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ORIGINAL ARTICLE

Prevalence of celiac disease serological markers in a cohort of Italian rheumatological patients

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ABSTRACT

Aim: To assess the prevalence of celiac disease (CD) serological markers in a cohort of patients referred to an Italian rheumatological outpatient clinic.

Background: Current guidelines do not suggest CD screening in patients with rheumatological diseases and these subjects are not considered to be at high risk for CD.

Methods: A total of 230 sera of rheumatological patients referred to the Division of Internal Medicine at the Department of Medical and Surgical Sciences between January 2005 and December 2013 were screened for CD by testing IgA antitransglutaminase (TTG IgA), IgG deamidated gliadin peptides (DGP IgG) and IgA antiendomysium (EMA) antibodies. Of the 230 patients tested, 67 had a diagnosis of rheumatoid arthritis (RA), 52 Sjögren's syndrome (SjS), 42 systemic sclerosis (SCL), 35 systemic lupus erythematosus (SLE), 15 mixed connective tissue disease, 11 polymyositis and 10 dermatomyositis.

Results: TTG IgA antibodies were identified in 7/230 cases (3%), 3 in SjS (3/42 – 5.8%), 2 in SCL (2/42 – 4.8%), 1 in RA (1/67 – 1.5%) and 1 in SLE sera (1/35 – 2.8%). All the seven sera were also positive for DGP IgG and EMA IgA. DGP IgG were the most frequent antibody detected, being found in 16 (7%) sera.

Conclusion: This study identified a high prevalence of CD antibodies in adult patients referred to a rheumatology outpatient clinic. These results highlight the importance of CD screening in subjects presenting with rheumatological features.

Keywords: Celiac disease, Rheumatological disorders, Screening, Anti-transglutaminase antibodies, Anti-deamidated gliadin peptide antibodies, Anti-endomysium antibodies.

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Introduction

Celiac disease (CD) is an immune-mediated systemic disorder evoked by gluten ingestion in genetically predisposed individuals and is characterized by a variable combination of intestinal and extraintestinal manifestations (1). Nowadays, the concept that CD can be associated with a number of autoimmune diseases is well known (2). The possible explanations for this spread of autoimmunity may be the ubiquitous distribution of tissue transglutaminase-2 (TG2) in various tissues in addition to the small bowel (3) and a common genetic susceptibility. Indeed, HLA-DQ2/DQ8 aplotype and HLA-B8DR3/DR4 region (associated with several autoimmune disorders) are in close linkage disequilibrium (4, 5). In this line, the association between CD and autoimmune rheumatological diseases, in particular Sjögren's syndrome (SjS), has been demonstrated in several studies (6-12), but this linkage remains still

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controversial with other autoimmune diseases, such as systemic lupus erythematosus (SLE) (13-16), systemic sclerosis (SCL) (17, 18), rheumatoid arthritis (RA) (19-23), polymyositis (PM) and dermatomyositis (DM) (24-26). CD screening in patients with autoimmune diseases, such as type 1 diabetes mellitus, autoimmune thyroiditis and autoimmune liver disease (e.g. primary biliary cholangitis) is recommended by the scientific community (27), however, CD serology is rarely sought in patients with rheumatic disease.

Although a gluten-free diet (GFD) did not show efficacy in modifying the natural history of rheumatic diseases, the detection of CD in these patients is useful to ensure the improvement of associated symptoms, reduce the risk of osteoporosis, restore intestinal absorption of immunosuppressive drugs and prevent CD-related complications. Nonetheless, current clinical guidelines do not recommend CD screening in patients with rheumatological manifestations (1).

The present study was aimed to determine the prevalence of CD specific antibodies in the sera of a cohort of patients referred to an Italian rheumatological outpatient clinic.

Methods

Population study

We performed a serological cross-sectional study on left-over sera from blood samples taken for diagnostic purposes. An existing serum bank was identified in the Clinical Immunology Laboratory of the University of Bologna. The serum samples were selected with the following criteria: a) adults (target group > 18 years of age); and b) any autoimmune rheumatological diagnosis at the time of storage. Sera had been previously collected over a period of 9 years (from January 2005 to December 2013). Each serum sample was completely anonymous and labeled only with a clinical diagnosis made by the rheumatology outpatient clinic according to the American College of Rheumatology guidelines (28). Each serum was tested for anti-transglutaminase antibodies of IgA class (TTG IgA) and anti-deamidated gliadin peptide antibodies of IgG class (DGP IgG). In case of positivity of at least one of these serological tests, the serum was also tested for anti-endomysium antibodies of IgA class (EMA) (29, 30).

Serological tests

tTG test

TTG IgA were measured by a commercially available ELISA kit (EuTG IgA, Eurospital, Trieste, Italy), using recombinant human tissue transglutaminase as antigen. The cut-off value of 16 AU, provided by the manufacturer, was used (31).

DGP test

DGP IgG were assessed by commercially available ELISA kits (a-glia PEP, Eurospital, Trieste, Italy) using an entirely synthetic peptide constructed in a conformational intact manner and then selectively deamidated. According to the manufacturer's instructions, the cut-off value was set up at 10 AU (32).

