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Bronchial Asthma in Children: Clinical and Epidemiologic Approach in Different Portuguese Speaking Countries

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INTRODUCTION

Bronchial asthma constitutes an important health problem, related with significant rates of morbidity and mortality, being the most frequent chronic childhood disease.[1]

Recently, multiple epidemiological studies, referring to the prevalence of asthma, atopy and bronchial hyperresponsiveness in different populations, have been presented showing a wide spectrum of results: for childhood asthma, rates between 0 to more than 30% were presented, suggesting the existence of a variable incidence of environmental risk factors in genetically similar populations and different asthma prevalence in populations submitted to apparently the same environmental variables, emphasizing the importance of environmental and genetic factors in this multifactorial disease.

In the last two decades, despite the significant advances in the knowledge and understanding of asthma pathogenesis, it is currently accepted that there is an increase in the prevalence of allergic diseases.[1] This could be related to an aggressive environment, acting in a genetically favorable background, but the conclusions based on the epidemiological investigation of the disease had been detrimented by bias, with regard to different definitions, diagnostic criteria and study methodologies.

An epidemiological collaborative worldwide study - International Study of Asthma and Allergies in Childhood (ISAAC)[2] - is now being conducted, applying the same methods to different pediatric populations, allowing uniformity into data collection, as far as different languages allow. Portugal participates in this project (National Coordinator: Prof. Dr. J. E. Rosado Pinto), with five centres: Lisboa, Porto, Coimbra, Portimão and Funchal. In another Portuguese speaking country – Brazil, South America - the same methodology was applied in seven centres (National Coordinator: Prof. Dr. Dirceu Solé): São Paulo, Porto Alegre, Recife, Curitiba, Salvador, Itabira and Uberlândia. In the 13 – 14 year-old group, 463.801 children participated, from 155 collaborating centres in 56 countries, 5.8% with Portuguese language (5th language).

Beyond the ISAAC study, since 1993, our group (Serviço Imunoalergologia, Hospital Dona Estefânia) has been working in the epidemiology of childhood allergic diseases (coordinator: Dr. M. Morais Almeida), using the same standard methods applied to pediatric populations in Madeira Island (Portugal, Europe), Sal and S. Vicente Islands (Cape Verde Republic, Africa) and Macau (Asiatic Region, with Portuguese administration).

The aim of this work is to discuss some epidemiological data collected from Portuguese speaking regions, with different genetic, cultural and environmental influences, that could explain the results found.

GEOGRAPHY AND DEMOGRAPHY

Portugal

Located in SouthWest Europe, it also includes Madeira and Azores Archipelagos. Has two climatic zones: northern, characterized by the influence of Atlantic air currents and the Spanish Meseta, with significant precipitation; southern, with a Mediterranean climate, with low annual precipitations and weather conditions influenced by the Azorean high pressure system. Madeira Archipelago, located in the Atlantic Ocean, nearby Morocco coast, has a sub-tropical climate, and is one of the Archipelagos that composes the Macaronesian Islands: Madeira, Azores, Canaries and Cape Verde. Estimated 1997 population: 9 807 700. Area: 92 082 Km^2. The ethnic majority is the Portuguese (99%),

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descendent of mixed racial stocks: Celts, Phoenicians, Greeks, Carthaginians, Romans, Vandals, Arabs and Berbers. Madeira also has a significant influence of populations that have migrated from Central and Northern Europe.

Brazil

Located in East Central South America, it has a tropical and subtropical climate characterized by high temperatures and moderate to heavy rainfall. Until the XIX Century, Brazil was a colony of Portugal. Estimated 1997 population: 165 405 300. Area: 8 511 965 Km^2. The Brazilians are composed of: indigenous Amerindians (1%); Caucasians (53%) (of which the Portuguese represent 15%, Italians 11%, Spanish 10% and Germans 3%); Mulattoes (22%), a mix of Caucasian and Black African; Mestizos (11%), a mix of Amerindian and Caucasian; Black African (11%); Japanese (1%).

Cape Verde

Located in the Atlantic Ocean, Guinea Golf, West Coast of Africa, it shares the same volcanic origin as Madeira. Composed by ten islands and five islets, it has a tropical climate with two seasons: a cold dry season from December to June and a warm season between July and November. Rainfall is rare. Tropical heat and high humidity is frequent. Discovered as desert islands, it was a Portuguese overseas province until 1975, when it became an independent republic. Estimated 1997 population: 391 200. Area: 4 033 Km^2. The ethnic majority are Creoles of mixed Black African and Portuguese descent; the remainder are mainly Black Africans with a small number of Caucasians. In Sal Island the majority of the population is Black African; in S. Vicente Island, the majority is Creole, mainly with influences from Portuguese and also North European people.

Macau

Located on the southern coast of China on the Pearl River, Asia, it.has a subtropical climate, marine, with cool winters and warm humid summers. The rainfall is significant. It is a special Chinese territory under Portuguese administration since 1557 and until December 1999. Estimated 1997 population: 396 000. Area: 16 km^2. The principal ethnic majority are the Chinese (more than 75%), predominantly Cantonese. The remainder is a mixture of Chinese-Portuguese descendants and Portuguese.

