Universidade de São Paulo
Faculdade de Saúde Pública

VOLUME 31
NÚMERO 5
OUTUBRO 1997
p. 441-7

Revista de Saúde Pública

JOURNAL OF PUBLIC HEALTH

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PEREIRA, Júlio C. R., Susceptibility of asthmatic children to respiratory infection. *Rev. Saúde Pública*, 31 (5): 441-7, 1997.

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Abstract

Objective A case-control study of patients with pneumonia was conducted to investigate whether wheezing diseases could be a risk factor.

Methods A random sample was taken from a general university hospital in S. Paulo City between March and August 1994 comprising 51 cases of pneumonia paired by age and sex to 51 non-respiratory controls and 51 healthy controls. Data collection was carried out by two senior paediatricians. Diagnoses of pneumonia and presence of wheezing disease were independently established by each paediatrician for both cases and controls. Pneumonia was radiologically confirmed and repeatability of information on wheezing diseases was measured. Logistic regression analysis was used to identify risk factors.

Results Wheezing diseases, interpreted as proxies of asthma, were found to be an important risk factor for pneumonia with an odds ratio of 7.07 (95%CI= 2.34-21.36), when the effects of bedroom crowding (odds ratio = 1.49 per person, 95%CI= 0.95-2.32) and of low family income (odds ratio = 5.59 against high family income, 95%CI= 1.38-22.63) were controlled. The risk of pneumonia attributable to wheezing diseases is tentatively calculated at 51.42%.

Conclusion It is concluded that at practice level asthmatics should deserve proper surveillance for infection and that at public health level pneumonia incidence could be reduced if current World Health Organisation's guidelines were reviewed as to include comprehensive care for this illness.

Asthma, complications. Pneumonia. Case-control studies.

Resumo

Objetivo *Investigar, através de um estudo caso-controle de pacientes com pneumonia, se as doenças chiadoras poderiam constituir-se em fator de risco.*

* Artigo resultante da tese de doutorado, intitulada "Avaliação das doenças chiadoras recorrentes da infância como fator de risco para pneumonia", apresentada à Faculdade de Saúde Pública, orientada por Gilberto Ribeiro Arantes, São Paulo, 1995.

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Edição subvencionada pela FAPESP (Processo 97/09815-2).
Recebido em 4.9.1996. Aprovado em 31.3.1997.

Métodos *De um hospital universitário, na cidade de São Paulo, Brasil, entre março e agosto de 1994, foi tomada uma amostra de 51 casos de pneumonia pareados por sexo e idade a 51 controles sadios e 51 controles não respiratórios. O diagnóstico de pneumonia e a presença de doença chiadora foram investigados de forma independente por cada pediatra tanto para casos quanto para controles. Foi confirmada pneumonia radiologicamente e a repetibilidade da informação sobre doença chiadora foi medida. Foi utilizada regressão logística para identifição de riscos.*

Resultados *As doenças chiadoras, entendidas como representantes de asma, mostraram ser importante fator de risco para pneumonia, com um* odds ratio *de 7,07 (IC95%= 2,34-21,36), controlados os efeitos de aglomeração no quarto de dormir (*odds ratio *de 1,49 por pessoa a mais no quarto, IC95%= 0,95-2,32) e a baixa renda familiar (*odds ratio *de 5,59 contra alta renda familiar, IC95%= 1,38-22,63). O risco atribuível às doenças chiadoras foi calculado de forma exploratória em 51,42%.*

Conclusão *Conclui-se que os clínicos devem ter atenção sobre asmáticos para o risco de infecção e que ao nível da saúde pública a incidência de pneumonia poderia ser reduzida se as orientações atuais da Organização Mundial da Saúde pudessem ser revistas para oferecer atenção integral para os doentes.*

Asma, complicações. Pneumonia, etiologia. Estudos de casos e controles.

INTRODUCTION

The major approach in the investigation of asthma and infection refers to the role of the latter as regards either the inception or the acute manifestations of the former. Accordingly, the effects of infection on the development of asthma and bronchial hyperreactivity have been exhaustively explored covering both viral and bacterial infections[5,7,13-18,20,23,25,27,30,32], while the reciprocal, namely the effects of asthma on the development of infection, has been overlooked. Clough and Dow[3], in an Editorial to Clinical Allergy in 1987, raised the subject but limited themselves to remark that a "hypothesis is that asthmatics may be more at risk of developing respiratory infections".

Stenius-Aarniala[29] in a review of the subject for Chest, maintained the *infection-towards-asthma* approach with the statement that "bacterial infections of nasal sinuses and bronchi are probably secondary to mucosal edema, hypersecretion, bronchospasm and mucocilliary dysfunction. There is no evidence that they are the primary cause of an exacerbation of asthma. It is possible that some bacterial infections will limit themselves if the pathologic state of the mucosa is reversed and its normal function restored by the antiasthmatic medication". Thus they acknowledged that an impaired function could predispose to infection though not focusing further on the matter. Indeed, bronchoalveolar lavage studies in asthmatics suggest that the respiratory lining becomes both susceptible and receptive to infection as defence is impaired[2] and a culture medium is formed by excessive mucus secretion[8]. Moreover, these studies suggest that an adequate control of asthma can revert this situation[6].