EMA test

EMA IgA were evaluated by indirect immunofluorescence using as substrate human umbilical cord cryostat sections (4 mm), cut in our laboratory. Sera were tested at the initial dilution of 1:5 and, when positive, titrated to the end point (33).

Ethics

The samples were left-over anonymous sera from blood aliquots taken for diagnostic purposes. Patients gave their informed consent for research purposes at the time of the blood collection and therefore a formal ethic committee approval was deemed unnecessary..

Results

A total of 230 serum samples (42 males and 188 females; age range 18-84 years) were included in the study. Of these, 67 had a diagnosis of RA (13 M, 54 F), 52 SjS (7 M, 45 F), 42 SCL (11 M, 31 F), 35 SLE (6 M, 29 F), 15 MCTD (all female), 11 PM (3 M, 8 F) and 10 DM (2 M, 8 F) (Table 1).

TTG IgA antibodies were identified in 7/230 cases (overall prevalence 3%), 3 in SjS (3/52 – 5.8%), 2 in SCL (2/42 – 4.8%), 1 in RA (1/67 – 1.5%) and 1 in SLE sera (1/35 – 2.8%). All the seven sera also tested positive for DGP IgG and EMA IgA (Table 1).

DGP IgG were the most frequently detected antibodies, being found in 16 (7%) of the 230 tested sera. In particular, 4 were from the 52 SjS sera (7.7%), 3 (7.1%) from the 42 SCL, 2 (3%) from the 67 RA, 3 (8.6%) from SLE, 1 (9%) from the 11 PM, 1 (10%) from the 10 DM and 2 (15.4%) from the 13 MCTD (Table 1). Notably, of these 16 cases the 7 with TTG

Table 1. Study population, rheumatological diseases and celiac disease related serology.

	N of patients	Male	Female	TTG IgA +ve	DGP IgG +ve	EmA +ve	Possible CD
SjS	52	7	45	3	4	3	3
SCL	42	11	31	2	3	2	2
RA	67	13	54	1	2	1	1
SLE	35	6	29	1	3	1	1
PM	11	3	8	0	1	0	0
DM	10	2	8	0	1	0	0
MCTD	13	0	13	0	2	0	0
TOTAL	230	42	188	7 (3%)	16 (7%)	7 (3%)	7 (3%)

Rheumatoid arthritis (RA), systemic lupus eritematosus (SLE), Sjögren's syndrome (SjS), systemic sclerosis (SCL), polymyositis (PM), dermatomyositis (DM), mixed connective tissue disorder (MCTD). TTG IgA, anti-transglutaminase antibodies of IgA class, DGP IgG, anti deamidated gliadin peptide antibodies of the IgG class, EMA, anti-endomysium antibodies of IgA class, CD, celiac disease, M, male, F, female, +ve, positive serology.

Table 2. Relationship between celiac disease and rheumatological disorders.

Rheumatological disease	% general population	% of the disease in CD patients	Reference	% of confirmed or suspected CD in the disease	Reference	Serological markers used	Duodenal biopsy
SjS	0.5	3.4	Calella (10)	14.7	Iltanen (8)	AGA, EmA	Yes
		3.3	Collin (11)	0	Bizzarro (7)	TTG, EmA	Yes
				10.0	Luft (9)	TTG, EmA	Yes
				2.0	Fasano (12)	TTG, EmA	Yes
				5.8	Caio*	TTG, EmA, DGP	No
RA	0.8	1.8	Collin (11)	0	Bizzarro (7)	TTG, EmA	Yes
		2.5	Calella (10)	0.6	Francis (16)	EmA	Yes
				0	Nisihara (21)	EmA	No
				1.8	Feighery (22)	EmA	No
				2	Luft (9)	TTG, EmA	No
				0	Paimela (23)	AGA	Yes
				1.5	Caio	TTG, EmA, DGP	No
SCL	0.004	0.6	Collin (11)	8	Rosato (17)	TTG, EmA	Yes
				7	Luft (9)	TTG, EmA	No
				0	Forbess (18)	TTG, EmA, DGP	Yes
				0	Bizzarro (7)	TTG, EmA	Yes
				4.8	Caio	TTG, EmA, DGP	No
PM/DM	0.005	1.4	Volta (26)	0	Caio	TTG, EmA, DGP	No
SLE	0.02	0.3	Collin (11)	0	Rensch (14)	AGA, EmA	No
				1	Marai (13)	TTG	No
				6	Luft (9)	TTG, EmA	No
				2.8	Caio	TTG, EmA, DGP	No
MCTD	0.003	0.3	Collin (11)	0	Caio	TTG, EmA, DGP	No

Rheumatoid arthritis (RA), systemic lupus eritematosus (SLE), Sjögren's syndrome (SjS), systemic sclerosis (SCL), polymyositis (PM), dermatomyositis (DM), mixed connective tissue disorder (MCTD). In brackets the related reference.). TTG, anti-transglutaminase antibodies, DGP, anti deamidated gliadin peptide antibodies, EmA, anti-endomysium antibodies.

IgA positivity showed a very high DGP titer (> 3 times the cut-off), whereas in the remaining 9 (testing negative for TTG IgA) the DPG titer was very low (< 2 times the cut-off).

