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SERUM URIC ACID LEVELS IN CHAGAS' DISEASE

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Uricemia was studied in a sample of 192 individuals from a highly endemic site for Chagas' disease (Bambuí, State of Minas Gerais, Brazil). The sample had 50 serologically negative individuals (controls) and the positive ones were classified on the basis of the presence of electrocardiographic alterations (63), altered esophageal emptying (16), or without any sign on sympton of the disease (76). Only the individuals with the digestive form of chronic Chagas' disease showed hyperuricemia, when compared with the appropriate controls. Family data suggest that hyperuricemia is an effect of the digestive pathology, rather than a cause, since the non-infected sibs of the megaesophagous patients did not show elevated levels of serum uric acid. Possible mechanisms responsible for these findings are postulated.

Key words – uric acid – Chagas' disease – uricemia

Some methabolic alteration are known in chronic Chagas' disease. Disturbances in neuroendocrine regulation of the thyroid, corticoadrenal and ovarian function are thought to be derived from lesions of the hypothalamic-hypophyseal central systems (Lomônaco et al., 1966; Lobo et al., 1962; Kimachi et al., 1974; Moreira, 1978; among others).

Atypical glycemia and galactosemia tolerance curves and fractional lipidemic aberrations were proposed to derive from rapid gastric transit leading to faster intestinal absorption of sugars and poorer emulsification of fats (Vieira & Meneghelli, 1970; Vieira et al., 1970; Forti et al., 1976; Giannini et al., 1976; Padovan et al., 1977). The chronic undernutritional state which accompanies the digestive system's megas of Chagas' disease has not been found to be associated with any other specific alteration of serum components (Rezende, 1979).

The finding of a significant inhibition of purine base uptake in *Trypanosoma cruzi* culture epimastigotes by urate, with possible alteration of the membrane permeability to purine bases (Guimarães & Gutteridge, 1987), led to a suggestion that uricemia levels might be implicated in the natural history of Chagas' disease.

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This report is a test of the hypothesis referred above, examining uricemia levels in a sample from Bambuí (MG), and endemic site of the disease in central Brazil, which is also being subjected to other genetic-epidemiological studies.

MATERIALS AND METHODS

A sample of 390 individuals was collected from Bambuí (MG) in order to study the inter and intra-familial variability of the human response to *T. cruzi* infection. These individuals belonged to families ascertained through serologically positive probands identified in the files of the *Centro de Pesquisas Ezequiel Dias* – FIOCRUZ and are the probands themselves and their first degree relatives.

The sample is characterized by a mean age of 43 years, a sex-ratio of 37.4% males and 73.6% of serologically positive individuals.

All individuals were examined for the presence of cardiopathy through ECG and megaesophagous through X-ray examination after contrast swallowing (Laranja et al., 1956 and Coura et al., 1984).

From each individual, a sample of about 2 ml of serum was obtained and stored at – 40 °C. Uric acid levels were determined on this material by the classic photocolorimetric method, utilizing the appropriate kits (Caraway, 1955).

The data were analyzed by multiple regression and non-parametric tests (Kruskall-Wallis) empolying specific programs from the GENIOC library, writen in Fortran 77 language for 16 bits microcomputers.

Significant contrasts referred in the Tables are: * = $P < 0.05$ and ** = $P < 0.01$.

RESULTS

The mean serum uric-acid level (UAL) was 4.03 ± 1.35 mg/100 ml, based on 196 tested individuals. These values were 4.12 among serologically negative individuals and 4.00 among positive individuals. From the latter, the average UAL was 3.99 among cardiopathic individuals; 5.20 among individuals with the digestive form of the disease and 3.86 among assimptomatic individuals.

These observed values are represented in the Figure. As can be seen, only the UAL of the patients with the digestive form showed a suggestive elevation. These UAL were compared trough Kruskal-Wallis' H test, as shown in Table I. The significant difference observed, when patients with the digestive form of Chagas' disease were compared with any of the other groups, support the suggestion derived from the Figure. With the aim of controlling concomitant variables that could be counfounded with the clinical forms classification, a stepwise multiple regression analysis was applied to the data. The independent variables were: age, sex, total serum protein, serum albumine, quantitative paleness, hematocrit, weight, height, obesity, the square of age and the interaction terms of sex x age and sex x age squared.

A natural logarithmic transformation was applyed to UAL in order to improve the shape of the distribution.

The only concomitant variables that significantly affect UAL were: sex x age and obesity, as can be seen in Table II. Again, the variable "digestive form of the disease" showed a significant elevation of UAL, even taking into account the concomitant variation of the above factors.

