

Unrecognized Celiac Disease in Children Presenting for Rheumatology Evaluation

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abstract

BACKGROUND AND OBJECTIVES: Current clinical guidelines do not consider patients with rheumatic conditions to be at high risk for celiac disease (CD) despite numerous reported associations between the two in adults and children. The objective of this study was to evaluate the prevalence of CD among patients presenting for pediatric rheumatology evaluation.

METHODS: A total of 2125 patients presenting for initial evaluation by the Division of Pediatric Rheumatology at the Hospital for Special Surgery between June 2006 and December 2013 were screened for CD as a part of the standard initial serologic evaluation. The charts of these patients were evaluated retrospectively at the end of this period.

RESULTS: 36 patients (30 girls, 6 boys, mean age 9.4 ± 4.3 years, range 2–16 years) received a diagnosis of CD after serologic testing and evaluation by pediatric gastroenterology. Eight additional patients with known diagnoses of CD presented during this time period. The total prevalence of CD over this 6.5-year period was 2.0%. The most common presenting complaints among patients diagnosed with CD were myalgias, arthralgias, and rash. Less frequently, patients reported gastrointestinal complaints including abdominal pain, nausea, and diarrhea. All patients reported improvement or complete resolution of their musculoskeletal symptoms after initiation of a gluten-free diet.

CONCLUSIONS: This study identified 36 new cases of CD among children presenting for rheumatology evaluation, for an overall prevalence rate of 2.0%. The majority of patients who ultimately received a diagnosis of CD presented with extraintestinal manifestations. These results underscore the importance of screening children presenting for rheumatology evaluation for CD.

WHAT'S KNOWN ON THIS SUBJECT: Associations have been reported between celiac disease (CD) and numerous autoimmune conditions in adults and children. However, current screening guidelines do not consider patients with rheumatic diseases to be at high risk for CD.

WHAT THIS STUDY ADDS: The prevalence of CD in children presenting for rheumatology evaluation was found to be 2% by routine serologic screening. The majority of screening-detected CD cases had no CD-associated symptoms. Gluten restriction was found to relieve some musculoskeletal complaints.

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Celiac disease (CD) is a T-cell mediated immune disorder resulting in inflammation of the small intestine after the ingestion of dietary gluten and related proteins in genetically susceptible people. The prevalence of CD in the general US population has been reported as ~0.7%, similar to that found in several European countries.¹ In children ages 2.5 to 15 years this prevalence has been reported as between 0.3% and 1.3%.²⁻⁴ Studies have shown an association between CD and numerous autoimmune and rheumatic conditions including rheumatoid arthritis,^{5,6} juvenile idiopathic arthritis (JIA),⁷⁻¹⁰ autoimmune thyroiditis,¹⁰⁻¹² autoimmune thrombocytopenic purpura, hemolytic anemia,⁶ vasculitis,^{5,6} polymyositis and dermatomyositis,^{13,14} systemic lupus erythematosus (SLE),^{5,6,15,16} scleroderma,^{5,6} mixed connective tissue disease,⁵ diabetes mellitus,¹⁷⁻²² Sjögren syndrome,^{6,10,23,24} and dermatitis herpetiformis.²⁴ Among the connective tissue disorders, only Sjögren syndrome appears to share the HLA DQ2/DQ8 haplotype with CD.²⁵ Additionally, a link has been reported between gene locus 4q27 and CD, rheumatoid arthritis, psoriatic arthritis, and JIA.²⁶ The prevalence of autoimmune disease in patients with CD is known to increase with age at time of CD diagnosis,²⁷ suggesting that these conditions may be interrelated. However, there are conflicting reports as to whether maintenance of a gluten-free diet (GFD) confers protection against the development of additional autoimmune diseases in patients with CD.²⁸

Despite the reported links between rheumatologic conditions and CD, current clinical guidelines for CD screening published by the American College of Gastroenterology and the North American Society for Pediatric Gastroenterology, Hepatology and

Nutrition (NASPGHN) do not consider such patients to be a high-risk group and do not specifically recommend screening of this population.^{29,30} At this time, little information is available about the coexistence of CD and rheumatic diseases in the US pediatric population. The aim of this study was to investigate the prevalence of CD in patients presenting to the pediatric rheumatology practice.

