Collagenous Gastritis in Children: Incidence, Disease Course, and Associations With Autoimmunity and Inflammatory Markers

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INTRODUCTION: **Collagenous gastritis (CG), a rare disorder of unknown etiology, has been postulated to have immune-mediated mechanisms. We investigated (i) the incidence and prevalence of CG in a pediatric population; (ii) the clinical, endoscopic, and histologic characteristics of childhood-onset CG; and (iii) the evidence for autoimmunity and/or inflammatory activity in these patients.**

METHODS: **Clinical, endoscopic, and histologic data were reviewed longitudinally in a population-based Swedish cohort of 15 patients with childhood-onset CG diagnosed in the period 2008–2019. A set of 11 autoantibodies, 4 blood inflammatory biomarkers, and the human leukocyte antigen DQ2/DQ8 genotype was analyzed cross-sectionally.**

RESULTS: **The incidence rate of childhood-onset CG was 0.25/100,000 person-years, with an incidence rate ratio of girls to boys of 4.2 (95% confidence interval, 1.2–15). The prevalence of CG was 2.1/100,000 in children aged younger than 18 years. The endoscopic and histologic findings remained pathologic in all the examined patients during a median follow-up of 4.4 years. Many patients had heredity for autoimmune disorders (47%) and/or tested positive for autoantibodies (40%) or human leukocyte antigen DQ2/DQ8 (53%). No associated autoimmune comorbidities were observed. The serum levels of calprotectin and amyloid A were increased in 10/15 (67%) and 5/15 (33%) of the patients, respectively, whereas plasma C-reactive protein levels were normal in all, but 1 patient.**

DISCUSSION: **The results indicate that childhood-onset CG is rare and has a chronic disease course. Although signs of autoimmune predisposition are frequent, early development of autoimmune comorbidities seems seldom. Serum calprotectin and amyloid A represent novel candidate biomarkers of inflammatory activity in CG (see Visual Abstract, Supplementary Digital Content 4, http://links.lww.com/CTG/A349).**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A335, http://links.lww.com/CTG/A336, http://links.lww.com/CTG/A337

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INTRODUCTION

Collagenous gastritis (CG) is a rare gastrointestinal disorder with fewer than 300 cases reported in the English-language literature (1–24). Of these cases, about one-third have been childhood-onset CG (15–45). The condition is characterized histologically by an increased subepithelial layer of collagen (conventionally defined as being >10 μm in thickness) in the gastric mucosa, together with an inflammatory cell infiltrate in the lamina propria (46,47). In most pediatric cases of CG, the collagenous mucosal inflammation is restricted to the stomach (22–24,41), whereas in adult-onset disease, concurrent involvement of the small bowel and/or colon is more common (1,23,24,46,48). Pediatric cases of CG generally

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present with severe iron deficiency anemia and/or recurrent abdominal pain (22–24,41), whereas diarrhea and malabsorption are the predominant symptoms in adults, presumably linked to the frequently observed concurrent intestinal involvement (32,46,49). Associated immune-mediated comorbidities, such as celiac disease and type 1 diabetes, have been reported in both pediatric (22–24,26,31) and adult (3–5,23,24,45,47,50) patients. CG is believed to be a chronic disease, and there is currently no effective treatment (46).

The current literature on childhood-onset CG consists mainly of case reports (15–20,27–37,42,43,51), apart from 6 small case series (21,22,38–41) and 3 histopathologic studies with limited clinical information and follow-up data (23,24,45). Consequently, the knowledge regarding the evolution of the clinical, endoscopic, and histologic features of the disease over time is sparse. Furthermore, although immune-mediated/autoimmune disease mechanisms have been hypothesized (47), convincing supporting evidence is lacking. In collagenous colitis, the human leukocyte antigen (HLA) DQ2.5 haplotype, encoded by the HLA DQ2/DQ8 genes, seems to be associated with increased disease susceptibility (52). However, no studies of the prevalence of the HLA DQ2/DQ8 haplotype in CG have been published. Moreover, the methodologies used in the previous studies of CG have not allowed estimations of the disease incidence or prevalence, although a possible female predominance has been noted (1,41).

The aims of this population-based cohort study, which combines longitudinal and cross-sectional approaches and involves 15 patients with childhood-onset CG, were to investigate: (i) the incidence and prevalence of CG in a pediatric population in western Sweden; (ii) the clinical, endoscopic, and histologic characteristics of childhood-onset CG through the course of the disease; and (iii) the frequencies of autoimmune comorbidities and heredity, as well as the prevalences of autoantibody development, increased blood inflammatory biomarkers, and the HLA DQ2/DQ8 haplotypes in patients with childhood-onset CG.

METHODS

Study design

The study was designed as a population-based cohort study that comprised 15 persons of White ethnicity with childhood-onset CG (12 female and 3 male patients) and age range of 8.7–23 years (median age, 15 years) recruited from western Sweden. All cases of CG diagnosed before the age of 18 years in the counties of Halland, Jönköping, Värmland, and Västra Götaland in western Sweden during the period of January 2008 through June 2019 were identified. These 4 counties comprise 26% of the Swedish population and in 2019 had a pediatric population (aged <18 years) of approximately 568,000 (53). The Department of Pediatric Gastroenterology, Hepatology, and Nutrition at Queen Silvia Children's Hospital, Gothenburg, Sweden, which serves as a tertiary referral center for these counties, was involved in the diagnosis of all the cases. Furthermore, an established practice in Sweden is that all pediatric endoscopies are performed under general anesthesia in county hospitals or higher-level medical institutions within the public healthcare system. This enables the identification of all eligible cases within the geographic area covered by the study. The recruitment of subjects was carried out at a clinical follow-up visit during the period of May 2019 to November 2019, at which time point all the blood samples were drawn. All eligible patients accepted to participate in the study.

