unique patients and provides a broad regional distribution of the United States representing approximately 15% of the population. Diagnoses, findings, and procedures are arranged into the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) hierarchy [8], while prescription drug orders are mapped into SNOMED and RxNorm [9]. The "Systematized Nomenclature Of Medicine – Clinical Terms" (SNOMED- CT) hierarchy is used to arrange diagnoses, findings, and procedures [7], while SNOMED and RxNorm are used to code for drug prescriptions [8]. Institutional Review Board (IRB) was not required as source data are de-identified. To protect patient confidentiality, the database rounds population counts to the nearest 10 and treats all counts between zero and 10 as equivalent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Access to the database is granted to participating healthcare systems.

Patient selection

A cohort of patients ranging from age 18 to 65 years old were included in our study between 1999 and 2022. We excluded patients with a history of autoimmune diseases including systemic lupus erythematosus, sarcoidosis, Reiter's disease, psoriasis, Behçet's disease, ankylosing spondylitis, inflammatory bowel disease, and rheumatoid arthritis. Patients with a history of cataract surgery or any type of eye infection were excluded as well. We included a subgroup of patients with a diagnosis of "uveitis" for further analysis. The control

group was identified as patients who did not have a diagnosis of uveitis.

Statistical analysis

Patients with a diagnosis of uveitis were compared to those who the control group. The overall period prevalence was calculated by dividing the total number of individuals with uveitis by the total number of individuals in our cohort. The prevalence of the most common manifestations of celiac disease was calculated by dividing the total number of individuals with the specific manifestation by the total number of individuals with celiac disease in the database. We divided the number of new cases of uveitis by the population of patients with celiac disease to obtain the incidence of the disease in the past 3 years. The prevalence of uveitis in the US population was also calculated by dividing the number of cases of uveitis by the total US population from 1999 to date. The risk of developing uveitis was calculated using a univariate logistic regression. A multivariate analysis was also done to account for confounding variables including African American ethnicity, male gender, sexually transmitted diseases, and celiac disease. A two-sided P value <0.05 was considered statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008). A graphic representation of the prevalence rate was performed using Microsoft Excel version 15.29.1.

Results

Descriptive epidemiology

70,632,440 patients were screened and a cohort of 46,895,750 individuals was selected for the final analysis after accounting for inclusion and exclusion criteria were met. The baseline characteristics of the patients are represented in Table 1. The prevalence rate of African American race (30.39%), type 2 diabetes mellitus (14.39%), benign hypertension (8.28%), obesity (19.46%), hypothyroidism (7.45%), celiac disease (0.50%), sexually transmitted diseases (5.47%), and smoking (5.75%) were higher in patients with a diagnosis of uveitis compared to control. The incidence of uveitis in patients with celiac disease in the past 3 years was 280 per 100,000 people. The prevalence of uveitis in the US population from 1999 to September 2022 was 150 per 100,000 people (0.15%).

The prevalence rate of the most common manifestations of celiac disease is represented in Figure 1 and is as follows: abdominal pain (49.74%), osteopenia (48.32%), depressive disorder (37.01%), diarrhea (30.79%), nausea (30.01%), vomiting (20.82%), iron deficiency anemia (12.87%), and weight loss (10.97%).

Risk and predictors of uveitis using a univariate regression analysis

Patients diagnosed with uveitis had a higher risk of being African American (OR: 3.20%; 95% CI: 3.14-3.26) and male (OR: 1.32; 95% CI: 1.12-1.16). Patients with uveitis were also more likely to have comorbid celiac disease (OR: 3.80; 95% CI: 3.35-4.28) and sexually transmitted diseases (OR: 4.12%; 95% CI: 3.96-4.29) as illustrated in Table 2.

