Hematologic values among warao indians with tuberculosis from the orinoco delta of venezuela

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Abstract

Tuberculosis (TB) is a public health problem in Venezuelan indian communities. This study describes differences in hematological parameters in TB patients from two populations, Warao indians (WP) and creoles (CP). Control groups included Warao adults (WC) and children (WCh) as well as creole adults (CC). The results showed that the WP and WCh had significantly lower hemoglobin (Hb) levels than the WC and CC groups. Warao patients and two Warao control groups had significantly lower concentrations of median corpuscular Hb (MCHC) than the CP and CC groups. Regarding leucocyte indices, we observed a significant increament in the monocytes percentage in WP, WC and WCh, compared to CP and CC. In contrast, the neutrophils percentage was significantly reduced in all the Warao groups compared with the creole groups. Both WP and CP patient groups had higher platelet counts than those of the WC and CC groups. In relation to the body mass index (BMI), used as nutritional status indicator in Warao indians, we observed that the highest BMI was obtained in the adolescent group; with a continuous decreased with age. In conclusion, both WP and WCh presented decreased levels of Hb with erythrocytic hypochromia. Similar to the WCh, indian adults, even in the absence of the disease, presented a formula of white blood cells characterized by monocytosis, high percentage of lymphocytes and low percentage of neutrophils.

Key words: Tuberculosis, Warao, creole, hemoglobin, concentration of median corpuscular hemoglobin, body mass index.

Valores hematologicos entre los warao con tuberculosis del delta venezolano

Resumen

indígenas de Venezuela. Este estudio muestra los valores de los parámetros hematológicos de dos poblaciones diferentes con TBC, los Warao y los criollos. Se estudiaron pacientes Warao (PW) y criollos (PC), controles adultos tanto Warao (CW) como criollos (CC) y niños Warao (NW). Los PW y los NW presentaron valores significativamente bajos de la hemoglobina (Hb) en comparación con los CC y CW. Todos los grupos Warao presentaron concentraciones significativamente disminuidas de los valores de la concentración de hemoglobina corpuscular media (CHCM) en comparación con los PC y CC. En cuanto a los glóbulos blancos, los grupos Warao, incluyendo los niños, presentaron un incremento significativo del porcentaje de monocitos y linfocitos en comparación con los PC y CC. Sin embargo, el porcentaje de los neutrófilos se encontró significativamente disminuido en comparación con ambos grupos criollos. Ambos grupos de pacientes así como los niños Warao presentaron incremento significativo en el número de plaquetas en comparación con los CW y CC. Los resultados del índice de masa corporal (IMC) en la población Warao, el cual fue utilizado como indicador del estado nutricional de la población mostraron que, éste alcanzó el máximo en el grupo correspondiente a la edad de los adolescentes y luego disminuyó a medida que aumentaba la edad de los individuos. En conclusión, tanto los PW como los NW presentan disminución de los valores de la hemoglobina, la cual se correlacionó con una hipocromía eritrocitaria. Al igual que los NW, los adultos Warao, aún en ausencia de enfermedad presentaron una fórmula leucocitaria caracterizada por monocitosis, aumento del porcentaje de linfocitos y disminución del porcentaje de neutrófilos.

Palabras clave: Tuberculosis, Warao, criollos, hemoglobina, concentración de hemoglobina corpuscular media, índice de masa corporal.

Introduction

Tuberculosis is the leading infectious killer of youth and adults and the second most common infectious disease worldwide. There were an estimated 8.4 million new TB cases in 1999, up from 8.0 million in 199729. About 21,125 Warao people, 17 % of the total Indians of Venezuela, live in the Orinoco Delta situated in Delta Amacuro State of Venezuela (Figure 1). Approximately 60% of the total population lives in traditional communities in houses on stilts over the water called "palafitos" 12. This population remained largely isolated for millennia and largely unknown due to its their difficult swampland habitat, so it is possible to think that their traditional social system remained intact and their contact with infections has been very limited until recently, when their contacts with individuals of European descent increased and when "criollos", members of the general Venezuelan population, and missionaries have entered their habitat in sizable numbers. The Warao Indian population has had increased contact with infectious diseases such as TB. A rate has been reported of 155 per 100,000 inhabitants 22, in contrast to the mestizo population from urban area creoles ("criollos") with a rate of 26.1 per 100,000 inhabitants in 199922. The State of Delta Amacuro has the highest prevalence of Indians with TB; in 1999 this State had a rate of 93.2 per 100,000 inhabitants. Of these, 90% of the cases were present in the Warao population22. TB may produce signs and symptoms that include hematologic abnormalities, hyponatremia and psychological disorders8,13. The most common hematologic manifestations of TB are increases in the peripheral blood leukocyte count and anemia 5,8.