Diagnostic criteria

The diagnosis of CG was based on histologic demonstration of increased (>10 μm) subepithelial collagen deposition in at least 1 biopsy taken from gastric mucosa during endoscopy, in addition to other histologic, endoscopic, and clinical findings supporting the diagnosis (32,47). The day when the first endoscopic examination that met the diagnostic criteria was performed was defined as the date of diagnosis.

Epidemiological analyses

The incidence rate of childhood-onset CG for the period spanning January 2008 to June 2019 was calculated according to the recommended principles for dynamic populations (54). To define the population at risk, the data on the annual numbers of children aged younger than 18 years registered in the counties of Halland, Jönköping, Värmland, and Västra Götaland during the period 2008–2019 were retrieved from the Swedish Government agency Statistics Sweden. The prevalence of CG in the population aged younger than 18 years in the 4 counties was calculated as of June 2019.

Clinical, endoscopic, and histologic data

The complete medical records and endoscopic reports for all the patients were reviewed. Demographic data, existing comorbidities, clinical symptoms related to CG, and outcomes from tested treatment modalities were retrieved during the follow-up consultations. Furthermore, heredity for autoimmune and other diseases among first-degree relatives was systemically evaluated.

Regarding the histopathologic evaluation, all cases had initially been re-evaluated by a senior gastrointestinal pathologist (M.W.) at the Department of Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, to confirm the diagnosis. For the purpose of this study, the gastric mucosal biopsies from all gastrointestinal endoscopies performed on study subjects during the follow-up were reviewed independently by a different senior gastrointestinal pathologist (A.W.). In this evaluation, the specific histologic parameters recently proposed for CG, such as the location of collagen deposits, the grade of active and chronic inflammation, and the presence of eosinophil- or lymphocyte-predominant type of inflammation in the gastric mucosa, were applied (23). In addition, the maximum number of intraepithelial eosinophilic granulocytes per high-power field (size, 0.24 mm^2) was determined. Moreover, the maximal thicknesses of the subepithelial collagen deposits in gastric mucosal biopsies were measured using an ocular micrometer in the microscope and collagen-specific stains (i.e., Masson trichrome, Van Gieson, or Sirius Red). Furthermore, mucosal biopsies acquired from other sites in the gastrointestinal tract were also reviewed, and any diagnostic abnormalities were recorded.

Laboratory parameters

All the blood laboratory parameters were analyzed on inclusion of the patient in the study, and they included 11 autoantibody specificities and 4 inflammatory markers. The following autoantibodies were measured in the serum samples: antinuclear antibody (ANA), antismooth muscle antibody, antimitochondrial antibody, antineutrophil cytoplasmic antibody, tissue transglutaminase IgA, antithyrotropin receptor antibodies, antithyroid peroxidase antibodies, antithyroglobulin antibodies, antiglutamic acid decarboxylase antibodies, antiintrinsic factor antibodies, and antiparietal cell antibodies. The blood inflammatory markers analyzed were plasma C-reactive protein (CRP), serum calprotectin, serum

amyloid A (SAA), and serum orosomucoid. The values of all the inflammatory parameters were continuous, with the exception of SAA, which had a detection limit of 11 mg/L with the analysis method used.

In addition, genotyping of HLA DQ2/DQ8 was performed. Moreover, the serum levels of albumin, blood total leukocyte counts, and blood absolute neutrophil counts, as well as the total serum levels of immunoglobulins A, M, and G (including IgG subclasses), were measured. The laboratory methods used and the cutoff levels and reference intervals applied in the study are listed in Tables S1a and S1b (see Supplementary Digital Content 1, http://links.lww.com/CTG/A335). All blood samples were drawn after a 12-hour period of fasting and analyzed in accredited laboratories at Sahlgrenska University Hospital, Gothenburg, Sweden, or at affiliated county hospitals. The blood analysis laboratory data were complete for all the study participants, with the exception of a blood absolute neutrophil count that was missing for a single patient.

Ethics

Written informed consent was obtained from all study participants and/or their parents. The study was approved by the Regional Ethical Review Board of Gothenburg, Gothenburg, Sweden (Dnr. 298-12).

Statistical methods

Owing to the limited sample size and non-normal distribution of the variables, the data are presented as medians with ranges. To calculate the confidence interval for the incidence rate ratio, a 2-sample *z*-test was applied. The Spearman test was used for determination of correlations between laboratory parameters. A 2-tailed *P*-value <0.05 was considered statistically significant. The *z*-test was performed using Microsoft Excel for Mac 2011 version 14.7.7 software (Microsoft, Redmond, WA). For all other statistical analyses, IBM SPSS Statistics version 22 software (IBM, New York, NY) was used.

RESULTS

Patient characteristics

The median age at the diagnosis of CG was 9.9 years (range, 4.4–17 years), whereas the median age at the initial presentation was 9.8 years (range, 4.3–16 years). The median duration of disease, measured from the initial presentation, was 6.2 years (range, 0.4–11 years) on inclusion in the study. The collagenous inflammation was restricted to the stomach in all, but 2 patients (13/15, 87%), and associated collagenous duodenitis and collagenous colitis were seen in 1 patient each. No patient had an established current or previous comorbidity involving other gastrointestinal, autoimmune, or inflammatory diseases. Allergic disease was seen in 2 (13%) patients, both of whom suffered from allergic rhinoconjunctivitis. Apart from 1 patient with concomitant collagenous colitis who was receiving budesonide therapy and 3 other patients who were being treated with proton pump inhibitors, the remaining 11 patients were not receiving any anti-inflammatory or immunosuppressive therapy.

