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Original Article

Celiac disease prevalence in patients with hydatid cyst

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Abstract

Aim: Hydatid cyst (HC), which is localized in the liver and lungs in most cases, has been associated with a variety of hematologic and biochemical manifestations. Celiac disease (CD) is a small-intestinal malabsorption syndrome caused by hypersensitivity to gluten in subjects who carry the HLA haplotypes HLA DQ2 and DQ8. This study has attempted to show the connection between CD and HC.
Material and Methods: We prospectively analyzed data from 211 HC patients, 62 of whom had extrahepatic involvement of HC; in addition, we also classified the patients' hydatid cysts by their radiologic features. All patients tested positive for HC by ELISA. Sera from the study population were also analyzed for IgA and IgG with ELISA using human recombinant tTG (AESKU. Diagnostics, Germany); the data were then analyzed statistically.
Results: Twelve cases of seropositivity of TTG IgA were found among patients with HC. In the control group, the rate of TTG IgG seropositivity was only 2 out of 211 patients (~2%), which was lower than those with HC. In patients with HC, the mean WBC level was higher in patients with TTG IgA seropositivity compared with those without TTG IgA seropositivity. Younger ages were independently associated with TTG IgA seropositivity in the HC group.
Conclusion: This study furthers the understanding of CD risk in HC. If confirmed by future studies, the study's data will assist in developing optimal strategies for the detection of CD in patients with HC. Understanding the infectious factors involved in CD is important for identifying new approaches to the early detection of CD.

Keywords: Celiac Disease; Hydatid Cyst; TTG IgA.

INTRODUCTION

Hydatid cyst (HC) in humans results from the larval stages of taeniid cestodes of the genus Echinococcus. The most prevalent areas for cystic echinococcosis in human and animal hosts are foundin warm-climate areas, including southern South America, the entire Mediterranean basin, southern and central portions of the former Soviet Union, central Asia, China, Australia, and some parts of Africa (1,2). Celiac disease (CD) is a chronic small-intestinal malabsorption syndrome that is caused by gluten hypersensitivity; the prevalence of CD averages roughly 1% of the general population worldwide. Environmental factors play a key role in immune attacks to the endothelial barrier of the duodenum, a leading area in lymphocyte-dependent inflammation that is associated with duodenal injury after gluten ingestion. Blocking gluten consumption through the intestine is thus an effective approach to treating CD (3); a recent study (4) also demonstrated that the commensal bacteria found in the gastrointestinal tract (i.e., the gut microbiota) were important for the development of autoimmunity in rodent models. Despite evidence that bacterial infections of the gut are associated with increased immune response, the impact of parasitic liver disease on CD has not been well characterized, and limited data exists on the prevalence of CD in patients with HC.

MATERIAL and METHODS

We prospectively analyzed data from 211 HC patients (mean age 36.2 ± 19.4 years; 87 male), 62 of whom had extrahepatic involvement of HC. In addition, patients' hydatid cysts were classified by their radiologic features (49 type 1, 42 type 2, 40 type 3, 18 type 4, and 9 type 5).

The comparator group (100 subjects; 50 male; mean

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age 38.5±18.6 years) was selected from subjects who had been admitted to our internal medicine clinic for other reasons. Patients with prior diagnosis of CD were excluded from the study. Because selective IgA deficiency occurs in up to 1 in 40 patients with CD, total IgA levels were determined in addition to specific IgA autoantibody levels.

Clinical laboratory results for biochemical and hematological tests were obtained from medical records. Radiologic classification of the patients' HC was conducted by ultrasound imaging of the liver.

Serologic Tests

Serum samples of patients suspected to have HC were sent from various clinics to a parasitology laboratory. The indirect hemagglutination test (IHT; Fumouze Laboratoires, France) was used to determine the presence of anti - Echinococcus granulosus antibodies according to the manufacturer's instructions. The sera were diluted to 1/80, 1/160, 1/320, and 1/640 and like increments in U-based microplates. After two hours of incubation with an antigen erythrocyte suspension, the precipitate was incubated until the point that it was evaluated as negative, while widespread and irregular agglutination was evaluated as positive. As mentioned in the test kit's procedure, values of 1/320 and above were also considered to be positive. The sera from patients and the control group were analyzed for IgA and IgG with ELISA using human recombinant tTG (AESKU. Diagnostics, Germany).

