

## Crohn's disease in one mixed-race population in Brazil

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had an earlier diagnosis and appeared to have had a more severe disease presentation than white patients.

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### Abstract

**AIM:** To evaluate the classification and severity of Crohn's disease in different racial groups.

**METHODS:** Patients with Crohn's disease from the outpatient clinic of the University Hospital Prof. Edgard Santos were enrolled in the study. This hospital is a reference centre for inflammatory bowel disease. Race was determined using self-identification. The Vienna's classification was applied for all subjects. The severity of Crohn's disease was determined according to the number of surgical procedures, hospital admissions in the last year and treatment with steroids and immunosuppressors. Statistical analysis was calculated using *t* test for means,  $\chi^2$  or F for proportions. A *P* value < 0.05 was considered to be significant.

**RESULTS:** Sixty-five patients were enrolled. Non-white patients were more frequently diagnosed with Crohn's disease in the age less than 40 years than white patients. The behaviour of disease was similar in both groups with a high frequency of the penetrating form. There was a tendency for non-white patients to have a greater frequency of hospital admissions in the last year compared to white subjects. Non-whites also had a higher rate of colonic and upper gastrointestinal involvement, and were also more frequently on treatment with immunosuppressors than white patients although this difference was not statistically significant.

**CONCLUSION:** Non-white patients with Crohn's disease

### INTRODUCTION

Genetic and environmental factors appear to have a role in the pathogenesis of Crohn's disease. The incidence of the disease among first degree relatives of patients is greater than the incidence in the general population<sup>[1]</sup>. So far it is believed that the illness is more common among whites than Afro-descendants<sup>[2]</sup>. The greatest prevalence is described in Jews<sup>[1]</sup> and a low prevalence is described in the Asian population<sup>[3]</sup>. The prevalence of Crohn's disease in Brazil is not known however the illness is considered to be of low prevalence in developing countries<sup>[4]</sup>. Data from Latin America have found an incidence of 0.03 cases per 100.000 person-years in the period of 1987 to 1993<sup>[5]</sup>.

In contrast to the increased number of studies about the behaviour of many other diseases according to the racial groups, there is relatively little knowledge about the influence of race in Crohn's disease<sup>[6]</sup>. Studies have noted the different characteristics of Crohn's disease among racial groups and the possibility of different pathogenetic mechanisms of this illness in different countries. A more severe disease on presentation and an earlier diagnosis in successive generations has been observed in some patients of Jewish ancestry<sup>[7]</sup>. A North American study has demonstrated a genetic heterogeneity between Afro-American patients and non-Jews Caucasians with Crohn's disease<sup>[8]</sup>. In the same study it was observed that the Crohn's disease is more common than ulcerative colitis in Afro-Americans with inflammatory bowel disease.

As there is a high miscegenation of races in the Brazilian population the characterization of Crohn's disease within each racial group has become an interesting topic. The evaluation of these aspects may contribute to the

knowledge of the importance of genetic and environmental factors to the development of this illness. The aim of the present study is to evaluate the classification and severity of Crohn's disease in different racial groups.

## MATERIALS AND METHODS

This is a sectional study in which patients with diagnosis of Crohn's disease who are followed up in the outpatient clinic of the University Hospital Prof. Edgard Santos were enrolled from March to December of 2006. This clinic is a reference centre for Crohn's disease. We included patients older than 18 years after they had signed the informed consent. The study was approved by the Ethics Committee of the Institution.

The diagnosis criteria for Crohn's disease were based on clinical, laboratorial, radiological, endoscopic and pathologic evaluations<sup>[9]</sup>.

The demographics variables analysed were: age, gender, self-identification of race and Jewish ancestry. The self-identification was based on the criteria of the Brazilian Governmental Statistics Agency (IBGE). The distribution of the population of Bahia according to the IBGE 2000 Demographic Census using these criteria is: whites, 23%; Afro-Brazilians, 13%; Asians, < 1%; mixed-race, 62%, and Indians, 5%. The state of Bahia has the largest number of self-identified Afro-Brazilians, as well as the one of the highest combined percentages (75%) of Afro-Brazilians and mixed-race residents<sup>[10]</sup>. In this study patients were classified according to race into whites and non-whites.