Incidence rate and prevalence

The annual number of persons aged younger than 18 years at risk for CG in the study's geographic area was in the range of 505,414–565,425 (corresponding to approximately 20% of the total population) during the study period and consisted predominantly of persons of Caucasian ancestry. The total number of person-years of follow-up (PYFU) in this population-based cohort was 6,020,927, which translates to an incidence rate of childhood-onset CG of 0.25 cases per 100,000 PYFU during the study period. Categorized by sex, the incidence rate for CG was 0.41 cases per 100,000 PYFU for girls and 0.097 cases per 100,000 PYFU for boys, yielding an incidence rate ratio (girls to boys) of 4.2 (95% confidence interval, 1.2–15). In June 2019, the prevalence of CG in children aged younger than 18 years was 2.1/100,000 in the counties of western Sweden.

Clinical picture and disease course

All but 1 patient had iron deficiency anemia on initial presentation, and in most of the cases, this was severe (Table 1). The chief complaint that prompted the patient to seek medical attention was related to the anemia (e.g., fatigue and pallor) in 5/15 patients (33%) or to gastrointestinal symptoms in 3/15 patients (20%). In the remaining 7 cases (47%), the iron deficiency anemia that initiated the diagnostic workup was an incidental finding, discovered when the patients were seeking medical attention for reasons unrelated to anemia or gastrointestinal symptoms, such as a respiratory infection.

In a targeted anamnesis, recurrent abdominal pain was reported by 6/15 patients (45%) on presentation, although in most of the cases, the pain was not severe and did not affect the activities of daily living. However, in the sole patient with associated collagenous colitis, the presenting symptoms were dominated by watery diarrhea. None of the patients showed hematemesis, melena, or hematochezia. Nonetheless, testing for fecal hemoglobin was carried out in 12/15 patients (80%) as part of the initial diagnostic workup. The testing did not indicate occult gastrointestinal bleeding in any of these patients. In 10 of the 12 girls in the study, all of whom had iron deficiency anemia at presentation, the diagnosis of CG was made before menarche. The remaining 2 girls reported no menorrhagia. At presentation, all the patients were on a regular diet, and no one was taking any medication.

All 14 patients who had iron deficiency anemia at presentation responded to iron supplementation with normalization of blood hemoglobin levels and iron parameters. After initial treatment, iron deficiency with or without associated anemia recurred within a median time of 1 year (range, 1–2 years) in 13 of the patients, most of whom continued to require repeated iron substitution subsequently during the follow-up. Orally delivered iron supplementation (ferrous asparto glycinate plus polysaccharide iron complex or iron sulphate) was the primary choice of therapy, and intravenous administration of iron (ferric carboxymaltose) was used primarily when oral intake of iron created bothersome gastrointestinal side effects, such as abdominal pain. Apart from the recurrence of iron deficiency, most of the patients remained asymptomatic during the median follow-up of 6.2 years (range, 1.0–11 years). Only 1 patient experienced recurrent abdominal pain that affected daily activities, whereas another patient who had concurrent collagen colitis experienced occasional bouts of watery diarrhea despite maintenance therapy with budesonide.

Treatment outcomes

Efforts were made to treat CG with proton pump inhibitors (n = 5) and dietary modifications (n = 7), such as cow's milk-free diet (n = 4), gluten-free diet (n = 2), and diet free of cow's milk, soy, egg, and wheat (n = 1). However, none of the patients showed endoscopic or histologic improvements during the treatment

Table 1. Chief complaints, blood hemoglobin levels, erythrocyte indices, and serum iron parameters at presentation of 15 patients with childhood-onset collagenous gastritis

Patient code	Sex	Age (yr)	Chief complaint(s)	Hb (g/L) [RI: 115–160]	MCV (fL) [RI: 75–102]	MCHC (g/L) [RI: 310–370]	Iron (μmol/L) [RI: 9–34]	Ferritin (μg/L) [RI: 20–200]	TIBC (μmol/L) [RI: 48–83]	sTfR (mg/mL) [RI: 1.9–5.0]	TS (%) [RI: 6–48]
A	M	4.6	Fatigue, pallor	28	52	255	<1.0	1.9	nd	54.0	2
B	F	10.1	Fatigue, pallor	49	54	285	1.7	2	100	57.5	2
C	F	13.1	Fatigue, pallor, palpitation	79	68	306	2.1	3	110	16.3	3
D	F	14.4	Fatigue, pallor, palpitation, headache	39	62	244	1.5	2	83	35.4	3
E	F	12.7	Fatigue, vertigo	40	64	233	0.6	<2	99	35.8	nd
F	F	9.8	Recurrent abdominal pain, non-bloody diarrhea	94	59	280	nd	3	nd	nd	nd
G	M	8.3	Recurrent abdominal pain, gastroesophageal reflux	137	83	350	nd	nd	nd	nd	nd
H	F	4.3	Watery, non-bloody diarrhea	105	80	309	3	6	nd	7.6	nd
I	F	12.5	Incidental finding of anemia	78	58	261	1	<2	73	nd	nd
J	M	7.8	Incidental finding of anemia	73	60	245	nd	2	nd	nd	nd
K	F	5.9	Incidental finding of anemia	59	61	267	2	4	nd	nd	nd
L	F	16.0	Incidental finding of anemia	55	55	273	1.2	2	95	60.1	2
M	F	13.0	Incidental finding of anemia	50	55	262	1.4	2	83	58.3	2
N	F	8.8	Incidental finding of anemia	47	68	274	1.8	2	110	30.7	2
O	F	8.6	Incidental finding of anemia	88	62	319	5	<2	74	2.84[a]	nd

Hb, Hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; nd, no data; RI, reference interval; sTfR, soluble transferrin receptor; TIBC, total iron-binding capacity; TS, transferrin saturation.