The sera from HC patients and control subjects were also analyzed for IgA and IgG with ELISA using human recombinant tTG (AESKU.Diagnostics, Germany). Aeskulisa tTg-A and tTg-G are solid-phase enzyme immunoassays used for the quantitative and qualitative detection of IgA-IgG antibodies against neo-epitopes of tTG in human serum. The assay that employed human recombinant transglutaminase crosslinked with gliadin-specific peptides displayed neo-epitopes of tTg, which ensures a significantly increased sensitivity and specificity of the test. The assay is a tool for the diagnosis and monitoring of celiac disease, also known as gluten-sensitive enteropathy.

Test description: Serum samples diluted to 1:101 were incubated in the microplates coated with the specific antigen. Patients' antibodies, if present in the specimen, bound themselves to the antigen. The unbound fraction was washed off in the step that followed. For conjugated horseradish peroxidase, the unbound conjugate was washed off in the next step. The addition of TMB-substrate generated an enzymatic colorimetric (blue) reaction, which was stopped by diluted acid; the color then changed to yellow. The intensity of the color formation from the chromogen is a function of the amount of conjugate bound to the antigen-antibody complex, which is proportional to the initial concentration of the respective antibodies in the patient sample.

Statistical Analysis

Differences in patient characteristics were assessed with chi-square tests and t-tests for categorical and continuous factors, respectively.

RESULTS

Among the study population, the mean age was significantly lower among males than among females (32.16±19.2 versus 39.19 ±19.16 years, respectively; p= 0.009). The mean hemoglobin and eosinophil levels among females were significantly lower compared to males (13.01±1.47 versus 14.3 ± 4.67; p=0.005; 363 ±476 versus 659 ±1144; p=0.014, respectively). No significant differences between genders were found in regard to other laboratory and radiologic parameters (all p<0.05). Among the study patients, 62 (29.4%) had extrahepatic HC. Around half (36 patients; 50%) had pulmonary involvement of HC. The only factor that was significantly associated with pulmonary HC was lower serum albumin levels (3.36±0.8 versus 3.9 ±0.65; p=0.043).

Twelve cases (5.7%) of seropositivity of tTG IgA were found among patients with HC. In the control group, the rate of tTG IgA seropositivity was only 2 cases (~2%),which was lower than for those with HC (p<0.05). In patients with HC, mean WBC levels were higher in patients with tTG IgA seropositivity compared with those without seropositive tTG IgA (11,333/mm³ versus 8,401/mm³; p=0.05), while younger ages were independently associated with tTG IgA seropositivity in the HC group (36.91±9.4 versus 25.8± 15.4years; p=0.043) Notably, the presence of tTG IgA antibodies in HC patients was not found to be related to age, gender, or extrahepatic involvement (all p>0.05). Further characteristics of the patients and control subjects are presented in tables 1 and 2.

DISCUSSION

Cystic echinococcosis (CE or HC) is caused by larvae of Echinococcus granulosus. It is one of the most important zoonotic diseases to cause morbidity and mortality among humans. The disease has worldwide distribution but is especially common in developing and undeveloped countries (5,6). The life-cycle involves two hosts: definitive and intermediate. The adult forms are found in the small intestine of canids, while the larval forms are found in the internal organs of humans and many other mammals. Humans generally become infected through the accidental ingestion of parasitic eggs derived from the final hosts (5,7). Eggs of the parasite hatch in the small intestine, where the larvae are released; they then penetrate the intestinal wall and migrate through the bloodstream to various organs: most commonly the liver, followed by the lung and brain. The larvae develop into a hydatid cyst that gradually grows (8).

The disease may remain asymptomatic for years. The appearance of clinical manifestation will vary depending on the size of the cyst and the organ in which it is located

[9]. Radiographic and serological studies are mainly used for the diagnosis of CE. The infection causes labor losses and serious damage to national economies because of the expensive diagnostic tests, surgical and drug treatment, and hospitalization duration related to the disease (10).

The pathogenesis of CD has both genetic (HLA haplotypes DQ2 and DQ8) and environmental factors. A patient's small-intestinal system produces mucosal antibodies (particularly IgA) to combat the gliadin subfraction of gluten when wheat-related gluten is ingested in the diet. These pathological immune reactions result in small-intestinal inflammation as well as mucosal breakthrough (11). CD may present with a range of symptoms and findings, including malnutrition, osteoporosis, iron-deficiency anemia, and increased mortality (12, 14). The prevalence of CD has reached roughly 1% of the general population worldwide, although there are significant regional and racial differences.