The interest in investigating the role of asthma in the development of infection might have been discouraged by the results of studies focused on asthma attacks which deny evidence of any association between them and infection. Hudgel et al.[11], studying adult patients in 1979, showed that even though asthmatics had chronic colonisation of the respiratory tract with pathogenic bacteria, their presence did not yield a greater frequency of asthma attacks. Likewise, Graham et al.[10] in a clinical trial with patients under asthma attacks, found that prescription of amoxycillin would not improve recovery. More recent studies, as the one conducted by Gbadero et al.[9], in Nigeria, come to the same conclusion, i.e., that routine antibiotic therapy should be avoided. Nonetheless, one should notice that lack of association between infection and asthma attacks

does not preclude a possible association between infection and asthma in the long run. It should also be noticed that the recurrent *what-infection-does-to-asthma* approach is maintained.

Recent studies have suggested that asthmatic children might be more liable to respiratory infection. Porro et al.[22], conducting a cross-sectional study with 2,304 schoolchildren in Italy, found that the odds ratio for upper respiratory infection was 2.20 (95% CI = 1.44 to 3.35) for asthmatics; Infant-Rivard[12], comparing 457 asthmatics to an equal number of controls matched by age and residence areas, found that the frequency of previous pneumonia was 3.12 (95% CI = 1.92 to 5.09) times greater in asthmatics than in their controls; and Victora et al.[31], investigating risk factors for pneumonia in a case-control study with 510 infants less than 2 years old, found that the odds ratio for pneumonia was 1.75 (95% CI= 1.16 to 2.63) among infants with a history of wheezing treated at home and 2.99 (95% CI = 1.53 to 5.83) among infants with a history of wheezing treated at hospital. A previous study[21] analysed 18,255 records of paediatric outpatient clinics and it was found that among the 1,371 cases of double diagnosis when the main diagnosis was asthma the odds for pneumonia were 4.98 (95% CI = 3.49 to 7.10). The same study reviewed 84,143 cases in death of children under five years of age and found that wheezing diseases and pneumonia were associated with an odds ratio of 3.0 (95% CI = 2.50 to 3.59).

The present study was conceived to further investigate this evidence. To avoid disputes over the diagnosis of asthma the presence of a non-infectious wheezing disease was chosen as a broader approach likely to cover the clinical conditions characterised by some degree of underlying bronchial hyper-reactivity and/or atopy.

MATERIAL AND METHODS

A teaching hospital of S. Paulo city based case-control study was designed as to compare paediatric cases of pneumonia with controls paired by age and sex. Two types of controls were devised for each case of pneumonia: one patient under treatment for a non-respiratory disease and one healthy child brought to hospital either to escort a diseased child or for routine development surveillance in an outpatient clinic. All children were registered as users of the local health system which comprises local health centres and out and inpatient services of the hospital at a referral level. The hospital studied is a general hospital that offers services to the academic community and to the general population of a delimited catchment area covering the neighbouring boroughs. Thus, the socio-economic composition of the users' community covered a wide range of people from slum dwellers to university students and teachers.

The sample size was calculated according to Schlesselman's[24] directions for studies taking two controls for each case. A level of significance of 5% and a power of 90% were taken and assumptions regarding frequency of wheezing diseases and odds ratio's were drawn from previous experience[21] (15% and 4, respectively, were taken as a basis for calculation). Thus a minimum number of 43 triplets was established. The two control strategy was aimed at achieving a pool of controls with a wide spectrum for all the variables measured.

Case selection: An assessment of the hospital demand suggested that a four month period should suffice to gather data. Accordingly all cases of pneumonia in children (age limit of 10 years) diagnosed either in outpatient clinics (referred patients) or in the casualty department (patients skipping primary care to seek medical assistance directly from the hospital) from March (*end of summer*) to July (*mid-winter*) 1994 were considered for entry. Only cases of community acquired pneumonia with no previous treatment were accepted. Diagnosis was confirmed by clinical and radiological investigation.

Control identification: For each case entering the study, a control was immediately sought among other children present at the hospital. A tolerance level of 3 months for children under 2 years of age and of 6 months for children older than that was established for the purpose of matching ages.

Data collection: Given parental consent, two senior paediatricians appointed by the University Paediatric Department independently applied standardised protocols to characterise the presence of pneumonia and wheezing diseases in both cases and controls. Thus, interobserver variation in the conclusions about these conditions was controlled and the investigation of their presence was made in the same fashion as that of their absence. Controls were spared from radiological investigation on ethical grounds. Field supervision provided by the authors checked compliance with standard observation procedures. A random sample of 20% of all children studied was taken to assess repeatability of the data collected to investigate history of wheezing.