[a]Analyzed at affiliated hospital laboratory with nephelometry-based method with reference interval of 0.80–1.76 mg/mL.

Table 2. Endoscopic and histologic findings at the time of diagnosis of collagenous gastritis for the patients in the study cohort

Patient code	Sex	Age (yr)	Current therapy	Macroscopic findings	Histologic findings in gastric mucosal biopsies					Other associated pathology
					Max. collagen thickness (μm)	Location of collagen	Collagen distribution[a]	Eos/ HPF	IEL/ HPF	
A	M	5.8	None	Edematous and nodular mucosa in gastric body and fundus; traces of coagulated blood	40	Corpus[b]	Patchy	40	<25	None
B	F	10.9	None	Nodularity in gastric antrum	20	Equal antrum and corpus	Focal	<15	<25	None
C	F	13.9	None	Nodularity in proximal part of gastric antrum	60	Equal antrum and corpus	Patchy	70	<25	None
D	F	15.4	None	Nodularity in gastric antrum, body and fundus; mild erythema in gastric antrum	40	Equal antrum and corpus	Patchy	30	<25	Subtotal villous atrophy in proximal duodenum; intraepithelial lymphocytosis in proximal and distal duodenum[d]
E	F	13.1	None	Hypertrophic and nodular mucosa with slight erythema in gastric body	100	Corpus predominant	Patchy	90	<25	None
F	F	9.9	None	Nodularity in gastric body and antrum	60	Antral predominant	Patchy	40	<25	None
G	M	8.5	PPI	Mucosal irritation in gastric body and antrum; nodular changes in duodenal bulb	40	Corpus predominant	Diffuse	100	<25	None
H	F	4.4	None	Unremarkable	40	Antrum[c]	Focal	30	<25	Total villous atrophy without intraepithelial lymphocytosis in duodenum[e]; collagenous colitis
I	F	12.6	None	Nodularity in gastric body	55	Corpus predominant	Patchy	40	<25	None
J	M	8.0	None	Nodularity with a few erosions in gastric body and fundus	80	Equal antrum and corpus	Patchy	150	<25	Total villous atrophy, intraepithelial lymphocytosis and collagen deposits in proximal duodenum[d]
K	F	6.4	None	Nodularity in gastric body and fundus	30	Corpus predominant	Patchy	50	<25	None
L	F	17.0	None	Erythema and raised mucosal stripes in gastric body and antrum; cobblestone appearance in antrum	80	Equal antrum and corpus	Diffuse	60	<25	None

Table 2. (*continued*)

Patient code	Sex	Age (yr)	Current therapy	Macroscopic findings	Histologic findings in gastric mucosal biopsies					Other associated pathology
					Max. collagen thickness (μm)	Location of collagen	Collagen distribution[a]	Eos/HPF	IEL/HPF	
M	F	13.1	None	Nodularity and pseudopolyposis in gastric body and fundus	15	Corpus predominant	Focal	30	<25	None
N	F	8.9	None	Nodularity in gastric antrum	25	Antrum[c]	Focal	10	<25	None
O	F	8.8	None	Nodularity in gastric antrum	80	Equal antrum and corpus	Diffuse	60	>25	None

Eos, Eosinophils; HPF, high-power field; IEL, intraepithelial lymphocytes; PPI, proton pump inhibitor.
[a]Extent of collagen distribution was categorised as focal (<30% of surface), patchy (30–69% of surface), or diffuse (≥70% of surface) depending on the magnitude of the affected surface area.
[b]Gastric mucosal biopsies were taken from the corpus only.
[c]Gastric mucosal biopsies were taken from the antrum only.
[d]Serum IgA transglutaminase antibodies were negative at the time of the endoscopy, thus not indicating the presence of celiac disease.
[e]Serum IgA transglutaminase antibodies were negative at the time of the endoscopy and the patient was not a carrier of the susceptibility haplotype HLA DQ2/DQ8 for celiac disease. Moreover, immunohistologic analysis of duodenal mucosal biopsies showed no increase in the numbers of T cells that expressed the T-cell receptor gamma/delta chains in the intraepithelial lymphocyte population.

period (see Table S2, Supplementary Digital Content 2, http://links.lww.com/CTG/A336). Apart from the patient with concurrent collagenous colitis who was on maintenance therapy with budesonide, no steroids or immunomodulators were administered to any of the remaining 14 patients.

Endoscopic and histologic features

The endoscopic and histologic findings in the gastric mucosa in the patient cohort at the time of diagnosis are listed in Table 2. The endoscopic appearance of the gastric mucosa was judged to be abnormal in all, but 1 case. However, this patient had aberrant macroscopic findings in the stomach in follow-up endoscopies. The most commonly observed endoscopic features were mucosal nodularity, hypertrophic gastric folds, and erythema. Only 1 patient demonstrated endoscopic signs of mucosal bleeding from the stomach. Biopsy-based tests showed no signs of concurrent *Helicobacter pylori* gastritis in any patient.