The prevalence/rate of CD diagnoses has increased in recent decades; this is likely due to targeted screening programs, particularly of first-degree relatives and patients with type 1 diabetes (15). Kondrashova et al. (16) showed that lower economic status and environmental factors were associated with a lower prevalence of CD, even among people with the same racial ancestry.

The majority of undiagnosed CD patients present at advanced stages that are not amenable to curative therapies. Catassi et al. (17) found a 3.1-fold excess of non-Hodgkin lymphoma (NHL) among Italian individuals with undiagnosed CD and a 16.9-fold excess for gut lymphoma. There is thus an urgent need for novel screening strategies to prevent complications of CD.

Pang et al. (18) recently showed that the percentage of Th9 cells and IL-9 cytokine levels were significantly increased amongthe CE patients examined in their study; after surgical treatment and the administration of albendazole, the percentage of Th9 cells and IL-9 cytokine levels were found to be significantly decreased.

Du Pré and Sollid (19) have also shown that within the small-bowel mucosa, gluten epitopes are presented to CD4+T cells through HLA-DQ2 and HLA-DQ8, thus leading to gliadin-induced T-cell activation. While there is growing evidence that the commensal bacteria in the gastrointestinal tract (i.e., the gut microbiota) influence the development of autoimmunity in rodent models, little is known about the interaction of helminthic diseases of the liver and the small bowel in human immune-mediated diseases (4). In addition, a significant number of patients with chronic liver diseases of different etiologies have been found to have detectable CD-related autoantibodies, particularly of IgA anti-DGP and IgA anti-tTG (20).

In the current study, the rate of tTG IgA seropositivity in patients with HC was found to be higher than those without HC. One potential explanation for this unique phenomenon is that relatively high levels of T-helpers and elevated cytokine expression may have contributed to higher rates of seropositivity for tTG IgA among patients with HC.

And, because of the lower hygienic status and general poverty of the study patients, those patients with HC may have been predisposed to gluten-sensitive enteropathy, which then caused increased rates of CD among patients with HC. In addition, given its role as an immunogenic agent, we speculate that HC causes a tTG IgA response from the small-intestinal mucosa. It is also tempting to speculate that chronic cross-reactivity with HC might cause higher rates of tTG autoantibody levels in the serum.

Young patients with early-stage CD may have significantly elevated blood-leucocyte levels. This suggests that there is greater inflammatory response than expected or that the removal of microbial products from the blood is less effective than is the case with normal subjects (21,22).

In the current study, the correlation between leucocyte levels and tTG IgA seropositivity suggests that a broad activation of white blood cells takes place in CD patients, possibly in response to microbial products. Taken together, the study data suggests that the presence of leukocytosis among younger patients may be an important indicator of CD in patients with HC.

This study does have certain limitations. First, we did not perform duodenoscopy with histopathological examination for patients who tested positive for tTG IgA; second, due to the limited sample size of the control group, the true number of CD cases may have been higher than estimated.

This study also has several strengths. In addition to examining tTG IgA seropositivity in a large number of HC patients, the trial attempted to show the connection between key laboratory parameters and tTG IgA seropositivity among a unique patient group. For the first time, this trial also showed that the rate of CD was higher in patients with HC, which indicates that the HC is not only a parasitic infection of the liver but is also a key player for developing CD.

In summary, further characterization of these mechanisms might provide a broader application for novel preventive approaches for CD.

Table 1. Baseline characteristics of the patients and descriptive statistics according to gender