The majority of blood white cells are polymorphonuclear leucocytes, which represent about 60-70% of the total normal blood leucocytes. Neutrophils represent over 90% of the circulating granulocytes16. The most important role of the neutrophil cells is in

able to eliminate many pathogens by phagocytosis. The importance of neutrophils in host defense is best illustrated by considering inherited defects in neutrophil maturation or antibacterial functions. Patients with such deficiencies suffer recurrent infections, often by bacteria and fungi that form part of the normal flora13.

The aim of the present investigation was to study the profile of the hematological parameters in two populations with TB from specific patterns of cultural, social and economic interactions, as well as genetic differences within the Venezuelan society; they are the Warao and creole populations.

Figure 1. Delta Amacuro State of Venezuela.

Materials and methods

Study Groups

This study was a descriptive cross-sectional type. The study groups were classified in: Patient Groups. a) Warao patients (WP) : patients with active TB before treatment (n=42, 21 female and 21 male) with mean age of 32.85± 12.45 years old (37 positive and 5 negative for tuberculin skin test) selected from the Warao indigenous community with Warao parents and grandparents who live in the lower Delta in San Francisco de Guayo and the surrounding communities. b) Creole patients (CP) : patients with active TB before treatment (n=19, 10 female and 9 male) with mean age of 34.40 ± 12.10 years old (14 positive and 5 negative for tuberculin skin test) selected from the Sanitary District of Dos Pilitas and the Hospital Vargas, both in Caracas. They are from urban communities of the capital of the country with different degrees of admixture of Caucasian, Amerindian and African ascendance (mestizos).

Control Groups. a) Warao controls (WC) : healthy controls (n=36, 16 female and 20 male) with mean age of 30.97± 11.94 years (32 positive and 4 negative for tuberculin skin test) selected from the Warao indigenous community with Warao

female and 11 male) with mean age of 18.85± 1.34 years (5 positive and 26 negative for tuberculin skin test) from urban communities with different degrees of admixture of Caucasian, Amerindian and African ascendance (mestizos). c) A healthy control group of Warao children (WCh) (n=24, 15 female and 9 male) with mean age of 8.65± 2.26 years was included in the study to compare the white cell indices between adults and children in the Warao population.

Inclusion criteria for all study groups: 1) Patients and controls included were adults between 15 and 60 years of age, except for the control group of children. 2) All Warao individuals were selected from the Warao indigenous community with Warao parents and grandparents. 3) Active TB patients: based on clinical diagnosis, thorax radiography, smears stained with Ziehl-Neelsen and/or microbiological culture with negative or positive tuberculin skin test ($\geq$ 10 mm). 4) Control groups: healthy subjects with no evidence of clinical, microbiological or radiographically active TB with negative or positive tuberculin skin test. 5) Only patients with TB who were HIV negative were included in this study. The results revealed no case of HIV-positive TB among the Warao population. 6) Warao indigenous O blood group Rh+ individuals were included in this study because the Venezuelan indigenous populations are fundamentally O blood group2 Rh+. All participants or their legal representatives signed a "consent form" agreement before blood samples were taken.

Clinical and Bacteriological Analysis for Tuberculosis Diagnosis

The Venezuelan National Program of Tuberculosis Control and the Laboratory of Tuberculosis of the Institute of Biomedicine has been diagnosing TB cases among the Warao communities, based on clinical evaluation and examination with a methodology previously reported11. Sputum samples were collected from Warao Indians with respiratory symptoms. Smears were stained by the Ziehl-Neelsen direct method. For each specimen two tubes of modified Ogawa egg medium and Lowë nstein-Jensen were inoculated with the swab method of Kudoh and Kudoh17. Specific treatment was initiated in all newly identified cases of TB following the norms of the Venezuelan National Program of Tuberculosis Control4.

Tuberculin Skin Tests

Tuberculin skin tests were performed on all the individuals of this study using two tuberculin units of purified protein derivative (PPD) of M. tuberculosis, strain RT-23, from the Statens Serum Institute in Copenhagen, Denmark. Testing and reading was done according to international guidelines3,25.

HIV Diagnostic Test

HIV testing was done with the Passive Particle Agglutination Test for the detection of antibodies to HIV-1 and/or HIV-2 of FUJIREBIO Diagnostics.

Hematological Tests

Venous blood samples were obtained from volunteers, patients and controls. The study was performed by coulter counter method (model S-PLUS JR Parameters) at the Municipal Blood Bank of the Capital District, Caracas.