Histologically, the maximal thickness of the subepithelial collagen deposits was in the range of 15–100 μm at diagnosis. Moreover, most (13/15, 87%) of the patients exhibited an eosinophil-rich (≥30 eosinophils/high-power field) inflammation of the gastric mucosa, with up to 150 eosinophils/high-power field. By contrast, intraepithelial lymphocytosis (>25 surface intraepithelial lymphocytes/100 epithelial cells) was seen in only 1 patient.

Duodenal mucosal biopsies had been acquired from all patients on diagnosis of CG, and 3 patients showed an associated subtotal or total villous atrophy with or without intraepithelial lymphocytosis (Table 2). One of these patients had collagen deposits in the duodenal bulb consistent with collagenous gastroduodenitis and tested negative for celiac disease in serologic tests. In the other 2 cases, no collagen deposits were detected in the duodenal biopsies (including follow-up endoscopies), and the serologic tests did not support a finding of celiac disease (see Table S2, Supplementary Digital Content 2, http://links.lww.com/CTG/A336). However, at the time of this study, a weak increase in the levels of tissue transglutaminase IgA antibodies had developed in one of these 2 patients, indicating that celiac disease was under development, thereby necessitating additional diagnostic work-up.

Follow-up gastroscopies with gastric and duodenal mucosal biopsies had been performed for 11/15 patients (73%), with the median time from the diagnosis to the latest gastroscopy being 4.4 years (range, 1.4–7.4 years). None of these patients had evidence of endoscopic or histologic normalization of the gastric mucosal pathology, including persistence of >10 μm-thick subepithelial collagen deposits in gastric mucosal biopsies (see Table S2, Supplementary Digital Content 2, http://links.lww.com/CTG/A336). However, there was no worsening of the mucosal inflammation over time, and no patient developed intestinal metaplasia or advanced mucosal atrophy in the gastric corpus. Furthermore, 11/15 patients (73%) had been evaluated with at least 1 colonoscopy with multiple mucosal biopsies during the follow-up period. With the exception of 1 patient with associated collagenous colitis, no additional pathologies were noted in the colonic or ileal biopsies of the remaining patients.

Autoimmune predisposition

In total, 9/15 patients (60%) had predisposition to autoimmune disease, defined as the presence of autoimmunity-related hereditary factors and/or autoantibodies in the circulation (Table 3). Approximately half (7/15, 47%) of the study subjects had hereditary factors for autoimmune diseases among their first-degree

Table 3. Family history of autoimmune diseases, presence of autoantibodies in serum, and HLA DQ2/D8 haplotypes in the study cohort

Patient code[a]	Sex	Age (yr)	Presence of autoimmune diseases among first-degree relatives	Detected autoantibodies	HLA DQ2/DQ8 haplotype
H	F	15.7	Mother with celiac disease; father with ulcerative colitis	SMA	Negative
I	F	13.8	Mother with hypothyreosis; father with psoriasis	SMA	DQ2.5 heterozygous
J	M	8.7	Mother with hypothyreosis and latent autoimmune diabetes in adults	ANA; anti-thyroid peroxidase antibodies	DQ2.5 heterozygous
C	F	21.1	Mother with hypothyreosis	ANA	DQ8 heterozygous
D	F	22.7	Father with type 1 diabetes	Tissue transglutaminase IgA	DQ2.2 and DQ8 heterozygous
K	F	12.9	Mother with celiac disease	None	DQ2.5 and DQ2.2 heterozygous
G	M	14.8	Sister with type 1 diabetes	None	Negative
L	F	17.2	None	ANA	DQ2.5 heterozygous
F	F	17.4	None	Atypical pANCA	Negative
M	F	17.3	None	None	DQ2.2 heterozygous
N	F	11.0	None	None	DQ2.5 heterozygous
B	F	19.3	None	None	Negative
O	F	14.8	None	None	Negative
A	M	9.7	None	None	Negative
E	F	13.2	None	None	Negative

ANA, antinuclear antibody; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; SMA, antismooth muscle antibody.
[a]The codes denote the same patients as in Tables 1 and 2.

relatives. Moreover, 6/15 patients (40%) tested positive for autoantibodies. The most common autoantibody specificity detected was ANA, which was detected in a fifth (3/15, 20%) of the cohort. One patient tested positive for antithyroid peroxidase antibodies but had normal levels of thyroid hormones. None of the patients tested positive for antimitochondrial antibody, antithyroglobulin antibodies, antithyrotropin receptor antibodies, antiglutamic acid decarboxylase antibodies, anti-intrinsic factor antibodies, or antiparietal cell antibodies. More than half of the patients (8/15, 53%) carried the HLA DQ2 or DQ8 haplotypes. The most common haplotype was DQ2.5, which was detected in 5/15 (33%) patients (Table 3).

Inflammatory parameters and immunoglobulins

The plasma level of CRP was discretely increased (i.e., 9 mg/mL; reference, <5 mg/mL) in only 1 patient. By contrast, the serum levels of calprotectin and amyloid A were increased in 10/15 (67%) and 5/15 (33%) patients, respectively (Figure 1a, b). For patients with increased values, the median level of serum calprotectin was 4,550 ng/mL (range, 3,600–11,000 ng/mL; reference, <2,300 ng/mL) and that of amyloid A was 22 mg/L (range, 12–55 mg/L; reference, <11 mg/L), respectively. In 4 of the 5 patients with elevated SAA, serum calprotectin was concurrently increased (Figure 1c); one of these patients also had an increased level of CRP. Moreover, serum calprotectin showed a strong positive correlation with the absolute neutrophil counts in the blood (Figure 1d), although the blood total leukocyte and absolute neutrophil counts were not above the reference range in any patient. The serum level of albumin was slightly decreased (i.e., 32 g/L) in 1 patient, and no patient showed increased serum levels of orosomucoid. A retrospective chart review revealed that erythrocyte sedimentation rate (ESR) had been analyzed in 14/15 (93%) and CRP in 13/15 (87%) patients during the disease course, in many cases repeatedly, and normal values were detected in all the patients.