Discussion

The association between gluten enteropathy and autoimmune diseases is currently well recognized (2). Moreover, the prevalence of autoimmune diseases is known to increase with age at the time of CD diagnosis, suggesting that a delay of CD identification can contribute to the development of autoimmune disorders (34). Indeed, CD is a peculiar immune mediated disease in which a food-derived protein triggers autoimmune mechanisms. Despite the trigger antigen is an exogenous protein, CD shows features of an autoimmune disease as indicated by HLA class II association, CD4+ T lymphocyte predominance, Th17 response and circulating autoantibodies (35). Cytotoxic T lymphocyte (CD8+) can target the enteric mucosa as well as other tissues in response to several stress signals, not only to a specific antigen (36). Evidence

indicates that CD has evolved from a gastrointestinal malabsorptive condition to a systemic immune disease (37). In CD, T cells electively recognize the post-translationally modified deamidated gluten (deamidated gliadin peptides) through the ubiquitous enzyme TG2 (38). This enzyme, which is the CD autoantigen, exerts a key role in wound healing since its activity is increased by inflammation and tissue damage (39). Likewise, TG2-mediated gluten deamidation, peptidylargininedeiminase (PAD) post-translational changes represent a fundamental pathophysiological step in RA, in which B and T cells recognize citrullinated and carbamylated peptides (40). Although polymorphisms in PAD gene have been related to RA development, a correlation between TG2 genetic variants and risk of CD has not been established. To date, only some hypotheses have been proposed to explain the co-occurrence of multiple autoimmune diseases in CD patients. In this line, the "antigen spreading hypothesis" implies the "unmasking" and recognition of new epitopes by the immune system during inflammation. This cascade of events is thought to develop secondary autoimmunity (41). Newly generated epitopes are recognized by the immune system via post-translational changes induced by the ubiquitous enzyme TG2 and its isoforms.

Several studies have demonstrated a link between CD and rheumatic diseases including RA, PM, DM, SLE, SCL, SjS and MCTD (6-26). So far available data on the prevalence of CD in rheumatologic diseases are not homogeneous and most studies are based on small number of patients and case reports. From a pathogenetic standpoint, a mild inflammation of the small bowel mucosa with an increased number of intraepithelial lymphocytes (IELs) has been identified in patients with RA and SLE (20). On the other hand, an involvement of joint and muscles with fibromyalgia like symptoms have been frequently identified in patients with CD (42). IELs have been shown to migrate from the gut mucosa to joints and vice versa. Notably, CD4+ T lymphocytes detected in synovial fluid of RA patients have been demonstrated to express NKG2D, a typical IEL marker of CD patients (20). Several studies have been carried out to assess the frequency of CD markers in rheumatological diseases, with conflicting results. Discrepancies among studies are mainly due to different study design and type of serological CD markers assessed. So far, most studies identified up to 14% prevalence of CD in SjS patients, thus unraveling a close association between these two conditions (8, 9) (Table 2). This finding is also supported by the fact that CD and SjS share the same HLA DQ2/DQ8 haplotype (8). At variance with SjS, other connective tissue diseases, i.e. AR, SCL, SLE, PM, DM and MCTD, did show conflicting results about their association with CD (Table 2). Our data showed a considerable number of previously unrecognized cases of CD in a large cohort of rheumatological patients by using standardized serologic screening. High titres of CD serological markers (TTG IgA, DGP IgG and EMA) were identified in 7 rheumatological patients (3%) indicating a very high probability of CD that should be confirmed by intestinal biopsy. A limit of the present study is indeed the lack of a histological assessment not only in the 7 cases with all CD antibody positivity, but also in the remaining 9 cases with isolated DGP IgG positivity. Further to the 7 cases (3%) of highly probable CD, the other 9 cases with isolated DGP IgG positivity may raise the CD prevalence up to 7% in our study. However, the increased presence of DGP IgG might represent a false positivity as previously described for native anti-gliadin antibodies in patients with SLE (14). Further studies are eagerly awaited to clarify whether DGP IgG false positivity actually occurs in rheumatologic diseases. Given the possible association between CD and connective tissue disorders as emerged by our study, a serological screening for CD should be advised in patients with joint and musculoskeletal symptoms.

Current international guidelines for CD screening (1) do not consider patients with connective tissue disorders to be a risk group, despite growing evidence on a possible association between CD and rheumatological disorders (e.g. SjS). Among patients referred for rheumatological evaluation, we found a high prevalence of possible CD cases (displaying positivity of both TTG IgA, EMA and DGP IgG) compared with the general population (3% *vs.* 1%). Our data suggest that adult patients presenting with rheumatological features may be at risk for CD, and therefore they should be eligible for serological screening. Because of the several benefits of GFD, the identification of CD is expected to improve

immunosuppressive drug absorption thereby ameliorating the outcome of different rheumatological disorders. In conclusion, we suggest serological screening in rheumatological patients in order to identify the CD subset for which gluten avoidance should be combined with specific immunesuppressive treatment.

Conflict of interests

The authors declare that they have no conflict of interest.

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