The characterization of the Crohn's disease has been made using the criteria of the Vienna classification: age at diagnosis, localization and behavior colonic disease was compared with non-colonic and penetrating disease with non-penetrating. Other variables analysed were: mean age, gender, smoking, family history of Crohn's disease, perianal and rectovaginal fistula, presence of granuloma in the biopsy and time of diagnosis.

Evaluation of severity of the disease included surgical procedures, hospitalization in the last year and use of immunosuppressors and steroids. Comparison between racial groups was carried out by the  $\chi^2$  or *F* when the expected value was less than 5. For comparison between means the *t* was used. The differences observed were considered significant when the probability of the alpha error *P* was < 0.05.

## RESULTS

During the study period sixty-five patients were enrolled, one patient refused to participate. Table 1 shows the characteristics of Crohn's disease in whites and non-white patients according to the Vienna classification; 21 (32.3%) were white, 28 (43.1%) were mixed-race Brazilians and 16 (24.6%) were Afro-Brazilians. Three individuals had Jewish ancestry: two were women, all had presented with ileal disease, and two were classified as L1 (ileum terminal) and one as L3 (ileocolonic). Jewish ancestry was detected only in white patients.

Table 2 shows other variables of the disease including mean age, gender, history of smoking, perianal fistula, rectovaginal fistula, and presence of granuloma in the biopsy

**Table 1 Vienna Classification in whites and non-whites patients with Crohn's disease in Bahia-Brazil, 2006**

Vienna Classification	Total <i>n</i> = 65	White <i>n</i> = 21	Non-whites <i>n</i> = 44	<i>P</i>
Age at diagnosis				
A1 (< 40)	45 (69.2)	11 (52.4)	34 (77.3)	<i>P</i> < 0.05
A2 ( $\geq$ 40)	20 (30.8)	10 (47.6)	10 (22.7)	
Behavior				
B1-Nonstricturing, nonpenetrating	24 (36.9)	8 (38.1)	16 (36.4)	
B2-Stricturing	5 (7.7)	2 (9.5)	3 (6.8)	
B3-Penetrating	36 (55.4)	11 (52.4)	25 (56.8)	NS <sup>a</sup>
Localization <sup>b</sup>				
L1-Ileum terminal	15 (25.4)	7 (36.8)	8 (20.0)	
L2-Colon	14 (23.7)	3 (15.8)	11 (27.5)	NS <sup>c</sup>
L3-Ileocolonic	23 (39.0)	8 (42.1)	15 (37.5)	
L4-Upper gastrointestinal tract (UGT)	7 (11.9)	1 (5.3)	6 (15.0)	NS <sup>d</sup>

NS: no statistically significant difference. <sup>a</sup>Comparison between penetrating and non-penetrating; <sup>b</sup>Data on 59 patients; <sup>c</sup>Comparison between colonic and non-colonic; <sup>d</sup>Comparison between UGT and non-UGT.

**Table 2 Others parameters in whites and non-whites patients with Crohn's disease in Bahia-Brazil, 2006**

Parameters	Total <i>n</i> = 65	Whites <i>n</i> = 21	Non-whites <i>n</i> = 44	<i>P</i>
Age (mean $\pm$ SD)	37.3 $\pm$ 13.0	39.4 $\pm$ 13.9	36.3 $\pm$ 12.6	NS
Females <i>n</i> /%	40 (61.5)	12 (57.1)	28 (63.6)	NS
Smoking				NS
Non-smoker	54 (83.1)	16 (76.2)	38 (86.4)	
Current smoker	4 (6.2)	1 (4.8)	3 (6.8)	
Ex-smoker	7 (10.8)	4 (19.0)	3 (6.8)	
Perianal fistula	30 (46.2)	10 (47.6)	20 (45.5)	NS
Rectovaginal fistula	3 (4.6)	1 (4.8)	2 (4.5)	NS
Granuloma in biopsy <sup>a</sup>	11 (17.2)	4 (19.0)	7 (16.3)	NS
Time of diagnosis				NS
Less than 10 yr	52 (80)	18 (85.7)	34 (77.3)	
Equal to or more than 10 yr	13 (20)	3 (14.3)	10 (22.7)	

NS: no statistically significant difference. <sup>a</sup>Data on 64 patients.

and time of diagnosis in all patients and in white and non-white patients. Only two white patients had family history of Crohn's disease and one of them had Jewish ancestry and a twin sister with the disease.