No patient had total serum levels of immunoglobulins consistent with hypogammaglobulinemia or selective IgA deficiency, although slightly decreased levels of IgG and IgA were seen in 3 patients (see Table S3, Supplementary Digital Content 3, http://links.lww.com/CTG/A337). None of the patients in the cohort had high levels of IgG4 in sera indicative of IgG4-related disease.

DISCUSSION

In this population-based study, we have investigated the clinical, endoscopic, and histologic characteristics of childhood-onset CG in a cohort of 15 patients during a median follow-up period of 6.2 years from the initial presentation. The results of this study support the view that CG in children follows a chronic disease course and has a skewed sex distribution, with female predominance (41). Furthermore, although more than half of the patients had hereditary factors for autoimmune diseases and/or had developed autoantibodies, the development of autoimmune comorbidities early in the disease course of CG was not seen. A novel finding was that despite normal levels of plasma CRP, the level of serum calprotectin was increased in two-thirds of the patients and the level of SAA was increased in one-third of the patients, indicative of systemic inflammation.

To the best of our knowledge, this is the largest cohort of CG with longitudinal follow-up reported to date, and this is the first

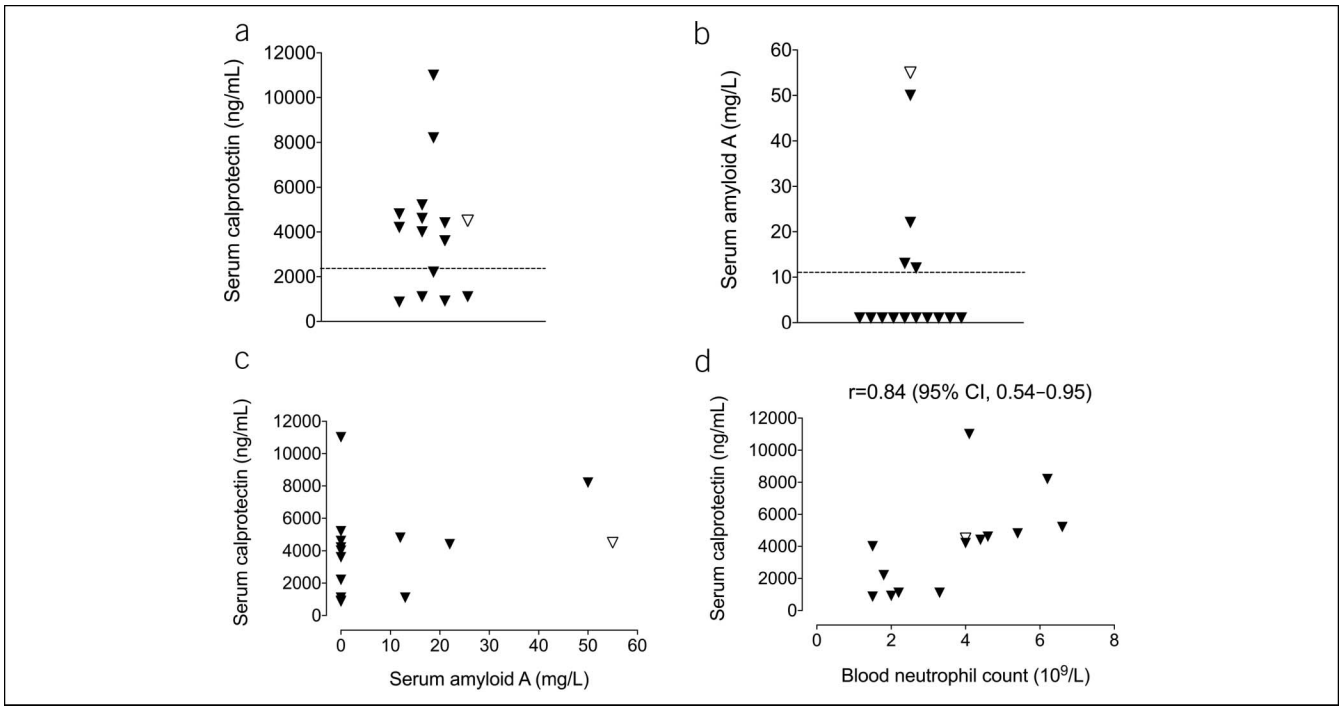

Figure 1. Levels of (**a**) serum calprotectin and (**b**) serum amyloid A in the cohort of 15 patients with childhood-onset collagenous gastritis. The cutoffs (indicated by dashed lines) applied were ≥2,300 ng/mL for serum calprotectin and ≥11 mg/L for serum amyloid A, respectively. The analysis method for serum amyloid A had a detection limit of 11 mg/L and the values below that level are given as zero. Relationship between serum levels of calprotectin and (**c**) serum amyloid A and (**d**) blood absolute neutrophil counts (n = 14). The correlation coefficient (*r*) with 95% confidence interval (CI) was determined using the Spearman test. The open triangle indicates the single patient in the cohort with concurrent collagen colitis.

