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Celiac disease in native Indians from Brazil: A clinical and epidemiological survey

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Abstract

Background: Celiac disease has been described in populations from around the world, with recent data emphasizing the occurrence of the disease in ethnic minorities. There are only a few studies evaluating celiac disease in native Indians. **Aims:** This study aimed to screen the anti-endomysial antibody (IgA-EmA) in Kaingang and Guarani Indians from southern Brazil, in order to establish a clinical serological evaluation of celiac disease in these individuals. **Material and Methods:** Serum samples from 321 individuals (125 male and 196 female; 4-86 years old) from Mangueirinha Indigenous Reserve, State of Parana, Brazil, and 180 non-Indigenous healthy individuals (62 male and 118 female; 2-81 years old) were analysed to the presence of anti-endomysial antibody class IgA by indirect immunofluorescence assay. Amongst the Indians, 158 were Kaingang, 98 Guarani and 65 of mixed race. Indians presenting complaints of diarrhea (N=12) were also evaluated to the IgG class of anti-endomisyal antibody. **Results:** None of the individuals showed positive results either to IgA or IgG anti-endomysial antibodies. **Conclusions:** Although the results indicate an absence of celiac disease in Kaingang and Guarani Indians, the authors call attention to the importance of following up indigenous children or adults presenting gastrointestinal complaints or other symptoms related to the disease. Consideration should be given to the genetic background of these individuals, allied to the inter ethnic marriages and the changing habits or occupational activities, that have gradually introduced diseases previously not described in indigenous populations.

Keywords: Celiac disease, Kaingang Indians, Guarani Indians, Brazilian Indians, anti-endomysial antibodies.

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Introduction

Celiac disease (CD) is one of the most common immune mediated disorders. It is a chronic enteropathy, with genetic, environmental and autoimmune components, triggered by the ingestion of wheat gluten and other related proteins. HLA-DQ2 is found in up to 95% of CD patients, and the HLA-DQ8 in most of the remaining patients [1, 2].

Clinically, CD varies greatly, and is now considered to resemble a multisystemic rather than a gastrointestinal disorder. It can be found in classical, atypical, silent and latent forms. While the classical form is characterized by chronic diarrhea and malnutrition, in the atypical form of CD extraintestinal features such as osteoporosis, infertility, anemia, short stature and neurological problems can also be found [3].

The development of accurate serological tests for CD over the last decades, such as the antiendomysial and anti-tissue transglutaminase antibodies provided a valuable tool for screening individuals, in as much as the general population as in CD high risk groups [4,5]. CD was considered to be of low-prevalence until the 1950s, but currently, due to the availability of high sensitivity and

specificity diagnostic tests, its prevalence has been shown to be much higher than previously thought.

CD has a worldwide distribution, being described in different ethnic groups from North and South America, Europe, south and west Asia, Australia and New Zealand [6, 7]. The disease is rare among Africans and not expected among populations with no HLA DQ2, like Chinese and Japanese, except in individuals presenting HLA DQ8 [2].

Although several autoimmune diseases have been described in native Indian populations from around the world, studies evaluating the occurrence of CD among those individuals are scarce. Araya et al. described clinical and serological features of CD in patients and relatives of a Chilean population carrying Amerindian traits [8]. In addition, Galvão et al. reported twenty cases of CD in North of Brazil in a mixed population (Europeans and local Indians) [9]. On the other hand, high prevalence and more severe disease, as well as increased comorbidity and mortality rates, were demonstrated in different Indian populations for other autoimmune diseases [10,11], such as rheumatoid arthritis [10,12,13], systemic lupus erythematosus [14,15], primary biliary cirrhosis [16-18], systemic sclerosis [19,20] and type I diabetes [21], amongst others. Both genetic and environmental components have been considered as the main factors influencing the development of these autoimmune disorders in native Indians.

Although Kaingang and Guarani represent the two largest Amerindian tribes living in south Brazil and some areas of Paraguay and Argentina, they are both culturally and genetically distinct from each other [22-24]. While Kaingang are semi-nomads and cultured, the Guarani are nomads and preserve secular customs and the Tupy native language. The Guarani represent the biggest indigenous community in Brazil, with approximately 46.000 individuals.

Several studies have evidenced genetic differences between Kaingang and Guarani Indians, specially related to MHC genes, also when compared with other South American Indians and other ethnic groups, such as Europeans and Africans [25-28].