Table 3 shows the comparison of parameters of the severity of Crohn's disease between whites and non-white patients.

## DISCUSSION

This study was carried out in the state from Brazil with the highest frequency of Afro-descendants. Perhaps this type of ancestry explains the low number of patients with Crohn's disease included in this study. This small number can limit the external validation of the result of the study, but it is important to note that this is a reference center and the study included almost all patients being followed up.

The comparison between whites and non-whites

**Table 3** Severity criteria in whites and non-whites patients with Crohn's disease in Bahia-Brazil, 2006

Severity criteria	Total <i>n</i> = 65	Whites <i>n</i> = 21	Non-whites <i>n</i> = 44	<i>P</i>
Treatment with immunosuppressors <i>n</i> (%)	28 (43.1)	8 (38.1)	19 (45.5)	NS
Treatment with steroids <i>n</i> (%)	46 (70.8)	13 (61.9)	33 (75)	NS
Hospitalisation in the last year <i>n</i> (%)	19 (29.2)	3 (14.3)	16 (36.4)	NS <sup>a</sup>
Surgery fistula <i>n</i> (%)	13 (20.0)	4 (19.0)	9 (20.5)	NS
Partial Colectomy <i>n</i> (%)	13 (20.0)	2 (9.5)	11 (25.0)	NS

NS: no statistically significant difference. <sup>a</sup>almost reached statistical significance (*P* = 0.07).

showed a statistically significant difference in the age at diagnosis. Similar results have been demonstrated by other studies that have detected a greater frequency of diagnosis of Crohn's disease before the age of 40 years in Afro-descendants<sup>[12]</sup>. This can be attributed to a more severe disease with earlier symptoms. We also found that the behaviour of the illness was similar in whites and non-whites, with a high frequency of patients with the penetrating form of the disease in both groups<sup>[11]</sup>. This result can be explained by the fact that this study has been carried out in a reference center for the treatment of Crohn's disease to where more complex cases are referred.

The colonic localization seemed to be more frequent among non-white patients. We believe that if we had evaluated a higher number of patients the comparison of this variable might have reached statistical significance. This finding is in agreement with an American study that found African American patients were more likely to have ileocolonic or colonic disease compared to white patients<sup>[13]</sup>. A large North American Cohort<sup>[14]</sup> observed that African American patients were more likely to develop upper gastrointestinal and colorectal disease than whites, but less likely to have ileum involvement. A Chinese study found a greater rate of upper gastrointestinal Crohn's involvement and less terminal ileum disease in Chinese patients<sup>[15]</sup>. This was also observed in the present study in non-white patients. Possibly a difference in the balance between genetic inheritance and environmental factors contribute to the differences in the location of the disease among white and non-white patients<sup>[1]</sup>.

The presence of ileal disease in all cases with Jewish ancestry raises the possibility of a genetic contribution in the location of this illness. Jewish ancestry was observed only in white patients. The immigration of individuals from countries of Jewish culture might be one of the forms for insertion of this disease in the white patients in the studied population.

In general, there is a slight female predominance in patients with Crohn's disease, although this is not described in all studies. The highest frequency of female patients observed in our study has been described before especially among women in late adolescence and early adulthood, suggesting that hormonal factors may play a role in disease expression<sup>[4]</sup>. A large North American cohort study<sup>[14]</sup> described a slight female predominance of inflammatory

bowel disease among African Americans compared to whites and Hispanics.