The parameters reported by the Model S-PLUS JR are: white blood cell (leukocyte count, WBC), number of leukocytes (lymphocytes, monocytes and neutrophils) in the specified volume of whole blood, (units of measure are, thousands of leukocytes per

(erythrocyte count, RBC), number of erythrocytes in the specified volume of whole blood, (units of measure are millions of erythrocytes per microliter of whole blood, 106 cells /μl) and hematimetric indexes: median corpuscular hemoglobin concentration (MCHC g/dl) and median corpuscular volume (MCV fentoliters).

Anthropometrical Parameters

Body mass index (BMI; in Kg/m2) measures in children were performed as described in the Fundacredesa guide to calculation of anthropometric indicators of nutritional status of Venezuelan children20 and in adults, the guide to use and interpretation of anthropometric indicators of nutritional status of the WHO28.

Statistical Analysis

The statistical analysis used to compare the significance of the differences between the means of the values of red and while cell indices were Student's t test and the Pearson test for correlations.

Results

Hemoglobin and Hematocrit Values

The Hb values are shown in Table I. The mean of the Hb was significantly decreased in WP (11.4± 1.9 g/dl) and WCh (11.43± 0.9 g/dl) in comparison to both control groups WC (12.4± 1.7 g/dl) and CC (14.3± 1.4 g/dl), p<0.0001. The mean of Hb was also decreased in CP (12.0± 2.0 g/dl) but it did not reach statistical significance when compared with other study groups (Table I). The mean of hematocrit percentage was also significantly decreased in the patient groups, WP and CP, in comparison to both control groups WC and CC (data not shown).

In order to investigate if there is difference of the Hb levels between males and females among the study groups, we carried out the study of the Hb by sex per group. We found a significant difference of the Hb between WC (12.9± 2.2 male and 11.2± 1.5 female) and CC (15.7± 0.8 male and 13.6± 1.1 female), p<0.016 and p<0.0001 respectively (data not shown).

Table I. Values of hemoglobin and median corpuscular hemoglobin concentration (MCHC), the absolute levels of leucocytes and platelets and percentages of lymphocytes, monocytes and neutrophils.

	Warao Patients (WP)	Warao Controls (WC)	Warao Children (WCh)	Creole Patients (CP)	Creole Controls (CC)	
Hemoglobin (12.0 – 16.0 g/dl)	11.4± 1.9(a)	12.4± 1.6(b)	11.4± 0.9(c)	12.0± 2.0	14.3± 1.3(d)	a,c vs b,d p<0.0001
(MCHC) (33.0 – 37.0 g/dl)	30.3± 1.7(a)	29.3± 1.9(b)	29.5± 2.2(c)	31.1± 1.6(d)	32.7± 0.7(e)	a,b,c vs d,e 0.05>p>0.0001

Leucocytes (4.8 – 10.8 x103)	9.6± 2.7(a)	8.9± 3.0(b)	10.4± 2.3(c)	7.9± 2.9(d)	7.0± 1.3(e)	a,b,c vs d,e 0.03>p>0.0001
Lymphocytes (20.5. – 51.1 %)	39.6± 13.8(a)	41.4± 9.8(b)	39.9± 5.9(c)	24.3± 9.3(d)	33.4± 7.9(e)	a,b,c vs d,e 0.006>p>0.0001
Monocytes (1.7 – 9.3 %)	22.0± 9.2(a)	25.2± 12.3(b)	25.2± 9.6(c)	6.9± 4.2(d)	10.2± 5.0(e)	a,b,c vs d,e p<0.0001
Neutrophils (42.2 – 75.2 %)	36.4± 16.3(a)	33.4± 13.6(b)	34.8± 10.8(c)	67.1± 10.7(d)	56.3± 9.5(e)	a,b,c vs d,e 0.005>p>0.0001
Platelets (150 –450 x103)	443.1± 147.6(a)	314.9± 104.9(b)	411.0± 108.3(c)	374.3± 132.7(d)	284.0± 69.5(e)	a,c,d vs b,e 0.003>p>0.000

Hematimetric Indices

The MCHC values of Warao and creole study groups are shown in Table I. The Warao groups presented significantly lower concentration of median corpuscular Hb (MCHC), WP [30.3± 1.7, (30.3± 1.9 male and 29.6± 2.5 female)] , WC [29.3± 1.9, (30.9± 1.6 male and 29.1± 2.2 female)] and WCh [29.5± 2.2, (29.9± 2.2 male and 29.0± 2.2 female)] as compared to CP [31.1± 1.6, (31.2± 1.4 male and 29.9± 2.4 female)] 0.05>p>0.001 and CC [32.7± 0.7, (33.2± 0.5 male and 32.5± 0.7 female)] 0.05>p>0.0001. The decrease of MCHC values was significantly correlated with a decrease of the Hb in WP (r= 0.575, p<0.0001). A significant difference of the MCHC in CC between male and female, p<0.006 was found.