TABLE I

Values of Kruskal-Wallis' H (with 1 D. F.) for several comparisons

Comparison	N	Mean UAL (mg/100 ml)	Average rank	N	Mean UAL (mg/100 ml)	Average rank	H
Negative x positive serology	50	4.12	101.6	146	4.00	97.6	0.14
Among serologically positive							
Indeterminate x Chagas' disease	76	3.86	69.6	70	4.15	77.7	1.35
Miocardiopathy x non-miocardiopathy	63	4.00	74.1	83	4.00	73.1	.02
Megaesophagous x non-megaesophagous	16	5.20	105.1	130	3.85	69.6	10.03**

TABLE II

Multiple regression analysis of Ln UAL on megaesophagous and concomitant variables

$\bar{Y} = 1.38 \pm 0.32$ $A = 0.91 \pm 0.02$

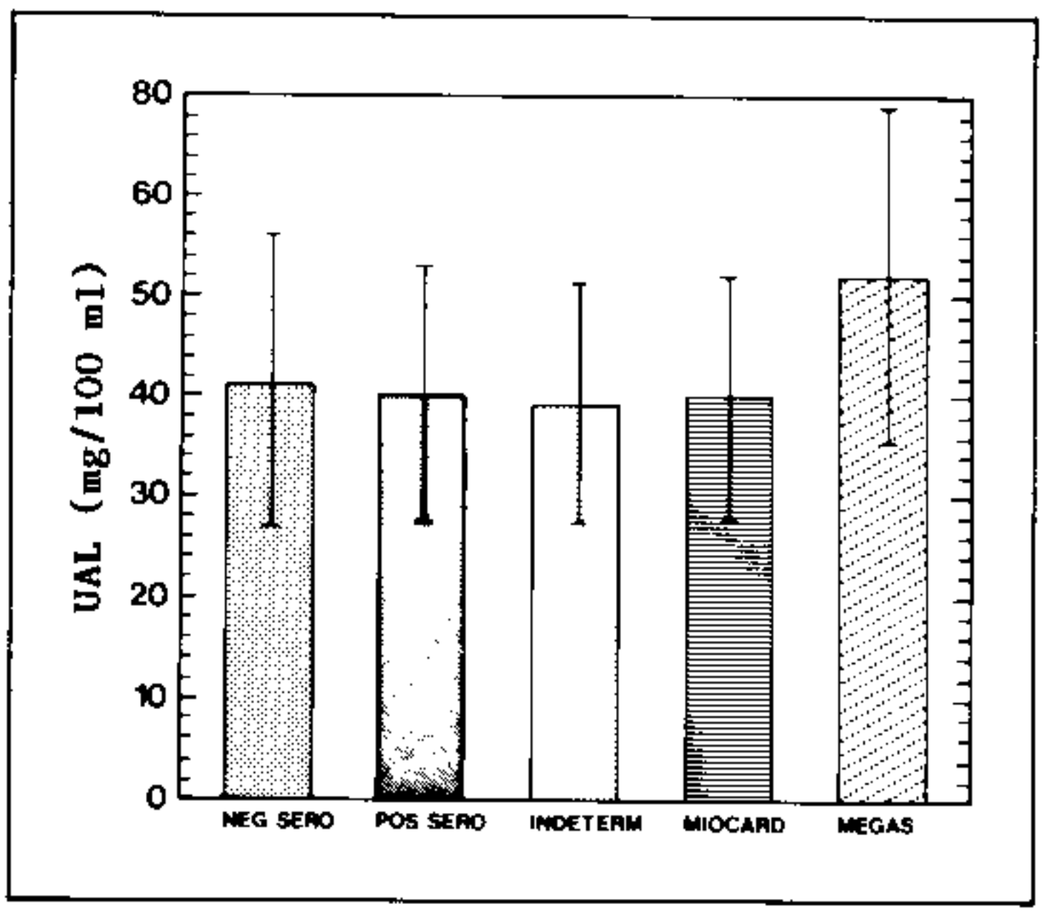
	$\bar{X}$	±	S. D.	B	±	S. E.
Sex x age	15.61		21.20	.006		.001**
Megaesophagous	0.10		0.31	.250		.090*
Obesity	1.4×10^{-5}		3.1×10^{-6}	2.4×10^{4}		9.0×10^{3} *

Variance Analysis

Source	DF	SS	F
Regression	3	2.50	9.97**
Residual	120	10.04	

Since the observed UAL elevation among the megaesophagous patients could be either an effect of the disease or of a previously existing condition that could be one of the causes of the development of the digestive form of the disease, a simple test of these contrasting hypotheses was performed. Based on the knowledge that UAL is a highly heritable trait (Neel et al., 1965; Gulbrandsen et al., 1979; Morton, 1979), one would expect that the non-infected sibs of the megaesophagous patients would show a similar UAL as compared with their affected sibs, if the elevated UAL were reflecting a predisposing cause.

