

SEX EFFECT ON THE FAMILIAL AGGREGATION OF ENDEMIC GOITER

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ABSTRACT

The results obtained in a genetic-epidemiological survey of goiter in a hyper-endemic area in the State of Mato Grosso, Brazil, were analyzed in relation to the association between parental phenotype and occurrence of goiter in the children. A familial aggregation of endemic goiter was found.

Multiple regression analysis showed that the degree of manifestation of the paternal phenotype is predictively associated with the severity of the disease in the male and female children, taken separately. The degree of manifestation of the maternal phenotype was associated only with the severity of the phenotype of the female children.

INTRODUCTION

Simple endemic goiter, *i.e.* goiter accompanied by sufficient amounts of hormonal secretion so as to satisfy organic needs, also called colloid goiter, is a diffuse hypertrophy of the thyroid gland not depending on its etiology and without any links with the functional state of the gland (Roche, 1961; Rosa, 1974). An area is arbitrarily defined as endemic if more than 10% of the population is shown to have goiter after a proper survey (recommendation by a Committee of the Pan American Health Organization; *cf.* Querido *et al.*, 1974).

A few well known environmental factors play an important role in the etiology of endemic goiter, the most important being iodine deficiency (see review in Freire-Maia, 1981). It should be pointed out, however, that not all individuals react in the same way to goiter-producing factors in the same endemic area. The cause of this individual differences may be of an environmental and/or genetic nature (Freire-Maia and Freire-Maia, 1970).

One of the methods used to study the influence of genetic factors in the genesis of a disease is to find out whether the disease shows familial aggregation (Beiguelman, 1977), and endemic goiter has been studied from this point of view for a long time. About 50 years ago, on the basis of studies by von Pfaundler and Davenport (*cf.* Fraser, 1963), genetic predisposition was believed to be a factor in the etiology of endemic goiter. Stanbury (1962) commented on the fact that, up to that time, the role of genetic factors in the etiology of endemic goiter was suspected but not proved. In several familial studies of endemic goiter (*cf.* Fraser, 1963) no pattern of mendelian inheritance could be detected. The familial studies carried out by Eugster more than 40 years ago (*cf.* Fraser, 1963, 1964) demonstrated the greater importance of environmental rather than genetic factors in the etiology of endemic goiter.

Hadjidakis *et al.* (1964) studied families with endemic goiter by separating the children into two groups: children with goitrous mothers, and children with normal mothers, and concluded that a hereditary factor predisposing to goiter development in a relatively iodine-deficient environment was present. These authors, however, did not carry out a complete familial analysis since they had no information on the fathers' condition.

London *et al.* (1965) studied the families of an East Kentucky mountain village and concluded that the occurrence of goiter in that community was more compatible with simple dominant inheritance, though admitting to some incompleteness in their survey. Covarrubias *et al.* (1969) performed familial analysis of nodular goiter only and found that, when both parents were affected, the prevalence rate in the children was three times that observed when neither parent was affected. These authors suggested the existence of polygenic genetic factors, among them the genes for sensitivity to PTC.

Lobo *et al.* (1969) also found a significantly greater prevalence of goiter in children with one or both affected parents when compared to children of normal parents. Thilly *et al.* (1972), in a study of families whose parents were both goitrous, of families with one goitrous parent, and of

families with normal parents, found higher prevalence of goiter in the children of parents who were both affected, and a decreasing prevalence in the other types of families. These authors concluded that a familial tendency to goiter may exist, though a weak one which could be explained both by a multigenic hereditary form and by the influence of etiological factors in the microenvironment. The conclusion reached by Thilly *et al.* (1972) seems to apply, in a way, to all studies carried out on familial aggregation of endemic goiter. Simple correlation between the parents' and the children's phenotypes is no guarantee for the existence of genetic factors. Considering that confirmation of familial aggregation in endemic goiter and control of at least some variables would be highly desirable, we decided to analyze the data obtained in an epidemiological study carried out in a hyperendemic area in the State of Mato Grosso, Brazil.

MATERIAL AND METHODS

The methodology for data collection and analysis has been described by Freire-Maia *et al.* (1980). Briefly, a study was made of 1525 families residing at 11 different locations in the State of Mato Grosso. The clinical examinations for determining the presence of goiter were always performed by technicians specially trained by a physician of the Public Health Service. The methodology used for analysis and classification of goiter was that adopted by the World Health Organization (PAHO, 1974).

The subjects were grouped according to type of goiter and the data were analyzed statistically. Contrasts among binomials (Goodman, 1964, 1965) and multiple regression models (Nie *et al.* 1975) were used. Analysis was carried out using the computer facilities of the University campus at Botucatu, UNESP, of the Health, Educational and Research Computer Center, University of Texas at Houston, and of the Population Genetics Laboratory, University of Hawaii at Honolulu. All analyses, except some multiple regression ones, excluded children younger than five, since it is only from this age on that goiter prevalence reaches more elevated levels (higher than 30%).

RESULTS

Goiter distribution in the children according to the presence or absence of goiter in the parents is found in Table I. All the contrasts performed were significant: the children of class I couples have a lower goiter frequency (35%) than the children of class II (57%) and class III (73%) couples; and the children of class II couples have a lower frequency than those of class III couples.

Multiple regression analyses were performed separately for the male (Table II) and female (Table III) subgroups in order to study the effect of sex on goiter prevalence (Freire-Maia, D.V. and Freire-Maia, A., unpublished results). The results obtained are summarized in Table IV. Of the 20 independent variables included in the multiple regression models (Freire-Maia, 1978), five in the male subgroup and nine in the female subgroup were shown to be significantly related with endemic goiter (Table IV). The "paternal goiter" variable was shown to be predictively associated with endemic goiter in both subgroups, while the "maternal goiter" variable showed significant effect only in the female subgroup.

