JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES, 2017
VOL. 7, NO. 6, 347–350
https://doi.org/10.1080/20009666.2017.1396169

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RESEARCH ARTICLE

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Prevalence of occult celiac disease in females with iron deficiency in the United States: an NHANES analysis

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ABSTRACT

Aim: The prevalence of celiac disease (CD) in patients with iron deficiency (ID) is estimated at 0–6% in European countries. The prevalence of celiac disease in patients with iron deficiency in the USA is unknown. Given the treatable nature of gluten hypersensitivity, estimating the prevalence of CD in patients with ID can help to determine the need to screen these patients for occult CD.

Methods: Data were obtained from the NHANES database, a nationally representative health survey conducted from 2009 to 2010. We included 2,105 females aged 6 years or older. Iron deficiency was defined as serum ferritin level <20 ng/ml and considered positive for celiac disease when subjects were tested positive for both immunoglobulin A (IgA) tissue transglutaminase antibody and IgA endomysial antibody. Subjects were divided between two groups (ID and non-ID). The association of CD and ID, which was the primary outcome, was obtained after adjusting for other covariates using logistic regression.

Results: Among the sample of 2,105 subjects, 569 had ID and 1536 did not have ID. Five people were identified as having CD among the ID group, as were two people in the non-ID group. After adjusting for selected covariates, the prevalence of CD was higher in female subjects with ID with OR of 12.5 (95% CI 1.74–90).

Conclusions: The overall prevalence of celiac disease in the USA' female population is low, however, the prevalence is higher in subjects with iron deficiency. Further prospective studies are needed to validate our findings.

ARTICLE HISTORY
Received 15 July 2017
Accepted 17 October 2017

KEYWORDS
Celiac disease; iron deficiency

1. Introduction

Celiac disease (CD) is a chronic autoimmune inflammatory disorder of the small intestine induced by the ingestion of wheat, rye, and barley in genetically susceptible people [1–3]. Its prevalence in the USA was estimated to be 0.71% and the prevalence in females was about 0.62% [3]. It was also estimated to be in the range of 1% among non-Hispanic whites and those of northern European descent, which has been reported to be increasing in the last few decades [4–7]. Many patients with CD are asymptomatic hence it could be underdiagnosed [8]. On the other hand, over the last few decades, due to the development of highly sensitive serologic tests, such as the endomysial antibody (EMA) and the tissue transglutaminase antibody (tTGA), the prevalence of CD has changed. CD is being diagnosed more often in subclinical cases and several high-risk groups [9–11].

In both the developing and developed world, iron deficiency (ID) is one of the most common causes of nutritional deficiencies leading to iron deficiency anemia (IDA) [12]. The most common causes of ID are blood loss and failure of the enterocytes of the proximal intestine to absorb iron from the diet in patients who have enough iron in their diet [13]. CD can lead to decreased absorption of many nutrients, including iron [14].

Given the treatable nature of gluten hypersensitivity, estimating the prevalence of CD in patients with ID can help to determine the need to screen these patients for occult CD. It is our hypothesis that CD should be found more often in people with ID than the iron replete, as iron is exclusively absorbed by the proximal small intestinal mucosa [14].

2. Methods

2.1. Study settings

Data were obtained from the National Health and Nutrition Examination Survey (NHANES) database, a nationally representative health survey conducted from 2009 to 2010 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. It is a continuous cross-sectional survey

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of the health and nutritional status of adults and children that uses sampling through complex, multistage, probability design and is representative of the non-institutionalized civilians of the USA. The first survey was conducted in 1971; however, it became a continuous program with a changing focus on a variety of health and nutritional measurements in 1999. Serologic testing for celiac disease using tTGA and EMA has been done since the 2009–2010 survey [15].

2.2. Study population and demographic data

The 2009–2010 survey included participants aged 6 years or older, who were interviewed, examined and tested for celiac disease. The data assessed individual and family demographics that included age (years), race/ethnicity (Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and other/multiracial), gender (male/female), and smoking status, among others. African American and Hispanic minorities were oversampled to increase the accuracy of estimates in population subgroups. There were 7,798 people who were screened for CD using an enzyme-linked immunosorbent assay IgA tTGA and 2909 people who were screened for iron deficiency based on the level of ferritin in the serum. Only 2105 patients who were screened for both ID and CD were exclusively female and represent our study population [15].

2.3. Laboratory biomarkers

Serum specimens of the sample population were tested for IgA tTGA using an enzyme-linked immunosorbent assay using human recombination antigen (Inova Diagnostics, San Diego, CA) [15]. The results were read as negative if <4.0 U/ml, weakly positive if 4–10 U/ml and positive if >10 U/ml. Weakly positive and positive results were tested for IgA EMA by indirect immunofluorescence [16]. We defined CD patients as those who tested positive for IgA EMA. A threshold serum ferritin level of <20 ng/ml was defined as ID as this value has been found to be useful in the detection of prelatent ID, although it has not been validated [17,18].

2.4. Statistical analysis

Data were analyzed using SAS program version 9.4 and SPSS Statistics version 23. Descriptive statistics were completed to examine demographic variables by group and overall prevalence by group. Independent t-test compared differences in mean age and key laboratory values (hemoglobin, hematocrit, red blood cell distribution widths, transferrin receptor level, and folates) by group. Logistic regression was used to analyze the relationship between CD and ID. Odds ratios with confidence intervals were calculated.

