RHEUMATOID ARTHRITIS AND ANTI-ENDOMYSIAL ANTIBODIES

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Abstract

Background: Several autoimmune diseases may occur in the same patient. Celiac disease (CD) is found in patients with *diabetes mellitus* type-1 and thyroiditis. Few studies have addressed the association between CD and rheumatic disorders such as rheumatoid arthritis (RA).
Objective: To study the prevalence of anti-endomysial antibodies in RA patients.
Methods: The presence of IgA anti-endomysial antibodies (EmA-IgA) was evaluated in 85 RA patients and in 97 healthy controls through indirect immunofluorescence using human umbilical cord as substrate.
Results: None of the RA patients or healthy controls was positive for EmA-IgA.
Conclusion: We could not find an association between RA and anti-endomysial antibodies in the studied population.

Keywords: celiac disease, gluten enteropathy, rheumatoid arthritis, anti-endomysial antibodies

Resumo

Introdução: Doenças auto-imunes podem ocorrer de maneira associada em um mesmo indivíduo. Doença celíaca (DC) com freqüência tem sido encontrada em pacientes com *diabetes mellitus* tipo-1 e tireoidites. São raros os relatos de associação entre DC e doenças reumáticas como a artrite reumatóide (AR).
Objetivo: Verificar a prevalência de anticorpos anti-endomísio em pacientes com AR.
Material e métodos: Estudou-se a presença de anticorpos anti-endomísio (EmA-IgA) em 85 pacientes com AR e 97 controles sadios, utilizando-se de técnicas de imunofluorescência indireta com cordão umbilical humano como substrato.
Resultados: Nenhum paciente com AR ou indivíduo do grupo controle sadio apresentou positividade para o EmA-IgA .
Conclusão: Não se encontrou associação entre AR e presença de anticorpos anti-endomísio na população avaliada.

Palavras-chave: doença celíaca, enteropatia glúten-induzida, artrite reumatóide, anticorpos anti-endomísio.

Introduction

Systemic or organ specific autoimmune diseases may occur simultaneously in the same person.[1] The attending physician must be alert for these associations, not only to make an early diagnosis but also to understand the overall clinical manifestations.

There is no clear-cut explanation for the associations of autoimmune diseases although it is noted that they may share a common genetic background or an exposure to a common etiological agent.[1]

Rheumatoid arthritis (RA) is an inflammatory articular disease with a particularly high incidence in the small joints of the hands and feet. RA is associated with high co-morbidity and increased mortality.[2]

Celiac Disease (CD) is an autoimmune disease that affects 0.3 to 0.5% of the general population. This is a chronic inflammatory and immunological mediated intestinal disease, genetically determined, that causes lifelong sensitivity to gluten, a cereal protein found in wheat, rye, barley and oat.[3]

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Crypt hyperplasia, villous atrophy and intra epithelial lymphocytic infiltration are the main pathological characteristics of CD.[4]

CD patients frequently develop prolonged diarrhea, abdominal pain and weight loss. Some may present iron or folate deficiency, osteoporosis, chronic fatigue, milk intolerance, dental problems, neuropathy, dementia and failure to thrive. This disease is also associated with infertility, lymphomas and other autoimmune diseases.[4] Sub clinical forms are quite common; it is not rare that CD patients with minor gastroenterological symptoms are misdiagnosed as having an irritable bowel disease or that the CD diagnosis is only detected after the investigation of iron deficiency anemia or low bone mass (osteoporosis/ osteopenia)[5].

Serological tests are valuable tools for the diagnosis of CD and may be used in the initial investigation because they are not invasive and have a high sensitivity. They can also be used to monitor treatment. Anti-endomysial (EmA-IgA) antibodies and anti-tissue transglutaminase antibodies (anti-tTG IgA) are the most commonly used. EmA-IgA antibodies have a specificity and sensitivity greater than 90% for the diagnosis of CD. The titer of these antibodies correlates with the degree of intestinal villous atrophy[6] and symptom severity.[7] The combination of serological tests with intestinal biopsy is the «gold standard» for CD diagnosis.[8]

The association between CD and other autoimmune diseases (particularly those that affect endocrine organs) such as type 1 diabetes mellitus (DM) and thyroid autoimmune diseases is common.[9,10] In Brazil, the association of CD with Type 1 DM is estimated to be 4.8%,[11] reaching 21.2% with thyroid autoimmune diseases.[12] Nevertheless, the relationship of CD with systemic autoimmune diseases such as RA is still controversial.