The general Brazilian population is known to present a high degree of miscigenation between Europeans, Africans and native Indians, with a predominance of European ancestry in the South. Recent data has shown prevalence for CD of 1:273 [29] to 1:417 [30] in this region. The present study aimed to screen the anti-endomysial antibody (IgA-EmA) in Kaingang and Guarani Indians from Southern Brazil, in order to evaluate clinically the occurrence of CD in these individuals.

Materials and Methods

A total of 321 Indians (196 female and 125 male), from Mangueirinha Reserve (latitude 25°56´28´´S; longitude 52°10´32´´O), in the state of Parana, South Brazil, were studied. Amongst them, 158 were Kaingang, 98 Guarani and 65 mixed races (Kaingang and Euro-Brazilian individuals). As a comparison group, 180 healthy, voluntary non Indian subjects, from European ancestry were included. All individuals belong to the same geographic area and were matched for age and sex. Demographic data of these groups are informed (Table 1).

Table 1 Demographic data from the studied populations.

Groups	Number	Sex (F/M)	Mean Age (Range)	Median
Indians (total)	321	196/125	26.9 (4-86)	21
Kaingang	158	100/58	30.8 (4-80)	27
Mixed	65	39/26	25.6 (4-86)	22
Guarani	98	57/41	21.6 (5-86)	17
Non-Indians	180	118/ 62	25.0 (2-81)	19

F: Female, M: Male, Mixed: Kaingang and non-Indian.

A structured questionnaire was used to collect socio-demographic data and symptoms and signs related to diseases. All Indian individuals presented good health conditions on blood collection and clinical evaluation. Some features related to their occupational activities, individual customs and some complaints or symptoms were summarized (Table 2).

Table 2 General characteristics from the studied populations

	Kaingang % (N)	Mixed % (N)	Guarani % (N)
Individual customs			
Alcohol users	13.4 (21/158)	7.7 (5/65)	14.3(14/98)
Tobacco users	32.3 (51/158)	12.3 (8/65)	31.6(31/98)
Drugs users	0 (0/158)	3.1 (2/65)	1.0 (1/98)
Tatoo	1.26 (2/158)	0 (0/65)	3.06 (3/98)
Occupational activities			
Agriculturist	18.3 (29/158)	13.8(9/65)	5.3 (5/98)
Student	27.8 (44/158)	24.6(16/65)	46.9(46/98)
Homeworker	38.6 (61/158)	27.7(18/65)	27.5(27/98)
Complaints			
Arthralgy	27.2 (43/158)	29.2(19/65)	30.6(30/98)
Diarrhea	1.3 (2/158)	6.1. (4/65)	6.1 (6/98)

Mixed: Kaingang and non-Indian

The study was approved by the ethical committee of the Clinical Hospital of the Federal University of Parana, National Council of Research (CONEP), National Foundation of Indians (FUNAI) and by the local leaders of the tribes.

Anti-endomysial antibodies (IgA-EmA) were evaluated in all serum samples, by indirect immunofluorescence assay (FITC), according to Volta et al. [31]. Cryostatic sections of human umbilical cord were used as substrate and FITC anti-IgA human as conjugate (Inova, San Diego, USA). Sera were considered positive if fluorescence was observed at a dilution of 1:2.5, and titred up to the

end-point. Positive and negative controls were used for each batch. Similarly, Indian individuals presenting complaints of diarrhea (N=12; Table 2) were also evaluated to the anti-endomysial antibodies class IgG (IgG-EmA), using FITC anti-IgG human conjugate (Dako, Denmark).

Statistical analysis was performed with Statistical (Microsoft USA) software, using the Fisher exact test. The adopted level of significance was $P<0.05$.

Results

The serological screening for CD based on IgA-EmA, performed in the Kaingang and Guarani Indians as well as in the non-Indian subjects, is in table 3. None of the investigated individuals showed a positive result to the IgA-EmA. The analysis of IgG-EmA in those Indians who informed in the structured questionnaire the occurrence of diarrhea with frequency also showed negative results (Table 3).