3. Results

There were 2909 people who were screened for ID by checking the ferritin level in their blood, and 7,798 people who were screened for CD by using an enzyme-linked immunosorbent assay IgA tTGA. Only 2,105 females were screened for both ID and CD and are included in our study for analysis. The mean age of our study population was 29.7 years; 28.0 years in the ID group and 30.3 in the non-ID group ($p < 0.001$). Non-Hispanic whites constituted (40.86%) of the total study sample, Hispanics were (11.73%), non-Hispanic Blacks were (18.24%), Mexican Americans were (22.23%) and all other races were (6.94%). The demographic characteristics of the study population are shown in Table 1.

There were 569 (27%) females who had ID and 1,536 (73%) who did not have ID. The overall prevalence of CD in the study population was 0.33% (7/2105). The prevalence of CD in ID females was 0.9% (5/569) and the prevalence of CD in non-ID females was 0.1% (2/1536) with an odds ratio (OR) of 6.79 (95% confidence interval, 1.31–35.2). All seven females with CD in this population were non-anemic and had a hemoglobin level ≥ 11.9 g/dl.

In multivariate analysis after adjusting for age, race, hemoglobin, serum folate level and red blood cell width (RDW), CD was associated with ID, with OR 12.5 (95% CI 1.74–90). CD was also associated with non-Hispanic whites, with OR 15.5 (95% CI 1.67–145). Although these results showed that CD did increase the risk of having ID in females, it did not show any difference in hemoglobin between celiac positive and celiac negative females with an OR of 1.75 (95% CI 0.61–5.05). Also, CD was not associated with a difference in RDW (Table 2).

4. Discussion

In 2017, the U.S. Preventive Services Task Force stated that the current evidence is inadequate to assess the balance of benefits and harms of screening for CD in

Table 1. Demographic characteristics of the study population.

	Total (n = 2105)	Iron deficient (n = 569)	Non-iron deficient (1536)	p-value
Mean age (years)	29.7	28.0	30.3	< 0.001
Race (%)				
White	40.86	33.0	43.8	
Black	18.24	21.3	17.1	
Mexican American	22.23	26.4	20.7	
Hispanic	11.73	12.3	11.5	
Other	6.94	7.0	6.9	<0.001
Celiac screening positive patient	7	5	2	0.015

Table 2. Association of celiac disease with iron deficiency and other variables.

Variables	Odds ratio	95% CI	p-value
Iron deficiency (ID vs non-ID)	12.5	1.74–90	0.015
Race (non-Hispanic whites vs rest)	15.5	1.67–144.9	0.018
Age	0.98	0.92–1.05	0.69
Hemoglobin	1.75	0.61–5.05	0.27
RDW	1.34	0.67–2.68	0.37

asymptomatic persons [19]. Also, there are no current guidelines to advise physicians screening patients with iron deficiency anemia (IDA) for occult CD. A recent survey among hematologists revealed that only 8.6% indicated that patients with IDA should be screened for CD, which in turn indicates that physicians overlook this association in the majority of the cases [20].

In this study, we investigated the association between ID and CD in females in the USA. Data was obtained from the National Health and Nutrition Examination Survey (NHANES) database, a nationally representative health survey conducted from 2009 to 2010, which consequently gave us a good sample size representing the general population in the USA. The major finding of this study is that CD is more prevalent in iron deficient females than in non-iron deficient females, which is in line with many different studies done in Europe [21,22] and Asia [8,23–25]. Also, the prevalence of CD in our patient population was 0.33% (1 in 303), which is lower than the results of studies in Europe [26–29].

As one in 113 iron-deficient females met the criteria for diagnosis of occult CD compared to one in 768 non-iron deficient females, screening for occult CD could help in diagnosing the cause of ID and subsequently help in treatment. Celiac serology offers a non-invasive test to detect gluten hypersensitivity in females with ID. A recent systematic review showed a high sensitivity and specificity of IgA tTGA and high specificity of IgA EMA in both symptomatic and asymptomatic cases. So, the sequential serological testing of IgA EMA in IgA tTGA positive individuals guaranteed the accuracy in detecting CD [30].

Our results point out that CD is more common in patients with ID. This is explained by the fact that CD is one of the causes leading to ID. Correspondingly, ID and anemia are very common laboratory abnormalities in CD [31,32]. ID can occur with or without the occurrence of diarrhea or steatorrhea in CD as iron is lost in the form of sloughed intestinal enterocytes or gastrointestinal bleeding or due to malabsorption of dietary iron [33,34].

On the other hand, there is no study looking into the downside of screening for CD in asymptomatic people. However, potential disadvantages of CD screening include increased anxiety, over-diagnosis, unnecessary serologic tests and increased need for unnecessary endoscopies with biopsy [19].

5. Limitations

The strength of this study is that it includes a representative sample from a national database, which was adjusted for minority groups. However, this study also had several limitations. The number of cases of CD was very small due to the relatively low prevalence of CD in the USA(0.71%) [3]. Another limitation was our criteria for the diagnosis of CD were based on serology only without histological confirmation, as duodenal biopsy is an invasive test difficult to perform in a population-based study. However, this limitation is partially balanced by the sequential serological testing of IgA EMA in IgA tTGA positive individuals. Another potential limitation is that patients with IgA deficiency were missed by the study as IgA deficiency was not tested. Additionally, this study, like many others, did not seek to identify or address any potential risks of CD screening.

6. Conclusion

Given the treatable nature of gluten hypersensitivity, this study suggests that CD testing should be considered in patients with refractory ID when other obvious causes have been ruled out. Ruling out other causes first will reduce over-diagnosis and unnecessary testing. Further prospective studies are needed to validate this finding and identify any potential risks of CD screening.

Acknowledgments

The authors would like to thank Katherine Negele for her help in English language editing and proofreading this manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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