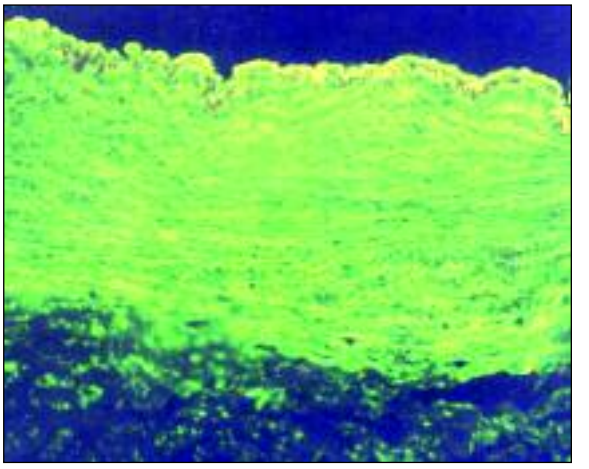
Feighery *et al.* found an 11% prevalence of anti-tTG antibodies in RA patients.[13] Song *et al.* described an anti-tTg antibodies' prevalence of 6.1% in RF positive sera.[14] Bizzaro *et al.* detected 1% prevalence of anti-tTg antibodies in RA patients.[15] However, the search for antigliadin antibodies in 40 RA patients, performed by Kochbati *et al.*, was completely negative.[16]

The aim of this study was to analyze the prevalence of IgA anti-endomysial antibodies in RA patients.

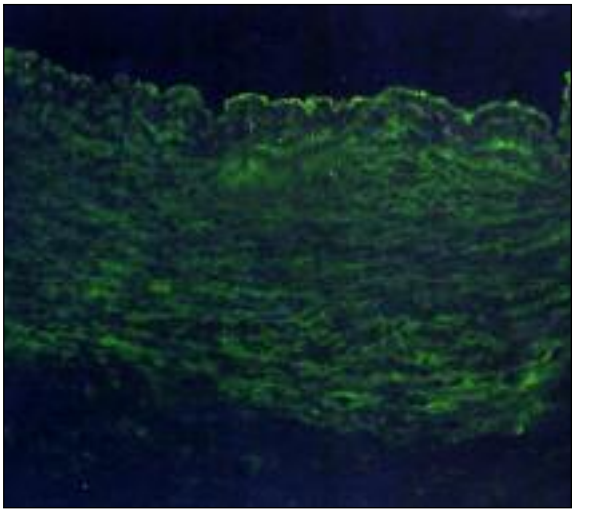
Methods

This study was approved by the local Ethics Research Committee. All patients were recruited from the Rheumatologic Unit of the Hospital Evangélico de Curitiba, Paraná, Brazil and fulfilled the American College of Rheumatology Classification Criteria for Rheumatoid Arthritis [17].

Patients: Eighty-five RA patients were included between March and October 2005, being 12.9% (11/85) males and 87.1% (74/85) females with a mean age of 47 years (minimum 23 and maximum 71 years). The patients were included in the study consecutively, as they attended the routine follow-



Positive EmA-IgA in cryostatic section of human umbilical chord (400X)



Negative EmA-IgA in cryostatic section of human umbilical chord (400X)

Figure 1. Positive and negative controls used for EmA-IgA determination.

-up. After formal consenting, 3 ml of blood were collected from each subject. Samples were centrifuged and the serum separated, aliquoted and immediately stored at -80º C until the tests were performed.

In this population, 68.3% (58/85) were RF positive. None of the patients had signs or symptoms of malabsortion at the time of inclusion.

Controls: As a control, 97 blood donors from the same geographical region, matched for age and sex, were studied.

EmA-IgA technique: All serum samples were screened for EmA-IgA by indirect immunofluorescence technique using cryostatic cuts of human samples of umbilical chord and anti-IgA fluorescent conjugate (INOVA, San Diego, USA), according to the technique described by Volta *et al*[18]. The serum was initially diluted to 1:2.5 with PBS pH 7.2**.** Positive and negative controls were included in each test battery (Figure 1).

All EmA-IgA positive patients were invited to perform an upper gastrointestinal endoscopy with duodenal biopsy for histological analysis.

Results

The EmA-IgA search was negative in all 85 RA patients tested. None of the controls were positive for EmA-IgA.

Discussion

RA is a common systemic autoimmune inflammatory disease, affecting 1% of the population[19]. A sub clinical intestinal mucosa inflammation has been described in 67% of the RA patients. This inflammation has been attributed to the use of nonsteroidal anti-inflammatory drugs in some cases[19,20].