METHODS

A total of 2125 new patients without preexisting rheumatic diagnoses who presented to the Division of Pediatric Rheumatology at the Hospital for Special Surgery, a tertiary care center in a major metropolitan area, were screened for CD by serologic testing as a standard part of the initial workup. The charts of all such patients seen between June 2006 and December 2013 were reviewed retrospectively at the end of this period. Laboratory results were reviewed for the presence of antigliadin antibodies (AGA IgA and IgG), anti-tissue transglutaminase antibodies (TTG IgA), and antiendomysial antibodies (EMA IgA). The EMA and TTG tests are highly sensitive and specific, with values for both parameters reportedly >95% in most studies.³¹ Sensitivities and specificities for the AGA tests are highly variable but are generally thought to be less reliable than TTG and EMA.³¹ A low positive AGA IgA or IgG titer alongside a negative TTG test was not considered suggestive of CD. Deamidated gliadin peptide testing was not routinely ordered, and results of this test, if available, were not recorded for the purposes of this study.

Additional data recorded included age at initial visit, gender, presenting complaints, family history, ultimate diagnosis or diagnoses, antinuclear antibody (ANA) status, and total serum IgA. Patients who were suspected to have CD based on

serologic testing were referred to pediatric gastroenterology for additional evaluation. For the purposes of this retrospective review, a patient must have had appropriate findings on serologic tests and have received a diagnosis of CD from a gastroenterologist. Patients were not referred to one particular practice, but rather the reports of several gastroenterology specialists were reviewed over the course of this study. Additional testing conducted by gastroenterology specialists involved endoscopies, tissue biopsies, and genetic testing as appropriate.

For patients recorded as having CD, additional symptoms were collected from the review of systems elicited from all new patients: presence of abdominal pain, nausea, vomiting, diarrhea, constipation, blood in stool, weight loss, growth parameters, and a thorough review of musculoskeletal complaints. A comprehensive review of systems, including detailed gastrointestinal (GI) complaints, is standardized among the authors.

Patients were excluded from analysis if they presented with a known diagnosis of inflammatory bowel disease (because they would have already had a complete GI review conducted) or were >18 years old at the time of presentation. Patients who presented with known CD must have already been under the care of a gastroenterologist. Reference ranges for CD serologies varied between local laboratories, and tests were recorded as positive if they fell above the reference range.

We conducted statistical analyses by using SAS software SAS version 9.3 (SAS Institute, Inc, Cary, NC). This study was approved by the institutional review board of the Hospital for Special Surgery, New York.

RESULTS

We reviewed the charts of 2125 new patients. Forty patients were referred

to pediatric gastroenterology based on suspicion of CD. Of these, 4 had negative GI evaluations for CD and 36 (30 girls, 6 boys; mean age 9.4 ± 4.3 years, range 2–16 years) were confirmed as having CD (Fig 1). Among these patients, 30 cases of CD were confirmed by endoscopy (with or without intestinal biopsy, as per gastroenterology). The remaining 6 refused the procedure but demonstrated significant mitigation of symptoms upon initiation of a GFD and were considered to have CD by a gastroenterologist. Thirteen additional patients were found to have positive serologies but were lost to rheumatology follow-up, did not follow up with gastroenterology referrals, or started a GFD without a diagnosis of CD by a physician. Additionally, 8 patients (7 girls, 1 boy; mean age 11.4 ± 4.6 years, range 3–17 years) presented during this time period with an existing diagnosis of CD established on the basis of serologic or endoscopic evidence. All patients were under the care of gastroenterologists and reported well-controlled CD at the time of presentation.

The majority of new patients with a diagnosis of CD (32/36) had a positive TTG-IgA test. Among all 44 patients with CD (both newly and previously diagnosed), we diagnosed many concurrent rheumatologic and autoimmune diseases; most common among these were JIA (including all subtypes per established International League of Associations for Rheumatology classification criteria),³² morphea, uveitis, and thyroid disease. Several patients received a sole diagnosis of CD (Table 1).