MATERIAL AND METHODS

In both studies, the sampling frame was schoolchildren, aged between 6 to 14 years. Standard, previously validated epidemiological methods were applied. The response rates were between 81.9 and 99.6%.[3]

1. ISAAC Study:[2,3] The aims and objectives of the study are 1) to describe the prevalence and severity of allergic diseases in children living in different regions, allowing comparisons within and between countries, and 2) to obtain baseline measurements for the assessment of future trends in allergic disease prevalence and severity, and 3) to provide a framework for further etiological research into lifestyle, environmental, genetic and health care factors affecting these diseases. The methods, organization and results of Phase 1 (Questionnaire modules, 13-14 years group) have already been published.[2,3] In Portugal and in Brazil (1993/96), two age groups were studied: 13-14 year-old group and 6-7 year-old group, enrolling 50,221 children. In this paper we will only discuss the results of 13-14 years age group self-answered questionnaire.[3,4,5]

2. **Portuguese Study of Childhood Allergic Diseases**: This study started in 1992 (validation of methods),[6] focusing on populations from Portuguese speaking regions. Randoml samples of schoolchildren from Madeira, Cape Verde and Macau, were included and studied with the same methodology: 1. Investigator-applied standard questionnaire (based on EC and ATS questionnaires), 2. Skin prick tests - SPT (standardized allergen extracts to common inhalant allergens: house and storage mites, cockroaches, moulds, pets and pollens – Merck Allergopharma and CBF-Leti) and 3. Bronchial provocation tests with methacholine (Lofarma), for the characterization of bronchial hyperreactivity – BHR (dosimeter method), performed among those who had had asthma symptoms in the last year, according to the questionnaire.

In significant house dust samples from Cape Verde and Madeira, collected in a standardized manner (Nilfisk® device, 2 minutes per m^2), the concentration of bedding house mite (HDM) antigens were assessed, using

monoclonal antibodies (Indoor Biotechnologies®), performed under supervision of Prof. Dr. Enrique Fernandez-Caldas (CBF-Leti, Madrid).

In 1993, in Sal Island, 235 children aged 6 to 16 years (total population of 2300 on this age group) were studied, mostly Black African; in 1994, a sample of 588 children, aged 6 to 10 years from S. Vicente, was included in the study, mostly Creoles (total of 8000 in this age group); in 1995, 1061 children aged 6 to 10 years were studied in Madeira Island, all Caucasians (total of 18000 in this age group); in 1997, 1385 schoolchildren aged 6 to 12 years were studied in Macau (total of 35000 in this age group), all Chinese. In Macau, the questionnaire was translated into Chinese and SPT were performed only in a sub-sample of 743 children.

DEFINITIONS: **Atopy** – *At least one positive SPT (wheal greater than 7 mm^2);* **BHR** - *$PD_{20}FEV_1$ methacholine lower than 7.8 µmol;* **Ever Asthma** - *Cumulative lifetime diagnosis;* **Active Asthma** – *Symptoms last year;* **Current Asthma** - *Symptoms last year plus positive BHR test.*

RESULTS

Table 1 represents the prevalence rates for positive symptoms of asthma/wheezing in the self-answered questionnaire. Significant differences between the two Portuguese speaking countries were found, with higher values in Brazil.[3,5,7] Within the countries, the differences were not so significant, with the exception of Itabira in Brazil (low prevalence). The comparison between S. Paulo (Brazil) and Lisboa (Portugal), two large, overcrowded, industrial cities, showed a statistically significant two-fold variation of ever and last year wheezing (45.4 and 23.3 Vs 21.6 and 10.9%, $p<0.001$). In severity, assessed by the number of attacks in the last year, the same trend was observed (more than 4 attacks last year: 4.4 vs 2.7%).

Table 1—ISAAC Study in Portugal and Brazil – prevalence in the 13-14 age group (%).

Country	N	Ever Wheezing	Wheezing Last Year	Ever Asthma
Portugal	11427	18.2	9.2	11.8
Brazil	20554	43.0	21.1	13.9

Among the Portuguese centres, Lisboa and Funchal (Madeira) showed the higher rates, with no significant differences, although having strikingingly different environmental local conditions.[7] The analysis of the Portuguese study results (Tables 2 and 3), revealed the highest prevalence of active asthma (14.6%) and atopy (54.1%) in Madeira,[8] 74% of asthmatics were atopic and 7% had at least one hospitalization. In Cape Verde,[9] active asthma had a similar prevalence to most European countries, but with much lower prevalence of allergen sensitization. With regard to atopic prevalence, differences were found between the two Islands studied (6.0 vs 11.9%); among asthmatics, 12% in Sal and 37% in S. Vicente, were atopics. The BHR tests were positive in 25, 66 and 70% of asthmatic children from Sal, S. Vicente and Madeira, respectively.

Table 2—Portuguese Study – Madeira, Cape Verde atopy/asthma prevalence (%)

Country Region	N	Atopy	Active Asthma	Current Asthma
Cape Verde				
Sal	235	6.0	10.6	2.6
S. Vicente	588	11.9	7.0	4.8
Portugal				
Madeira	1061	54.1	14.6	10.2

In Macau, the questionnaire and SPT results (Table 3), showed the lowest active asthma prevalence identified, associated with a significant atopic sensitization rate, similar to that found in Madeira.