Table 3 Anti-endomysial antibodies in Indian and non-Indian individuals of Southern Brazil

	Kaingang (%)	Mixed (%)	Guaraní (%)	Non-Indians (%)
IgA-EmA				
Positives	0 (0)	0 (0)	0 (0)	0 (0)
Negatives	158 (100)	65 (100)	98 (100)	180 (100)
IgG-EmA				
Positives	0 (0)	0 (0)	0 (0)	0 (0)
Negatives	2 (100)	4 (100)	6 (100)	-

EmA : Endomisial antibody, Mixed: Kaingang and non-Indian

Discussion

The population of native Indians in Brazil at the time of its discovery in 1500 was approximately 6 million individuals. However, recent data estimates this number to be only 460000 [32]. During the centuries, millions of native Indians were exterminated due to the colonization process, slavery and diseases.

This is the first report of serological and clinical evaluation of CD in Kaingang and Guarani Indians from southern Brazil. The results showed an absence of CD in these native indigenous, as well as in the control group of non-Indians from southern Brazil. None of the individuals were positive to IgA-EmA, although approximately 6% of Guarani and Mixed group had complaints of diarrhea (Table 2). This group of individuals was also negative for IgG-EmA (Table 3). Probably the high frequency of intestinal parasitosis and lack of nutritional diets of some Indians may be the cause of diarrhea in these individuals to subjects [33, 34]. The presence of other autoimmune disease markers like rheumatoid factor and anti-nuclear antibodies, in association with clinical manifestations of rheumatic diseases, as to was previously described in these individuals by the authors [35], who observed complaint of arthralgy in almost 30% of the subjects (Table 2). Similarly, Utiyama et al. [36] observed the occurrence of autoantibodies in Kaingang and Guarani Indians from Rio das Cobras and Ivai Indigenous Reserve in South Brazil.

Recent reports have showed the occurrence of CD among ethnic minorities and therefore there was reason to believe that this disease be under- diagnosed in those groups, as described by Brar et al. [37] in African-American patients. Although the disease has been considered uncommon in India until recently, Sood et al. observed a prevalence of 1:310 in school children of the Punjab, showing that CD is not rare in wheat-eating areas of North India [38]. Similarly, Freeman described CD in 14 adult Asian individuals from a single Canadian teaching hospital, living in North America, including 10 patients from Punjab, two from Japan and one from China [39]. In addition, Butterworth reported clinical and laboratorial features on 40 CD patients of South Asian origin living in the United Kingdom [40]. According to the authors, special attention needs to be given to methods that encourage adherence to gluten-free diet in affected individuals of minority groups [37, 40].

Interestingly, the differences in HLA alleles observed in CD patients from South Asia when compared with Caucasian patients, suggested that non-HLA genes play a stronger role in the susceptibility and presentation of the disease in the former group [41].

Analyses of HLA-DQA1 and HLA-DQB1 class II gene polymorphism in Kaingang and Guarani Amerindians from southern Brazil, showed four different DQA1-DQB1 haplotypes:DQA1*0401-DQB1*0402,DQA1*0501-DQB1 *0301, DQA1*03-DQB1*0302 and DQA1*03-DQB1*03032 [24]. In this context, considering that CD is closely associated with genes that code for HLA-DQ2 in 95% of the patients (DQA1*05/DQB1*02) and HLA-DQ8 in most of the remainder (DQA1*0301/DQB1*0302) [2], it is reasonable to suppose a certain degree of susceptibility to CD in these investigated populations, especially in the Mixed group, due to the inter ethnic marriages that have occurred in the last centuries.

In addition, the gradual change in the traditions, cultural practices and nutritional habits amongst Indians have introduced several factors that might represent a risk to autoimmune diseases in this population. Among these, it must be emphasized the ingestion of wheat gluten and related cereal proteins (rye, barley) by individuals whose nutrition was formerly based on foods, such as fruits, meat and fish.

Although none of the Indian individuals analyzed in the present study showed positivity to EmA-IgA, the authors consider it important that physicians who attend indigenous populations stay alert and follow up children or adults that present persistent gastrointestinal complaints or other symptoms related to CD. The genetic background, allied to hormonal and immunological factors, besides the changing of habits or even occupational activities, may gradually lead to the occurrence of diseases previously not seen in these native populations, as observed in other

ethnic minorities [38 – 41]. It must be considered also, that individuals previously negative to the serological markers of CD may become positive in the future. Furthermore, in cases with uncertain diagnosis it is important there is an assessment of HLA DQ2 and DQ8, since absence of those alleles make CD unlikely [42].

Finally, the involvement of non-HLA genes among Asiatic CD patients also suggests their importance in ethnic related populations, such as Amerindians, which must also be considered in future studies.

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The authors declare no conflict of interest.

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