Interestingly, 19 out of 36 also had a positive ANA (ranging between 1:40 and 1:640). Additional serologic workup was done at the discretion of the treating physician and was not done for all patients. Of 8 patients presenting with known CD, 4 had a positive ANA (ranging between 1:160 and 1:640), and none had positive celiac serologies at the time of presentation, suggesting good adherence to the GFD (Table 2).

Notable is that the majority of the patients with newly diagnosed CD (22/36) presented with musculoskeletal complaints in the

absence of GI symptoms. Five patients with CD presented with GI complaints without musculoskeletal complaints, and 7 presented with both GI and musculoskeletal complaints. Two patients had only symptoms (including rash, fever, and headaches) that fit neither category (patients 16 and 35). All 8 of the patients with existing CD presented with musculoskeletal complaints. Four of these 8 patients additionally reported GI symptoms that had not resolved upon the restriction of gluten (Table 3).

Among all patients with CD (both known and newly diagnosed cases), 35 out of 44 reported a family history of autoimmunity or rheumatic conditions when prompted. (Patients were specifically asked about JIA, rheumatoid arthritis, osteoarthritis, SLE, mixed connective tissue disease, back pain, ankylosing spondylitis, inflammatory bowel disease (Crohn disease and ulcerative colitis), psoriasis, diabetes mellitus type 1, thyroid disease, acute rheumatic fever, and Lyme disease). Six patients reported a family history of CD when prompted (although only 3 were in first-degree relatives). All patients in whom CD was diagnosed by endoscopy were started on a GFD. Patients who refused the procedure but were suspected of having CD on the basis of positive serologies were also initiated on the GFD by their gastroenterologists. All patients reported either partial or complete resolution of their complaints (including musculoskeletal symptoms) upon initiation of the GFD. Ten of the 36 newly diagnosed patients (patients 14, 19, 20, 21, 24, 26, 28, 31, 34, and 36) never needed any medications and reported complete resolution of their symptoms with the restriction of gluten.

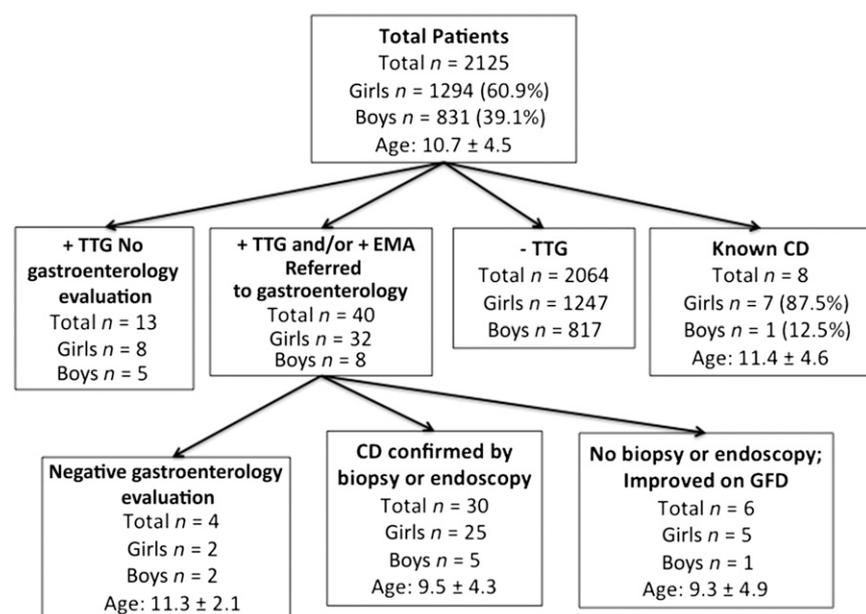


FIGURE 1
Patient demographics.