Table 3—Portuguese Study - Macau atopy/asthma prevalence (%).

Country Region	N	Atopy	Ever Asthma	Active Asthma
Portugal				
Macau	1385	-	3.5	1.3
	(743)	48.6	-	-

In all the regions studied, HDM antigens were the most common source of sensitization, although with significant differences between centres. The children bed mean concentrations of Der p1 and Der f1 are shown in Table 4. As expected by the ecological local conditions (temperature and humidity), in Cape Verde, relating to the low prevalence of HDM sensitization, significant levels of

antigens were found in both Islands, with no statistically significant differences ($p>0.05$).[10] In Madeira Island, although atopic prevalence were higher, lower HDM concentrations, namely Der f1, were determined.

Table 4: Portuguese Study - House dust mite in μg/g dust (geometric mean).

Country Region	N	Der p1	Der f1
Cape Verde			
Sal	25	12.9	3.1
S. Vicente	27	5.1	6.5
Portugal			
Madeira	87	3.0	0.3

In Madeira, 69% of the mattresses had more than 2 μg Der p1/g dust, 25% more than 10 μg/g dust and 9% more than 100μg/g dust. For Der f1, only 6% of beds had more than 2 μg/g dust. In Sal Island (the lowest HDM prevalence of sensitization), similar percentages of mattresses had Der p1 levels higher than 2 (56%) and 10 μg/g dust (24%), respectively.

DISCUSSION

In these studies, the significant variations of asthma and atopy prevalence found in the pediatric populations studied, remain under discussion although genetics, linked to race, seems to play a central role, modulated by environmental variables and lifestyle. Of interest is the fact that significant variations were found between populations sharing the same language and ethnic background. The environmental factors are likely to be strikingly relevant.

The results found in Cape Verde, namely the differences in atopy and current asthma, between the two Islands studied with their important ethnic variations, point out the importance of genetics. The low prevalence of atopy in this country, also found in other African and Eastern Europe countries,[11,12] was not related with absence of exposure. Different wheezing phenotypes could be implicated,[13] even in 6 to 16 year-old patients. Recurrent respiratory infections may play a major role. The high mean value of total serum IgE found in Cape Verde, even in non-atopic individuals, probably related to the parasite load of this population, could be important in the modulation of the allergic response.[14]

The determination of HDM allergen contents found in Madeira Island mattresses, were lower than those found in Cape Verde. In Madeira Island, genetics and environment seem to act simultaneously, resulting in a substantial prevalence of allergic diseases and atopy.

In Macau, a low prevalence of asthma was found, similar to the values described in China, sharing the same ethnic background, but much lower than in Hong Kong.[15] In contrast, atopic sensitization was identical to China, Hong Kong[15] and also Madeira. Interestingly, rhinitis and eczema cumulative prevalences found in Macau (34.3 and 16.0%) were similar to the rates in Hong Kong and much higher than in China. In addition to atopy, other risk factors, such as «Western lifestyle»,[12] may be important on allergic disease expression in these regions.[3]

In the near future, it will be important to focus on the characterization of genetic markers, relating race to atopy and allergic disease prevalence, and also on the identification of environmental risk factors for these high prevalent chronic childhood disorders. The possibility of studying insular populations (as in Madeira and Cape Verde), with low demographic fluctuations, allows this approach.

As a consequence of these spatial projects, it will be possible to plan health care programs on allergic diseases, for which direct and indirect costs will certainly strongly increase in the next Century.

SUMMARY

Background: Geographical differences in asthma prevalence are currently accepted, but evidence is sparse due to the lack of multicentre studies using the same protocol. **Objectives:** To compare the prevalence of asthma and atopy among schoolchildren from Portuguese speaking countries (ISAAC and Portuguese Study) and evaluate some environmental variables, such as house dust mite exposure. **Material and Methods:** Significant random samples of schoolchildren studied with standard validated methods – questionnaires, skin prick tests, methacholine bronchial challenge tests; dust bed sampling for analysis of mite antigens. **Results:** In the ISAAC study, in the 13-14 year-old age group, statistical significant differences were found, with higher wheezing prevalence in Brazil than in Portugal (two-fold). In the Portuguese Study, atopy prevalence ranged between 6.0 and 11.9% in Sal and S. Vicente (Cape Verde), up to 48.6 and 54.1% in Macau and Madeira. Active asthma had the higher values in Madeira (14.6%), and the lower in

Macau (1.3%). Cape Verde had intermediate asthma prevalence (10.6 and 7.0%). The bronchial challenge test was positive in 25, 66 and 70% of asthmatic children from Sal, S. Vicente and Madeira respectively. Significant HDM antigen concentrations (Der p1) were found in Cape Verde and Madeira. **Conclusions:** There are significant variations in asthma and atopy prevalence between these pediatric populations. The reasons remain under discussion, but genetics linked to race, seem to play a central role, modulated by environmental and lifestyle variables.

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