study of such a cohort with a population-based methodology that allows calculations of incidence and prevalence values. The incidence rate of childhood-onset CG is 0.25/100,000 person-years of follow-up, and the prevalence is 2.1/100,000 children aged younger than 18 years in western Sweden, which substantiates the idea that this is a rare disease. Furthermore, the incidence rate of childhood-onset CG was approximately 4-fold higher in female patients than in male patients, supporting the notion that there is female predominance in the childhood-onset type of CG. The skewed sex distribution has previously been suggested by aggregated data from published reports of CG for both the pediatric age group (41) and the whole (i.e., pediatric and adult combined) population (1). For the associated condition of collagenous colitis, female predominance is well documented in population-based studies in adults, reporting female-to-male ratios of up to 9:1 (55–58).

Approximately half of the patients in our cohort exhibited heredity for autoimmune diseases among their first-degree relatives, and 40% had developed autoantibodies. These findings support the view of an autoimmune/immune-mediated mechanism underlying the disease process, as previously indicated mainly by the frequent association with autoimmune comorbidities, such as celiac disease, in adults with CG (1,32). The frequency of heredity for autoimmune diseases observed in the present study is high, considering the estimated prevalence of autoimmune diseases in the Scandinavian general population of <10% (59–61). Similarly, the prevalences of the 2 most frequently observed autoantibody specificities in our study, ANA (20%) and antismooth muscle antibody (13%), can be compared with reported frequencies of <5% for the same autoantibodies in healthy children (62,63). Interestingly, the rate of autoantibody development is comparable with that reported for collagenous colitis in adult studies, e.g., ANA positivity in 10%–26% of the patients (64,65).

Although the frequencies of heredity for autoimmune diseases and autoantibody development in our cohort are relatively high, none of the patients developed any autoimmune disease during the follow-up period, which extended up to 11 years from the initial presentation. To our knowledge, in the English-language, peer-reviewed literature to date, 10 cases with development of concomitant autoimmune disease (22–24,26,31) among a total of 79 pediatric cases of CG have been reported (15–24,26–37,39–41,43–45). Therefore, despite the low rate of autoimmune comorbidities observed in the short term in our study, childhood-onset CG may still be associated with an increased long-term risk of developing these diseases.

Half of the patients in our cohort were HLA DQ2/DQ8-positive, which is similar to the prevalence of DQ2/DQ8 haplotypes in the general Scandinavian population (66,67). However, the DQ2.5 haplotype was detected in 33% of the patients, which can be compared with the reported frequency for this haplotype of 20%–25% in healthy controls in Scandinavian studies (52,67,68). There are no previous studies on the prevalence of the HLA DQ2/DQ8 in patients with CG. Notably, however, the frequency of the DQ2.5 haplotype in adult patients with collagenous colitis has been reported as 32%–45% (52,69,70), with 1 report providing data to support an association between the DQ2.5 haplotype and an increased risk of collagenous colitis (52).

A novel finding of the present study is that the serum levels of calprotectin and amyloid A are increased in two-thirds and one-third of the patients, respectively. This suggests that serum

calprotectin in particular, but also SAA, is more sensitive than CRP for estimating the severity of inflammatory activity in patients with CG. To our knowledge, serum calprotectin and SAA have not previously been investigated in relation to CG. Although a few previous reports have provided data on inflammatory markers in childhood-onset CG, those studies have limited themselves to examining CRP and ESR (16,31–34,39,41). In keeping with our results, those previous studies have demonstrated normal levels of CRP and/or ESR in children with isolated CG.

Serum calprotectin and SAA have been proposed as complementary blood biomarkers to CRP and ESR for monitoring disease activity in other inflammatory conditions, such as rheumatoid arthritis (71–75) and inflammatory bowel disease (71,76–79). Calprotectin is produced by activated neutrophils and monocytes both locally at the site of inflammation and in the circulation (80), but the acute-phase protein SAA is synthesized by the hepatocytes in the liver (81). Although the increased serum levels of calprotectin noted in the present study may reflect in part local mucosal inflammation, the increased levels of SAA are indicative of systemic inflammation. Moreover, the positive association observed between serum calprotectin levels and blood absolute neutrophil counts has previously been reported for patients with inflammatory bowel disease (79) and cardiovascular disease (82).

In our cohort, the collagenous inflammation was confined to the stomach in all but 2 patients who had concurrent collagenous duodenitis and colitis, respectively. This rarity of concurrent collagenous inflammation in other parts of the digestive tract is consistent with the compiled results of previous pediatric reports. Overall, 79 pediatric patients with CG have, to our knowledge, been reported in the peer-reviewed, English-language literature to date (15–24,26–37,39–41,43–45). Of these, only 7 patients have concurrent collagenous colitis (22–24,26,40) and 4 patients have concurrent collagenous inflammation in the small bowel (17,23,24,39). In 3 additional reported cases, the collagenous inflammation affects all 3 locations in the gastrointestinal tract (24,30,35). This contrasts with adult patients, in whom CG is predominantly seen in combination with collagenous inflammation engaging the small bowel and/or colon (1,23,24).

The pathologic endoscopic and histologic features of CG persisted in all the study participants for whom follow-up endoscopies were performed, indicating a chronic disease course without spontaneous improvement. The endoscopic picture was dominated by mucosal nodularity, hypertrophic gastric folds, and erythema, which have been reported also by others as the most common findings in cases of childhood-onset CG (22–24,41). Histologically, a variation in the thickness of the subepithelial collagen bands in the gastric mucosa was noticed between different patients and longitudinally in the same patient. This might be attributable to sampling bias and the patchy distribution of subepithelial collagen bands in the gastric mucosa. The same explanation might be forwarded for the spontaneous "resolution" of collagen deposits previously reported for a few patients with CG (23).