DISCUSSION

To our knowledge, this study represents one of the largest pediatric

TABLE 1 Clinical Features and Diagnoses of Newly Identified Cases of CD

Case	Gender	Age	Bx/E	Symptoms			Family History of CD	Family History of Autoimmunity	TTG	EMA	ANA	Clinical Findings or Additional Diagnoses, if Any
				MSK	GI	Non-MSK, Non-GI						
1	F	2	Y	+	—	—	—	++ ^a	+	—	—	JIA
2 ^b	F	16	Y	+	—	—	++	++	+	+	+	JIA
3	F	8	Y	+	—	—	—	+	+	+	—	JIA
4	F	6	Y	+	—	—	+	+	+	+	+	JIA
5	F	5	Y	+	—	—	—	++	+	+	+	JIA
6	F	14	Y	+	—	—	—	++	+	—	—	JIA
7	M	11	Y	+	+	+	—	—	+	+	—	JIA
8	F	5	Y	+	—	—	—	++	+	UNK	+	JIA, uveitis
9 ^b	F	6	Y	+	—	—	—	—	+	+	+	JIA, hypothyroidism
10 ^b	F	11	Y	+	—	+	—	++	—	+	+	JIA, hypothyroidism, IgA deficiency
11 ^b	F	7	Y	+	+	—	—	++	+	—	—	JIA, thyroid disease
12	F	9	Y	+	—	—	—	+	+	+	+	Psoriatic arthritis
13	F	13	Y	+	—	—	—	—	+	UNK	+	Arthralgias
14 ^c	F	8	Y	+	+	+	—	++	+	+	+	Arthralgias
15	F	8	Y	+	—	+	—	++	+	+	+	Raynaud, morphea, autoantibodies
16 ^b	F	15	Y	—	—	+	—	++	+	+	—	Raynaud, thyroiditis
17	M	8	Y	—	+	+	—	++	—	UNK	—	Periodic fever, aphthous pharyngitis, and cervical adenopathy
18	F	8	Y	+	—	+	—	+	+	+	—	Myositis
19 ^c	M	7	Y	+	—	—	—	—	+	UNK	+	SLE
20 ^c	F	7	Y	+	—	—	—	+	—	+	—	Lyme
21 ^c	M	6	Y	+	—	+	—	++	—	UNK	—	Lyme
22 ^b	F	16	Y	—	+	+	++	++	+	+	+	No other
23	F	8	Y	+	+	—	—	+	+	+	—	No other
24 ^c	M	2	Y	—	+	+	—	+	+	+	—	No other
25	F	16	Y	+	—	—	—	+	+	+	+	No other
26 ^c	F	15	Y	+	+	—	—	++	+	—	+	No other
27	F	14	Y	—	+	+	—	++	+	—	+	No other
28 ^c	F	5	Y	—	+	+	—	+	+	+	+	No other
29	F	12	Y	+	+	+	—	—	+	UNK	+	No other
30	F	16	Y	+	+	+	—	++	+	+	—	No other
31 ^c	M	5	N	+	—	—	—	++	+	+	—	JIA
32	F	8	N	+	—	—	—	+	+	—	—	Vitiligo, arthralgias
33	F	13	N	+	—	—	+	+	+	—	+	Arthralgias
34 ^c	F	13	N	+	—	—	—	+	+	+	+	Raynaud
35	F	3	N	—	—	+	—	—	+	+	—	Uveitis
36 ^c	F	14	N	+	—	—	+	+	+	+	—	Morphea, autoantibodies

Bx/E, biopsy or endoscopy; F, female; M, male; MSK, musculoskeletal; UNK, unknown; +, indicates general family history of autoimmunity; ++, indicates a history of autoimmunity in a first-degree relative; —, negative result or absence of the symptom.

^a A ++ indicates first-degree relative.

^b Fulfilled NASPGHN guidelines for screening.

^c Did not need medications other than gluten-restricted diet.

cohorts ever evaluated for CD in the United States.³ We diagnosed 36 previously unrecognized cases of CD by standardized serologic screening of 2125 new patients who presented to our pediatric rheumatology practice. Along with the 8 preexisting cases of CD, this indicates a period prevalence of 2.0% (over 6.5 years), or approximately 1:48 patients over that period. Our data suggest that children presenting for rheumatology evaluation are at an elevated risk for CD, and standard screening of these patients should be considered.

We may have underestimated the prevalence of CD in our cohort because of the criteria required for diagnosis: Any patient with positive titers who did not follow up with gastroenterology or rheumatology or who started a GFD without an official diagnosis of CD was excluded from our study. Additionally, it is possible that some patients who were tested for CD serologies were already on self-initiated GFDs at the time of presentation and would not have been identified in this retrospective review.