Risk and predictors of uveitis using a multivariate regression analysis

In order to account for confounding variables, multivariate logistic regression was performed and showed an increased risk of being African-American (OR: 3.20%; 95% CI: 3.14-3.26) and male (OR: 1.13%; 95% CI: 1.12-1.16); and having a diagnosis of celiac disease (OR: 3.80%; 95% CI: 3.35-4.28) and sexually transmitted diseases (OR: 4.12%; 95% CI: 3.96-4.29) in patients with uveitis (Table 3).

Discussion

The way in which Celiac disease may initially present is varied, ranging from diarrhea and abdominal pain to depression and iron deficiency anemia. Recent population-based studies demonstrated that the prevalence of CD in the United States is much greater than previously thought, such

		Uveitis (%)	No Uveitis (%)
	Total	n= 50,600	n= 46,845,150
Gender	Male	24,020 (48.00)	21,082,250 (45.00)
	Female	26,310 (52.00)	25,455,980 (55.00)
Race	Caucasian	26,330 (52.03)	23,853,440 (50.92)
	African-American	15,380 (30.39)	5,255,800 (11.22)
	Asian	860 (1.69)	786,840 (1.67)
Comorbidities	Type 2 Diabetes Mellitus	7,280 (14.39)	2,338,620 (4.99)
	Benign Hypertension	4,190 (8.28)	1,029,580 (2.19)
	Hyperlipidemia	12,270 (24.25)	4,275,500 (9.13)
	Obesity	9,850 (19.46)	3,247,990 (6.93)
	Hypothyroidism	3,770 (7.45)	1,556,940 (3.32)
	Celiac disease	250 (0.50)	73,690 (0.15)
	Sexually transmitted diseases	2,770 (5.47)	442,290 (0.94)
Substance abuse	Alcohol	2,910 (5.75)	2,637,950 (5.63)
	Smoking	2,910 (5.75)	783,400 (1.67)