The MCV values were significantly decreased in both patient groups, WP [86.3± 9.3, (86.5± 7.6 male and 88.4± 12.6 female)] and CP [85.6± 6.6, (88.9± 5.9 male and 83.9± 8.0 female)] , in comparison to the control groups WC [95.6± 8.6, (96.0± 5.6 male and 89.6± 6.6 female)] and CC [90.9± 3.2, (90.3± 2.9 male and 91.0± 3.5 female)] . In these patient groups, the decrease of the MCV was significantly correlated with a decrease of the MCHC (WP, r= 0.421, p<0.005 and CP, r= 0.453, p<0.051), (data not shown).

Total Leucocyte Counts

A significant increase of the leucocyte absolute levels were present in all Warao groups. WP (9.6± 2.7) WC (8.9± 3.0) and WCh (10.4± 2.3) as compared to both creole groups, CP (7.9± 2.9) and CC (7.0± 1.3), 0.03>p>0.0001, (Table I). A significant increase of lymphocyte and monocyte and decrease of the neutrophil absolute levels were also present in the Warao groups, WP (3.7± 1.6, 2.2± 1.3 and 3.5± 2.0, respectively) WC (3.4± 1.1, 2.3± 1.6, and 2.9± 1.9) and WCh (3.9± 0.9,

2.4± 0.9 and 3.4± 1.3) as compared to both creole groups, CP (1.8± 0.9, 0.8± 0.8 and 4.7± 1.5, respectively) and CC (2.3± 0.5, 0.7± 0.3 and 4.1± 1.3), 0.03>p>0.0001, (data not shown).

Percentage of Lymphocytes

The percentage of lymphocytes of the study groups is shown in Table I. All Warao groups presented a significant increase of the percentage of lymphocytes, WP (39.6± 13.8), WC (41.4± 9.8) and WCh (39.9± 5.9) in comparison to CP (24.3± 9.3) and CC (33.4± 7.9), 0.006>p>0.0001, (Table I).

Percentage of Monocytes

The results of the percentage of monocytes of all study groups are shown in Table I. Similar to the increase in the percentage of lymphocytes, a significant increase of the percentage of monocytes was also present in all Warao groups, WP (22.0± 9.2), WC (25.2± 12.3) and WCh (25.2± 9.6), in comparison to both creole groups, CP (6.9± 4.2) and CC (10.2± 5.0), p<0.0001, (Table I).

Percentage of Neutrophils

The data of the percentage of neutrophils of the study groups are shown in Table I. The percentage of neutrophils was significantly reduced in all Warao groups, WP (36.4± 16.3) and WC (33.4± 13.6), and also in WCh (34.8± 10.8), in comparison to CP (67.1± 10.7) and CC (56.3± 9.5) groups, 0.005>p>0.0001, (Table I).

Percentage of Malnutrition

Malnutrition based on the BMI as the anthropometric parameter is shown in Figure 2. The highest percentage of malnutrition (66%) was observed in children between 1 and 2 years old, which is significantly different from the second highest, which was in adults older than 60 years old (34%), followed by children between 2 and 6 years old (25%), then by adults between 30 and 60 years old (18%) and finally in infants less than one year old (15%).

Disscussion

The present study showed that in Warao groups, principally WP and WCh groups, the levels of the Hb were reduced, in comparison to the creole groups. The decrease of the Hb levels was significantly correlated with a decrease of the MCHC values. It has been reported that the iron deficiency may be acquired through extrinsic factors, for example malnutrition conditions[4,26,27]. If so, the lower MCHC observed in Warao groups probably could be associated to a deficit of iron as a result of their nutrition conditions. When the BMI was performed to assess the Warao nutritional profile, we found that it increased to reach the highest BMI in the adolescent group; however, after that it decreased with age, probably because of high percentages of indigenous malnutrition 18% and 34%, in adults between 30 and 60 and older than 60 years, respectively. It has been reported that the different nutritional profile in a population results from specific patterns of social, cultural and economic conditions of each population[1]. The BMI parameter does not indicate the corporal composition, but it is useful in epidemiological surveys since it gives an idea about the percentage of malnutrition because the BMI is used as an indicator of nutritional status in adults[1,10]. Unlike the Warao population, a study performed in Malasyan indigenous groups showed that BMI distribution increases with age, while that of height decreases with age[19].