The majority of the newly diagnosed CD cases, 22 out of 36 (61.1%), presented with musculoskeletal complaints alone and none of the classic symptoms of CD, such as abdominal pain, short stature, weight loss, and failure to thrive. In fact, only 12 patients reported a history of GI-related complaints. This is consistent with 2 recent reports that similarly found a low correlation between GI symptoms and CD positivity. These studies both concluded that symptom-based case finding is

TABLE 2 Clinical Features and Diagnoses of Patients Presenting With Known CD

Case	Gender	Age	Age at CD Diagnosis	Symptoms			Family History of CD	Family History of Autoimmunity	ANA	Clinical Findings or Additional Diagnoses, if Any
				MSK	GI	Non-MSK, Non-GI				
37	F	17	UNK	+	—	—	—	—	+	JIA
38	F	13	10	+	+	—	—	++ ^a	+	JIA
39	F	10	7	+	—	+	—	++	+	JIA, type 1 diabetes, hypothyroidism, autism, seizure disorder
40	F	12	4	+	+	+	++	+	+	Autoantibodies, IgA deficient
41	F	9	8	+	+	—	—	—	—	Hypermobile joint syndrome
42	F	10	9	+	—	+	—	+	—	No other
43	F	3	3	+	—	—	—	+	—	No other
44	M	17	12	+	+	+	—	+	—	No other

MSK, musculoskeletal; UNK, unknown.

^a A ++ indicates first-degree relative.

insufficient to identify a majority of children with CD.^{33,34}

The current clinical guidelines provided by the NASPGHN recommend screening children with failure to thrive, persistent diarrhea, recurrent abdominal pain, constipation, and vomiting for CD. Screening is currently recommended for the following extraintestinal symptoms: dermatitis herpetiformis, dental enamel hypoplasia, osteoporosis, short stature, delayed puberty, iron deficient anemia, asymptomatic children with diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency, and a history of first-degree relative with CD.³⁵ If applied, these recommendations would have missed all but 6 of the asymptomatic cases (patients 2, 9, 10, 11, 16, and 22) we identified by standardized

screening. Given the potential association between CD and musculoskeletal complaints that our data suggest, patients with musculoskeletal complaints may need to be given special consideration with regards to CD testing.

For patients with a known diagnosis of rheumatic disease who have not demonstrated satisfactory clinical improvement with appropriate treatment, CD may be considered as a potential concomitant diagnosis. Furthermore, given that ≥ 2 of our patients with newly diagnosed CD had previously tested negative for celiac antibodies, retesting may be considered for patients who have not had a satisfactory response to medical therapy. However, it should be noted that we did not routinely screen patients who presented with preexisting rheumatologic diagnoses for CD.

In our cohort, gender and CD were shown to not be independent by χ^2 analysis ($P = .036$). When we adjusted for age, thyroiditis, and JIA (each of which had a statistical association with both gender and CD) by logistical regression, girls were 2.25 times more likely to be diagnosed with CD (95% confidence interval, 1.01–5.05) compared with boys ($P = .048$). Previous studies have reported that CD is female predominant by a female-to-male ratio of 3:1 or 2:1 in adults.^{36,37}

Interestingly, 23 of all 44 patients with CD were found to be ANA positive. The presence of serologic abnormalities in CD has not been comprehensively studied. The increased presence of antigliadin antibodies in patients with SLE has been considered to represent false positivity, which is consistent with the presence of false positive autoantibodies for numerous other conditions in patients with SLE.¹⁵ One study by Lerner et al³⁸ observed that in a group of patients with CD, 23% had anti-dsDNA and 14% had anticardiolipin antibodies. However, a study by Caglar et al³⁹ found no significant differences in the frequency of a number of anticytoplasmic and antinuclear antibodies between patients with CD and healthy controls. Additional studies are necessary to clarify the significance, if any, of these serologic abnormalities.