The role of intestinal inflammation in the etiopathogenesis of RA is not well understood but it is thought that antigens from intestinal microbiota may have an arthritogenic potential[20]. There are also some isolated reports suggesting that a gluten free diet may reduce joint inflammation and that such improvement is associated with a decrease in the level of antibodies against food antigens[21].

CD, dermatitis herpetiformis, recurrent mouth ulcers and IgA nephropathy are diseases associated with gluten hypersensitivity. CD has a worldwide distribution with a higher prevalence in Anglo-Saxon and Nordic populations[22].

It is important to remember that only a minority of patients has the classical and symptomatic form of CD with diarrhea, nausea, vomiting and weight loss. Most of them have minor gastrointestinal complaints such as pain, dyspepsia, flatulence and changes in the intestinal habits. Others are totally asymptomatic from the gastrointestinal point of view[5,23].

There are some arguments in favor of a possible association between RA and CD. In fact, both diseases share a Th1 mediated physiopathology [24] and patients with RA have frequent gastrointestinal complaints that sometimes are not fully clarified[25].

In this study, the investigation of the presence of EmA-IgA antibodies in 85 RA patients failed to show any positive case. Therefore, there was no need for endoscopy and duodenal biopsy in any of them. Although intestinal biopsy is the best test for CD diagnosis, serological markers are extremely useful as screening tools due to their high sensitivity. The sensitivity of anti-tTG-IgA ELISA test and EmA-IgA indirect immunofluorescence is equivalent, although the EmA-IgA indirect immunofluorescent test has a better specificity [26,27,28]. Kotze *et al.* showed that both tests had a good correlation with results from intestinal biopsy [3].

Association between CD and systemic autoimmune diseases has been studied in patients with systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA) and Sjögren syndrome (SS), among others. Rensch *et al.* studied patients with SLE and found high prevalence of antigliadin antibodies (23.3%) but in the same study the positivity for EmA-IgA antibodies was low and patients had no clinical features of CD, so the presence of antigliadin antibodies was not considered indicative of CD[29].

A study of 151 JIA patients with a high number of hypothyroidism cases and autoimmune thyroid disease showed a 6.6% prevalence of CD[23]. In SS patients, the prevalence of anti-tTG antibodies was found to be three times more common than in the normal population. Most of these patients had some complaints[25].

There are some previous studies analyzing serological markers for CD in RA patients. Feighery *et al.* found anti-tTG antibodies in 11% of the 53 RA patients studied[13]. Bizzaro *et al.*, studying 400 patients with connective tissue disease (SS, SLE, scleroderma and RA), failed to demonstrate increased

Table I. Celiac Disease Antibodies and Rheumatic Diseases

Disease	Antibodies	Postivity	Country	Reference
SLE	Anti-gliadin	23,3%	USA	29
SLE	Anti-tTG- IgA	1%	Italy	15
JIA	EmA-IgA	6,6%	Italy	33
SS	Anti-tTG- IgA	12%	USA	25
SS	Anti-tTG-IgA	0%	Italy	15
Scleroderma	Anti-tTG- IgA	0%	Italy	15
Psoríasis	Anti-gliadin	16%	Sweden	30
Psoriatic arthritis	Anti-gliadin	17,4%	Sweden	31
RA	Anti tTG-IgA	11%	Ireland	13
RA	Anti-tTG- IgA	1%	Italy	15
RA	Anti-gliadin	0%	Tunisia	16
RA	EmA-IgA	0%	Brasil	Nisihara *et al.*

SLE: Systemic lupus erythematosus; JIA: Juvenile idiopathic arthritis; SS: Sjogrens' sindrome;
RA: Rheumatoid arthritis; Anti-tTG: Anti-transglutaminase tissue antibody;
EmA-IgA: Anti-endomysial antibody.

rates of CD[15]. Michalesson *et al* found raised CD auto-antibodies in patients with psoriasis that had showed improvement of skin lesions after being submitted to a gluten free diet[30]. Lindqvist *et al.* also found a high number of CD autoantibodies in patients with psoriatic arthritis but they didn't evaluate the effects of a gluten free diet on these patients[31]. These results are summarized in Table I. Genetic and geographical background may be responsible for the variability of the results. One should also note that the specificity of the autoantibodies used in these studies is different. Anti-gliadin antibodies and anti-tTG antibodies can be positive in other diseases such as autoimmune hepatitis and inflammatory bowel diseases[32].

In the present study no association could be found between adult RA and anti EmA –IgA antibodies. The authors conclude that a routine search for CD in RA patients is not necessary except in cases where the clinical suspicion of CD is high.

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