Table I - Distribution of goiter in the children according to the parents' phenotype.

Parents*	Children	
	Goiter**	Total
I. N x N	165(0.35)	465
II. N x G	423(0.57)	744
III. G x G	263(0.73)	362
Total	851(0.54)	1571

* N = Normal; G = Goiter 1 + 2 + 3.

** Relative frequencies in parentheses. Significant contrasts (critical value at 0.05 = 2.40):

I < II (G = 7.69); I < III (G = 11.82); II < III (G = 5.41).

Table II - Multiple regression analysis of goiter, considered as a quantitative character, in males. all ages. $\alpha = 0.1373$.

x_i^{**}	b_i	S.E.	F
Paternal goiter	0.1072	0.0327	10.71*
Region	0.4936	0.0521	89.81*
Civil status	-0.7216	0.1215	35.26*
Age	0.0510	0.0034	227.16*
Birth place	0.2574	0.0868	8.80*

ANALYSIS OF VARIANCE			
Source	df	ss	F
Regression	20	187.66	20.89*
Residue	911	409.23	
Total	931	596.89	

* $P < 0.05$ $R^2 = 0.3144$ S.D. = 0.6702
 ** See footnote to Table IV.

Table III - Multiple regression analysis of goiter, considered as a quantitative character in females, all ages. $\alpha = 0.0072$.

x_i^{**}	b_i	S.E.	F
Maternal goiter	0.0985	0.0248	15.79*
Paternal goiter	0.0900	0.0268	11.28*
Region	0.6236	0.0465	179.65*
Household conditions	0.0359	0.0156	5.26*
Residential density	0.0279	0.0118	5.62*
Paternal inbreeding	0.0065	0.0027	5.91*
Marital status	-0.5197	0.0884	34.60*
Age	0.0582	0.0031	360.95*
Maternal education	-0.0587	0.0291	4.07*

ANALYSIS OF VARIANCE			
Source	df	ss	F
Regression	19	303.94	41.16*
Residue	1016	394.89	
Total	1035	698.83	

* $P < 0.05$ $R^2 = 0.4349$ S.D. = 0.6834
 ** See footnote to Table IV.

Table IV -Sex effect of the independent variables on the occurrence of endemic goiter considered as a quantitative character, all ages included.*

Independent variables	Effect**		
	Type	Males	Females
Maternal goiter	normal --- → goiter 3	—	Pos
Paternal goiter	normal --- → goiter 3	Pos	Pos
Region	A ----- → B	Pos	Pos
Household conditions	bad ----- → good	—	Pos
Residential density	low ----- → high	—	Pos
Paternal inbreeding	F = 0 ----- → F = 1/8	—	Pos
Marital status	single ---- → married	Neg	Neg
Age	increase with age	Pos	Pos
Maternal education	low level → high level	—	Neg
Birth place	urban----- → rural	Pos	—

* Only variables which reached significance are shown. For an analysis and discussion of the results relating to all the independent variables, with the exclusion of Maternal and Paternal Goiter, discussed in the present paper, the reader is referred to Freire-Maia (1978).

** Pos = Significant positive effect; Neg = Significant negative effect; — = Not significant effect.

DISCUSSION

To the best of our knowledge, ours is the first study to apply multiple regression models to endemic goiter family data. The models applied to the total sample (Freire-Maia, D.V., Freire-Maia, A., Schull, W.J., Morton, N.E., Quelce-Salgado, A. and Lobo, L.C., unpublished results) always showed positive results with respect to the predictive influence of parental phenotype on child phenotype. However, the separate analysis of the male and female subgroups presented here showed that the degree of severity of the abnormal maternal phenotype was not significantly associated with the degree of severity of the abnormal phenotype in the male children.

Apparently, the results in the literature and those presented here do not disprove that, in an endemic area: (a) the parents' phenotype may be significantly associated with the possibility of goiter occurrence in their sons and daughters; (b) the degree of goiter severity in the daughters may depend on the degree of severity of both the paternal and maternal goiter; (c) the degree of goiter severity in the male children may depend on the degree of severity of the paternal goiter, but may not depend on the degree of severity of the maternal goiter.

The first possibility (a) seems to have been supported in a series of papers published in the literature. The second possibility (b), in addition to being quite reasonable and, in a way, expected, is supported by the results presented here. The third possibility (c) though suggested by the present analysis, immediately leads us to ask a question: why would the degree of goiter manifestation in male children not depend on the severity of the disease in their mothers? We have no satisfactory answer to this question, and some statistical artifacts may have occurred.

Of course predictive capacity does not necessarily represent explanatory capacity, control of concomitant variables is only true in a predictive sense, and unmeasured variables like diet and water supply are certainly important. We have therefore no intention to conclude that familial association is genetic. Complex genetic models were applied to the family data and the results will be published elsewhere (Freire-Maia *et al.*, in preparation).

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RESUMO

Os resultados obtidos em uma análise genético-epidemiológica do bócio em uma área hiperendêmica do Estado de Mato Grosso são analisados relativamente à as-

sociação entre o fenótipo dos pais e dos filhos. Confirma-se a existência de uma associação familiar do bócio endêmico.

Análises de regressão múltipla, com o emprego de 20 variáveis concomitantes, mostraram uma associação preditiva entre o grau de manifestação do fenótipo paterno e a severidade da doença nos filhos e filhas, analisados separadamente. O grau de manifestação do fenótipo materno mostrou associação preditiva apenas com a severidade do bócio nas filhas.

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