TABLE 3 Presenting Symptoms of Patients Ultimately Diagnosed With CD

Presenting Symptoms	Patients With Known CD (<i>n</i> = 8) ^a	Patients With Newly Diagnosed CD (<i>n</i> = 36) ^a
Non-GI symptoms		
Myalgia or arthralgia	5	24
Fever	1	6
Rash	2	5
Headaches	0	5
GI symptoms		
Abdominal pain	1	8
Nausea or vomiting	1	4
Diarrhea	2	2
Constipation	0	4
Poor appetite	0	1
Foul-smelling stool	0	1

^a Some patients presented with multiple symptoms.

Untreated CD in adults has been linked to an elevated risk of malignancy^{35,40–42} (although no such link has been found in children, presumably because of earlier initiation of a GFD),⁴³ cardiovascular disease,⁴⁰ and mortality.⁴⁴ Prompt recognition of CD is essential to the early initiation of a GFD and the avoidance of unnecessary immunosuppressive therapies. Interestingly, 10 of our 36 patients with newly diagnosed CD reported complete resolution of their GI and non-GI symptoms upon initiating the GFD and needed no additional medications. However, we acknowledge that this improvement was self-reported by patients and was not systematically evaluated. Although there have been no studies confirming the benefit of treating asymptomatic CD in patients with other autoimmune conditions, 1 case report showed that in a patient with idiopathic hypoparathyroidism and CD, parathyroid immunoreactivity disappeared in parallel with a decrease in serum celiac antibodies during a period of gluten restriction.⁴⁵ However, another report demonstrated that successful treatment of CD in patients with primary Sjögren syndrome did not relieve sicca symptoms.⁴⁶ It has been calculated that the prevalence of autoimmune diseases is 5.3 per 1000 patient-years during a period of adherence to a GFD, compared with 11.3 per 1000 patient-years during nonadherence to a GFD,⁴⁷ suggesting an elevated risk for additional autoimmune conditions in patients with untreated CD. This finding again underscores the importance of prompt CD screening for patients with suspected rheumatic conditions. Although it was not the intention of this study to identify the number of patients needed to test for CD to have favorable financial and clinically

significant outcomes, these types of calculations have been conducted by other groups.^{33,48}

Finally, patients with concurrent diagnoses of JIA and CD who report clinical improvement of musculoskeletal complaints on the GFD alone raise an intriguing question: Can patients such as these really be considered to have “idiopathic” arthritis if it resolves with the treatment of the CD? Deposition of immune complexes originating from the small intestinal mucosa in other organs was proposed to explain the association between CD and a range of autoimmune diseases as early as 1975,⁴⁹ but this connection has not yet been satisfactorily clarified. Our data suggest that there may be a subset of patients with “silent” CD who present with isolated musculoskeletal symptoms and that perhaps JIA is not an appropriate diagnosis in these cases. Clinicians must be vigilant in cases such as these to evaluate appropriately for CD.

CONCLUSIONS

Currently, the American College of Gastroenterology and NASPGHN recommendations for CD screening do not consider children with rheumatic disease to be a high-risk group, despite numerous reported associations between autoimmune diseases and CD and despite the positive effect of GFD on the development and treatment of autoimmune conditions. Among patients presenting for initial pediatric rheumatology evaluation, we found an unexpectedly high number of previously unrecognized CD cases compared with the general population (2% vs 0.7%). Furthermore, the most common presenting complaints among

patients with an ultimate diagnosis of CD were musculoskeletal rather than GI. Although this finding is not surprising given that the cohort is from a pediatric rheumatology practice, where patients would be expected to present with musculoskeletal rather than GI symptoms, we discovered a surprising number of “silent” cases of CD that presented with no GI complaints at all. Because of the potential benefits of early initiation of a GFD in patients with CD, along with the dangers of unnecessary immunosuppressive therapies in unidentified celiac cases, we believe that children presenting for rheumatologic evaluation should be considered a high-risk population and screened for CD as part of the standard initial laboratory evaluation.

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ABBREVIATIONS

AGA: antigliadin antibody
ANA: antinuclear antibody
CD: celiac disease
EMA: antiendomysial antibody
GFD: gluten-free diet
GI: gastrointestinal
Ig: immunoglobulin
JIA: juvenile idiopathic arthritis
NASPGHN: North American Society
for Pediatric
Gastroenterology,
Hepatology and
Nutrition
SLE: systemic lupus
erythematosus
TTG: anti-tissue transglutaminase
antibody

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