The figures of Table III show that the face values of UAL among non-infective sibs is similar to that of the patients with the indeterminate form of the chronic infection, being, therefore, lower than that of their affected sibs. Although the number of informative families is rather small, in our sample, these results strongly suggest that UAL elevation in megaesophagous patients is an effect of the disease rather than a possible cause.



Average of Uric Acid values (UAL) and their respective standard deviations for four groups of individuals, according to the type of infection by *Trypanosoma cruzi*. Neg sero, Pos sero = negative and positive serology, respectively; Indeterm, Miocard, Megas = Indeterminate, miocardiopathy and megasyndromes forms of chronic Chagas' disease, respectively.

TABLE III

Comparisons between individuals with megaesophagous with their serologically negative normal sibs, and between the latter and the general sample controls

Average UAL levels (in mg/100 ml)		Kruskal-Wallis' H
Megaesophagous	Normal sibs	
4.3	3.1	1.8
General controls		
3.7	3.1	0.7

DISCUSSION

Uricemia is an extremly complex phenotype. Urate metabolism is influenced by multifactorial and/or polygenic complexes of causes (Wyngaarden & Kelley, 1978; Morton, 1979; Gulbrandsen et al., 1979; among others). At present, no ready simple explanation can be advanced for the detected association of megaesophagus and hyperuricemia. However some stimulating reasoning can be put forward, in order to have a better understanding of the mechanisms involved in this process.

The components of the physiopathology of chagasic megaesophagous which should be thought of as the most likely causes of hyperuricemia are: a) overproduction of urate in the undernourished state where the catabolic route of purine metabolism predominates over the anabolic route. Dietary and endogenous recycled purines would not be adequately sequestered in the cellular purine anabolic pools and/or in nucleic acids and so would be more easily available to the catabolic pathways: b) overproduction of urate in the infectious state where mononuclear leucocytes are being overproduced and rapidly destroyed, a hemopoietic-hemocateretic dyscrasia with increased turn-over of immune cells, associated to the tissular inflammation with an increased local destruction of inflammatory and parenchymal cells. The destruction of parasites could also be considered part of this item but the usually low levels of parasitemia in the chronic phase of Chagas' disease would suggest its contribution to the hyperurecemia not to be quantitatively important; c) hemoconcentration derived from dehydration of the patients. Rezende (1979) refers this factor as responsible for the near-normality of most biochemical blood determinations which would be expected to be lowered due to undernutrition in the chagasic megaesophagous.

In the case where intestinal statis might be associated with the esophageal pathology, it could participate in the genesis of hyperuricemia by generating urate in the intestinal mucosa; the intestinal bacterial flora could also contribute with the generation of urate to be reabsorbed; the participation of the hepatic xanthine oxidase might be thought of in this situation, where its activity could be stimulated by portal venous transport of intestinal contents (Spilberg, 1975). We have no indication for the possibility of increased plamatic binding of urate. We also have no reason to think of a renal tubular alteration which could lead to under-excretion or under-secretion of urate. Studies of renal function and hemodynamics in chronic Chagas' disease (Acquatella & Puigbó, 1974; Kimachi et al., 1978) showed alterations which would not seem to contribute to hyperuricemia: a lowered renal plasma flow in the compensated cardiopathics would be counterbalanced by a higher natriuresis (tested after blood volume expansion) and a lowered concentrating capacity of the kidney (tested after controlled hidropenia). The latter alteration is thought to be consequent to the defficient neuro-endocrine regulation of antidiuretic hormone secretion.

It is relatively clear that some of the above speculations may be pertinent to the present findings. However, it should be stressed that although the present data are consistent in showing an effect of the digestive form of Chagas' disease on UAL, studies in other populations are important, in order to allow a generalization of the present findings.

RESUMO

Níveis de ácido úrico sérico na doença de Chagas — A uricemia foi estudada em uma amostra de 192 indivíduos de uma região altamente endêmica para a doença de Chagas (Bambuí, Estado de Minas Gerais, Brasil). A amostra continha 50 indivíduos sorologicamente negativos (controles) e os positivos foram classificados na base da presença de alterações eletrocardiográficas (63), esvaziamento esofagiano alterado (16), ou ausência de sinais ou sintomas da doença (76). Somente os indivíduos com a forma digestiva da doença de Chagas crônica mostraram hiperuricemia, quando comparados com controles adequados. Dados familiares sugerem que a hiperuricemia é um efeito da patologia digestiva em vez de causa, uma vez que os irmãos não afetados dos pacientes com megaesôfago não apresentaram níveis elevados de ácido úrico sérico.

São postulados alguns mecanismos possivelmente responsáveis pelos achados.

Palavras-chave: ácido úrico – doença de Chagas – uricemia

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