Table 1: Baseline characteristics of patients with uveitis and control

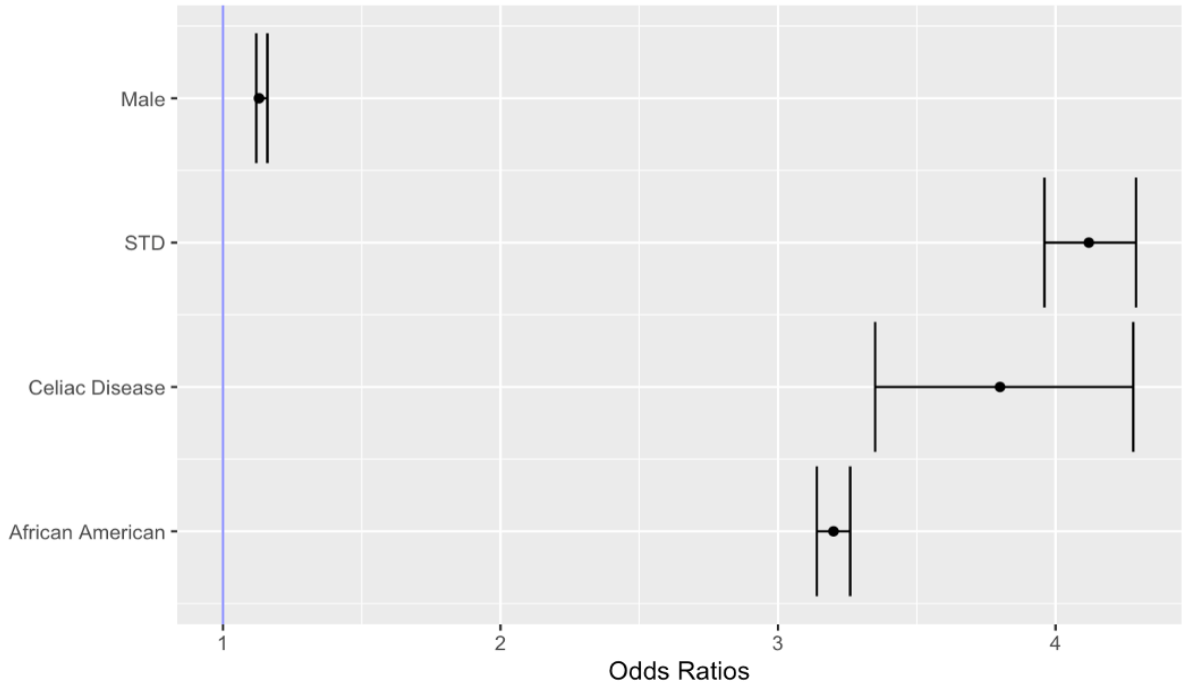

Figure 1: Prevalence rate of Celiac disease manifestations

	Uveitis	
	OR (95% CI)	P-value
African-American	3.45 (3.38-3.52)	<0.001
Celiac Disease	3.27 (2.89-3.69)	<0.001
STD	6.08 (5.85 -6.32)	<0.001
Male	1.04 (1.08-1.12)	<0.001

Table 2: Risk of developing uveitis using univariate regression analysis model. Abbreviations: CI, confidence interval; OR, odd ratio; STD, sexually transmitted diseases

	Uveitis	
	OR (95% CI)	P-value
African-American	3.20 (3.14-3.26)	<0.001
Celiac Disease	3.80 (3.35-4.28)	<0.001
STD	4.12 (3.96-4.29)	<0.001
Male	1.13 (1.12-1.16)	<0.001

Table 3: Risk of developing uveitis using multivariate regression analysis model
Abbreviations: CI, confidence interval; OR, odd ratio; STD, sexually transmitted diseases

that a trend of underdiagnoses is suspected to have occurred for several years [1,2,3]. Many newly diagnosed uveitis cases, 48%, have been classified as idiopathic uveitis even after a complete workup was done [4].

Several studies have been published in which a correlation between uveitis and CD is reported. One such nationwide study conducted in Sweden reported an absolute risk of 50-100,000 person-years for uveitis in individuals with CD [10]. Additionally, available case reports discuss the resolution of recurrent uveitis following the implementation of a gluten-free diet, suggesting disease management may vary greatly depending on whether the underlying inflammatory etiology is identified.

The findings of this study further emphasize the importance of a thorough workup to evaluate for an underlying inflammatory process prior to diagnosing uveitis as idiopathic. Both CD and Uveitis have been associated with various autoimmune diseases (Type 1 Diabetes Mellitus, Rheumatoid arthritis, ankylosing spondylitis, Bechet's disease) demonstrating some immunological factors playing a role in both entities and recent studies have shown a strong linkage to the human leukocyte antigens specifically HLA-B27, HLA-B51, and HLA-A29 for Uveitis [13], HLA-DQ2 and HLA-DQ8 for CD [13-14]. Both entities are then thought to be a TH1-mediated disease, where the release of cytokines such as interferon (IFN)-γ, IL-2, IL-8, IL-9, IL-12, IL-15 is seen [15-16-17].

Following a review of currently available literature, this is the first population-based retrospective cohort in the United States that identifies the prevalence of uveitis in persons with CD. Explorys platform has been validated as a database in several different fields including gastroenterology [18-19-20]. This study has several limitations. With the database used, we are unable to verify patient information since they were de-identified, leading to misclassification and misrepresentation of a diagnosis. Another limitation of using such a large database is the lack of information on how the disease was diagnosed, laboratory results, pathology reports, etc. In addition to these limitations, there was no access to the patient's clinical data to confirm whether the diagnostic criteria of Uveitis and CD were respected.

Conclusion

In conclusion, we established that patients with celiac disease are at increased risk of developing uveitis after excluding and controlling for any confounding variables. Celiac disease and Uveitis have both debilitating long-term side effects. Considering that a large proportion of newly diagnosed uveitis is idiopathic, CD should be

added to the list of differential diagnoses, in addition to clinicians conducting a thorough review of systems and adding the appropriate lab work to look for it. In further studies, it could be interesting to investigate the impact of gluten-free diet in patients with celiac disease on the risk of developing uveitis.

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