		N	Mean	Std.Dev	Min	Max	p
Gender	1	87	32,16	19,20	80	2	,009
	2	124	39,19	19,16	82	6	
	Total	211	36,29	1944	21800,0	2	
WBC1 (uL)	1	87	8498,002	3653,27	21800,0	8,7	,959
	2	121	8523,231	3385,74	22800,0	10,9	
	Total	208	8512,678	3491,47	22800,0	8,7	
Hemoglobin (g/dl)	1	87	14,306	4,67	47,8	7,9	,005
	2	121	13,018	1,47	16,8	9,3	
	Total	208	13,557	3,27	47,8	7,9	
Hematocrit (%)	1	87	2925,769	26905,60	251000,0	24,4	,239
	2	121	39,159	4,40	53,3	28,0	
	Total	208	1246,539	17400,94	251000,0	24,4	
Eosinophil(%)	1	84	,659	1,14	6,10	,00	,014
	2	113	,363	,47	3,50	,00	
	Total	197	,4898	,84	6,10	,00	
PLT2 (uL)	1	87	288804,60	112216,55	712000	76000	,732
	2	121	293727,27	94586,38	642000	43000	
	Total	208	291668,27	102098,18	712000	43000	
Glucose (mg/dl)	1	77	97,31	23,09	173	62	,419
	2	94	101,31	37,87	422	71	
	Total	171	99,51	32,04	422	62	
AST[3](U/L)	1	79	34,54	34,97	283	10	,152
	2	114	28,53	23,23	184	11	
	Total	193	30,99	28,69	283	10	
ALT[4] (U/L)	1	80	31,75	37,33	265	7	,550
	2	118	28,42	39,08	270	6	
	Total	198	29,77	38,32	270	6	
Albumin (g/dl)	1	43	3,677	,76	4,7	2,0	,047
	2	50	3,966	,62	5,1	2,1	
	Total	93	3,832	,70	5,1	2,0	
Globulin (g/dl)	1	28	3,132	,98	6,1	1,6	,614
	2	34	3,241	,71	6,0	2,3	
	Total	62	3,192	,83	6,1	1,6	
ALP[5] (U/L)	1	58	243,64	305,55	1697	15	,025
	2	84	156,87	143,33	1012	37	
	Total	142	192,31	227,30	1697	15	
GGT[6] (U/L)	1	53	48,82	53,61	265	4	,995
	2	81	48,75	66,88	386	5	
	Total	134	48,78	61,76	386	4	
Caudocranial Diameter of Cyst (mm)	1	77	5,94	3,99	20	1	,567
	2	93	6,28	3,64	18	1	
	Total	170	6,13	3,80	20	1	

[1] white, blood cell, [2] platelet, [3] aspartate transferase, [4] alanine transferase, [5] alkaline phosphatase, [6] gamma glutamyl transpeptidase
1:male 2:female

Table 2. Descriptive statistics according to tTG IgA and comparison results (0: tTg Ig A negative; 1: tTg Ig A positive)

		N	Mean	Std. Deviation	Minimum	Maximum	p.
Age	0	199	36,92	19,418	82	2	,050
	1	12	25,83	17,487	60	6	
WBC (uL)	0	196	8401	3251,6165	21800,0	8,7	,043
	1	12	11333	6175,2193	22800,0	4000,0	
Hemoglobin(g/dl)	0	196	13,546	3,3617	47,8	7,9	,855
	1	12	13,725	1,3363	16,0	11,0	
Hematoctrit(%)	0	196	1320,314	17925,7218	251000,0	24,4	,805
	1	12	41,550	3,9903	49,2	36,0	
Eosinophil (%)	0	186	,4925	,86227	6,10	,00	,857
	1	11	,4455	,28058	,90	,20	
Platelet (uL)	0	196	290147,96	103799,874	712000	43000	,387
	1	12	316500,00	66683,104	411000	151000	
Glucose (mg/dl)	0	160	100,33	32,848	422	62	,201
	1	11	87,55	11,699	100	71	
AST (U/L)	0	181	30,88	29,035	283	10	,835
	1	12	32,67	23,937	103	16	
ALT (U/L)	0	186	29,73	38,837	270	6	,952
	1	12	30,42	30,714	122	10	
Albumin (g/dl)	0	82	3,804	,7436	5,1	2,0	,287
	1	11	4,045	,1368	4,3	3,9	
Globulin (g/dl)	0	52	3,150	,8998	6,1	1,6	,373
	1	10	3,410	,3348	4,0	3,0	
ALP(U/L)	0	132	192,33	234,706	1697	15	,996
	1	10	192,00	87,551	310	87	
GGT (U/L)	0	124	49,58	63,841	386	5	,601
	1	10	38,90	23,492	80	4	
Caudocranial size of cyst (mm)	0	159	6,09	3,815	20	1	,596
	1	11	6,72	3,696	12	1	

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