Figure 2 Body mass index (BMI). Data representing the percentage (%) of malnutrition based on the body corporal index of the groups classified by age.

The Warao patients had significant monocytosis compared to the creole patients. The latter and the findings mentioned above correlate with the most common hematologic manifestations of TB, which are increases in the peripheral blood monocyte counts and anemia, each of which occurs in approximately 10% of patients with apparently localized TB[5,8,15]. In relation to another parameter of the white blood cell counts, all Warao groups presented a significant reduction in the numbers of neutrophils, in comparison to the creole groups. The fact that both monocytosis and the reduction in the numbers of neutrophils were present even in the absence of TB in Warao adults and children suggests that the profile of the white blood cell counts in Warao adults resembles the profile of the white blood cell counts present in Warao children. In addition, the percentages of the lymphocytes were significantly increased in all Warao groups, as compared to the creole groups.

Similar to the increase in the peripheral blood monocytes that may occur with TB, an increase of neutrophil cell counts has been reported[26,27]. In contrast, a decrease of neutrophil cells counts in Warao groups was observed. In relation to the latter, quantitative deficiencies in neutrophils can range from an almost complete absence of cells, called agranulocytosis, to a reduction in the concentration of peripheral blood neutrophils below 1500/mm3, called granulocytopenia or neutropenia[16]. In our study, although the decreased levels of neutrophils do not constitute a neutropenia, all Warao groups presented a significant reduction in the numbers of neutrophils. It has been reported that signs of reduction in the numbers of neutrophils include populations with high prevalence to recurrent infections, unusual opportunistic infecting agents and chronic infections such as TB[13,15,16]. It has been reported that the intravenous administration of the anti-neutrophil monoclonal antibody RB6-8C5 during the first week of M. tuberculosis infection led to selective and severe neutropenia associated with an enhancement of bacillary growth in the target organs of infected mice[24].

As mentioned above, the fact that the profile of the white blood cell counts in Warao adults resembles the profile of the white blood cell counts present in Warao children could be the result of extrinsic factors such as malnutrition, viral, bacterial and parasite infections. It has been reported that in the Warao population, intestinal infections and malnutrition are common9,12. In our study, we found that in the Warao population, both children and adults are polyparasited with protozoa and helmintic parasites as, for example, Entamoeba coli and Ascaris lumbricoides and/or Ancylostomidae, respectively (data not shown). Thus, the high number of monocytes and lymphocytes and the low number of neutrophils observed in the Warao population could be the result of recurrent or overwhelming parasite infections and also malnutrition at early ages. Both conditions, parasite infections and malnutrition, could also explain the decrease in Hb values and the lower MCHC observed in Warao groups. Furthermore, malnutrition and overwhelming parasite infections could also be the stimuli for the high levels of platelets present in the Warao children population. Supporting the latter is the fact that platelets, in addition to their role in blood clotting, they are involved in the immune response, especially in inflammation and are capable of killing various types of parasites, including schistosomules, T. gondii and T. cruzi. Like other effector cells, their cytotoxic activity is enhanced by treatment with cytokines such as IFNg and TNFa . Furthermore, they possess class I MHC products and also bear Fc receptors for IgG and IgE on their surface membrane, by which they mediate antibody-dependent cytotoxicity6.

Since many different infections including M. tuberculosis infection are prevalent within the Warao population, a reduction in the numbers of neutrophils, malnutrition and parasite infections from early age could explain the high susceptibility of this population to infections. In addition, other risk factors must be taken in account such as the fact that this population has been isolated from contact with the tubercle bacillus for so many years. Maybe all these conditions could predispose this population to suffer from recurrent infections, including infection by M. tuberculosis9,16,23, even though inherited conditions can not be excluded. In 1988, the Warao were tested for HLA-A,B, HLA-Cw, HLA-DR and HLA-DR/DW 1-8 antigens. The findings confirmed the existence of the DR/DW dissociation previously observed in North American Indian, Japanese and Caucasian populations, and showed inheritance and segregation of DW specificities (DW 8,3, DW 16, DW 22) defined only with homozygous typing cells of Warao origin. These data illustrated HLA haplotypes, linkage-disequilibrium, and DR/DQ associations not seen previously in other human populations18. In summary, in the tuberculous and non tuberculous Warao adults as well as in the Warao children, the formula of white blood cells is characterized by monocytosis with high number of lymphocytes and low number of neutrophils. The findings suggest that within a naive population, high number of lymphocytes and monocytes probably had conferred a definitive but small protection against infections. However, TB may have been or may still be an important selective factor in driving the maturation of the immune system of Warao, and in shaping the immune response to infections, including TB.

Acknowledgements

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