The presence of family history and the high frequency of a previous history of smoking among white patients point out to the importance of genetic aspects and smoking as possible risk factors for the illness in this group of patients. The presence of family history of Crohn's disease only in whites in comparison to non-whites has been previously demonstrated and the authors noted the probable influence of genetic factors in these patients in contrast to the non-white individuals<sup>[14]</sup>. Possibly, environmental factors are contributing to the development of the illness in the latter group. Likewise, in a study involving 65 Chinese patients with Crohn's disease the absence of mutation in the CARD15 gene raises the question of whether environmental factors, such as lifestyle, are important in the pathogenesis of this illness. One study that evaluated Western patients has proposed a new hypothesis in which ingestion of highly fermentable but poorly absorbed short-chain carbohydrates and polyols to the distal small intestinal and colonic lumen is an important factor underlying the susceptibility to Crohn's disease<sup>[17]</sup>. Further studies are needed in order to address the importance of lifestyle in these patients especially regarding food intake.

Studies about single-nucleotide polymorphisms of the TNF- $\alpha$  promoter gene have found some differences in these polymorphisms between racial groups. Caucasians appear to more frequently have the phenotype of high production of TNF<sup>[18]</sup>. Several studies that evaluated cytokine genes polymorphisms have concluded that they have a greater influence on the classification of Crohn's disease rather than in the susceptibility to the illness<sup>[19]</sup>. Possibly the evaluation of cytokine gene polymorphisms will be another important topic in the inheritance of Crohn's disease.

The non-white patients had an increased period of time from diagnosis, equal or greater than ten years. This result could be explained by the earlier age at diagnosis in non-white patients and similar ages in both groups at the moment of the study. The greater duration of disease in non-white patients did not influence any change in the behaviour of disease as it would be expected probably because this difference in time was not great enough.

The analysis of severity of the disease showed a greater frequency of partial colectomy and hospitalisation in the last year and treatment with steroids and immunosuppressors in non-white patients. Probably the small number of patients can explain the lack of statistical significance. Nevertheless, it is interesting to note that the variable hospitalisation in the last year almost reached statistical significance. As these patients were evaluated in a single center by the same group of physicians who use a similar therapeutic approach this reinforces the possibility for a more severe illness in non-white patients.

The importance of the description in medical charts of the racial group was emphasized in a former publication which concluded that ethnic and racial differences in the causes, expression and prevalence of some illnesses exist<sup>[20]</sup>. In countries with high level of miscegenation, the study of the characteristics of multi-factorial illnesses, as it is the case of Crohn's disease, in the different racial

groups will be able to contribute to the knowledge of its genetics and environmental determinants. The identification of groups at risk for high prevalence and greater severity of the illness may lead to an earlier diagnosis, better treatment response and better quality of life of these patients.

In conclusion, the presence of family history and Jewish ancestry in white patients with Crohn's disease reinforces the importance of the genetic inheritance in these subjects. In this study, non-white patients presented with an earlier diagnosis of the disease and seemed to have had a more severe illness without aspects that might strengthen the influence of genetic inheritance. These data suggest a possible role of environmental factors in the presentation of the disease in non-white patients. Further studies aiming to evaluate the genes associated with Crohn's disease may help in the comprehension of the pathogenetic mechanisms of this illness in this population.

## COMMENTS

### Background

Crohn's disease is a multifactorial disorder and its pathogenesis is not entirely understood. Environmental and genetic factors are involved, but so far is still not clear the definitive relevance of racial factors.

### Research frontiers

There are many studies about genetics aiming to elucidate the factors involved in the pathogenesis of Crohn's disease. So far several studies have found that there are genetic markers differences between races. In addition the importance of environmental factors for some racial groups has been emphasized.

### Innovations and breakthroughs

Some studies have showed differences between racial groups in the presentation and severity of Crohn's disease. This article found that non-white were more frequently diagnosed with Crohn's disease in the age less than 40 years than white patients in one population with high rate of miscegenation.

### Applications

This article emphasizes the importance to give special attention to racial aspects during follow-up and therapeutics of patients with Crohn's disease because probably distinct racial groups have different aspects in the pathogenesis of the disease. Therefore studies that evaluate the role of genetic markers in Crohn's disease need to consider racial features when describing the studied population.

### Peer review

This article included some interesting data for the researchers in this field.

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