Regarding the inflammatory cell infiltrate in the gastric mucosa, the histologic profiles of most of the patients were characterized by an eosinophil-rich inflammation, whereas increased intraepithelial lymphocytosis was seen in only 1 patient at diagnosis. This is in line with previous histopathologic studies, in which an eosinophil-rich inflammatory infiltrate was apparent in 50%–62% of the children with CG, but a lymphocytic gastritis-like pattern was seen in $<$10% of the cases (23,24). The opposite has been noted in adults with CG, in whom the eosinophil-rich inflammation seems to be less prevalent, whereas the lymphocytic gastritis-like pattern may be more common, as compared with children with CG (23,24).

Iron deficiency anemia was the dominant feature in the clinical picture of childhood-onset CG in this study. It was observed in approximately 90% of the patients at the initial presentation. Furthermore, iron deficiency with or without associated anemia showed a high rate of recurrence. Our results are in accordance with the few small case series of childhood-onset CG published to date, which have reported a variable prevalence of anemia (up to 92%) at presentation (22–24). The recurrence of iron deficiency has also been reported to be common (21,22). It is plausible that the high prevalence of iron deficiency observed in our cohort is attributable to CG *per se* rather than the result of other potentially biasing factors, such as dietary iron deficiency or menstrual blood loss.

The mechanism(s) leading to iron deficiency in (childhood-onset) CG remain unclear. Although understanding this mechanism was not the focus of our study, our data indicate neither overt nor occult gastrointestinal bleeding as underlying causes in most patients. Nonetheless, it has been previously suggested that iron deficiency associated with CG is because of chronic bleeding from dilated capillaries entrapped in the collagen layer of the gastric mucosa (27). Although clinical and/or endoscopic evidence of gastric bleeding has been noted in some cases (17,22–24,28,34), most children with CG seem to lack such signs. Instead of occult bleeding from the gastric mucosa, one can speculate that the iron deficiency in these patients results from decreased iron absorption due to gastric hypochlorhydria or other mechanisms.

Although a few cases of CG and associated common variable immune deficiency (4,24) or selective IgA deficiency (5) have previously been reported, such cases were not detected in our cohort. Moreover, we found no evidence of underlying IgG4-related disease in any of our patients because none of them had increased serum levels of IgG4. An indication of an IgG4-related disease mechanism was previously found in 1 patient with CG who had IgG4-positive plasma cells in the gastric mucosa (23).

One of the main strengths of the present study is the comprehensive clinical, endoscopic, and histologic characterization of the patients with childhood-onset CG. Furthermore, all eligible patients in a population-based setting were included. In addition, detailed follow-up data were available for all patients regarding the clinical course and endoscopies, with the longest median follow-up time reported for a cohort of patients with CG. A potential limitation is the relatively small sample size, which is mitigated by the rarity of the disease.

The main clinical significance of the present study is that it highlights the chronic nature of CG in children, thereby motivating long-term monitoring and follow-up of these patients. Awareness must be heightened regarding the potentially increased long-term risk for autoimmune/immune-related diseases. Furthermore, CG should be suspected in all children with unexplained iron deficiency anemia, and an upper endoscopy needs to be considered, even in an otherwise asymptomatic patient.

In conclusion, this study shows that childhood-onset CG is rare, follows a chronic disease course, and has a skewed gender distribution with female predominance. Although signs of autoimmune predisposition were frequent, early development of autoimmune comorbidities seems to be a rare phenomenon in childhood-onset CG. Serum calprotectin and amyloid A may represent novel markers of inflammatory activity in CG.

CONFLICTS OF INTEREST

Guarantor of the article: Robert Saalman, MD, PhD.
Specific author contributions: T.K. and R.S.: planning and conducting the study, data acquisition, analysis and interpretation, and drafting the manuscript. C.W.: planning the study, data interpretation, and drafting the manuscript. C.L.: planning the study, data interpretation, and critical review of the manuscript. A.W. and M.W.: data acquisition and interpretation, and critical review of the manuscript. B.D.B., R.A., J.H., and J.A.: data acquisition and critical review of the manuscript. All the authors approved the final draft.
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Study Highlights

WHAT IS KNOWN

- ✓ CG is a rare gastrointestinal disorder characterized histologically by inflammation of the gastric mucosa together with increased subepithelial deposition of collagen.
- ✓ The clinical picture seems to differ between childhood-onset and adult-onset disease.

WHAT IS NEW HERE

- ✓ The incidence rate of childhood-onset CG in western Sweden was 0.25/100,000 person-years of follow-up and significantly higher for girls than for boys, whereas the disease prevalence was 2.1/100,000 in children younger than 18 years old.
- ✓ Childhood-onset CG seems to have a chronic disease course without endoscopic or histologic improvement and is associated with a high frequency of recurrent iron deficiency.
- ✓ Although heredity for autoimmune disorders and autoantibodies were commonly detected in the CG cohort, early development of autoimmune comorbidities was rarely observed.
- ✓ No clear evidence of an association between childhood-onset CG and HLA DQ2/DQ8 haplotypes was found.
- ✓ Increased serum levels of calprotectin and amyloid A were commonly observed and could be useful as markers for monitoring disease activity.

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