Data analysis: An initial univariate approach compared means or modes, as applicable (ANOVA or Kruskal-Wallis, respectively), of variables in cases and controls. Variables found with significant differences between cases and controls were considered for a multivariate logistic regression to assess the possible risk of exposition to wheezing diseases in the presence of pneumonia whon potential confounders were controlled. Children were considered as exposed to wheezing disease if they could be labelled current wheezers according to either a previous medical diagnosis of asthma and at least one episode of wheezing in the last 12 months or a history of wheezing and at least 3 episodes responsive to bronchodilator, out of cold spells, in the last 12 months.

Some conditions, thought likely to interfere with the relationship studied, were computed into new variables from original data and were also considered for the logistic model:

1. *Environmental pollution:* ranging from 0 to 4, this was computed as the sum of the presence of exposition to fumes from wood or coal cookers, low exposure of child's bedroom to sunlight, presence of humidity and mould within the house, and presence of fumes, smells and vapours from industrial plants in the neighbourhood of the child's house;
2. *Personal history of atopy:* ranging from 0 to 2, this was computed as the sum of positive history of rhinitis and eczema, provided that at least one episode had been referred during the preceding 12 months;
3. *Family history of atopy:* computed as the number of first degree relatives with a positive history of atopy;
4. *Family history of asthma:* computed as the number of first degree relatives with a positive history of asthma.

RESULTS

Data collection effectively took place between 14 March and 2 August, 1994. Fifty one cases of pneumonia met the entry criteria and were duly paired to controls. Table 1 shows age and sex distribution of the study groups.

No significant difference in race was detected among cases and controls and 114 (76%) of the 153 children studied were Caucasian. Likewise, no difference in nutritional status was found, assessment being carried out as recommended by World Health Organization guidelines[19]. Causes for medical attendance among non-respiratory controls were mainly diarrhoea (52.94%), followed by trauma (9.8%), meningitis (3.92%), arthritis (3.92%) and otitis with no upper respiratory disease (3.92%).

All the 51 cases of pneumonia were diagnosed as bacterial in origin, 40 (78.4%) were admitted to hospital for treatment and the others were treated as outpatients. Radiological images showed lobar consolidation in 15 patients (29.4%), patchy alveolar consolidation in 41(80.4%), atelectasis in 3(5.9%), pleural effusion in 8(15.7%) and hyperaeration in 1(2%). Degree of clinical severity, assessed by level of dyspnoea, was mild for 46 patients (90%), moderate for 4(7.8%) and severe for 1 patient (2%). None required intensive care.

Table 1- Age in months of the children studied according to sex and study group.

Study group	Male			Female		
	Mean	S. Error	n	Mean	S. Error	n
Cases	18.09	3.47	24	28.12	3.73	27
Non-respir. Controls	18.42	3.40	24	28.90	3.85	27
Healthy Controls	17.99	3.54	24	27.63	3.75	27
Total	18.16	1.98	72	28.22	2.15	81

Re-application of the protocol to investigate the history of previous exposition to wheezing disease in 30 randomly selected children involved 12 cases (40%), 13 non-respiratory controls (43%), and 5 healthy controls (17%). The item by item agreement ranged from 11.1% (Kappa =0, *for the question on number of wheezing episodes during the last 12 months*) to 100% (Kappa =1, *for the question on wheezing response to smells and fumes*). Classification of the child as exposed or not exposed to wheezing disease had an agreement of 80.0% (Kappa = .60, 24 of the 30 children). The time lag between the first and second interviews was 45 days on average and some children had indeed changed their status during this period.

Univariate analysis of 120 variables detected 10 instances of significant differences between the study groups, as listed in Table 2.

All these variables, along with the previously defined potential confounders, were considered for a logistic model. Family income was recorded to three ranks of the observed distribution. The analysis was carried out by the conditional backward stepwise method establishing .05 as minimum significance level for a variable entering the model and .10 for one exiting. Table 3 shows the results of the first step of the analysis where all variables are forced into the model regardless the significance level and the results of the last step in which only the variables with due significance level are maintained.

The final model was found to be consistent (Goodness-of-fit $X^2 = 101.71$, $p = .52$). Comparison of the initial and final models suggests that although parental education, environmental pollution, family history of asthma, and personal history of atopy (odds ratios >1) did not achieve significance level in the sample studied they might be risk factors detectable in larger samples. Such an approach should also help towards the elucidation of the paradoxical suggestion that events like exposition to smokers, atopy in family, and bad housing conditions could be protective to pneumonia (odds ratios < 1).

Taking the calculated odds ratio for current wheezers as an approximation to the relative risk and the frequency of wheezing diseases among controls

Table 2 - Frequencies/mean values of variables with significant differences among the groups studied.

Variables	Study group			Statistics*
	Cases	Non-respiratory controls	Healthy controls	
Housing				
•Lodging type				x^2=7.13
Familiy	43	42	50	p= .02
Collective	8	9	1	
•Sanitation				x^2=13.79
Toilette inside	41	36	49	p= .00
Toilette outside	10	13	1	
No toilette	0	2	1	
Environment				
•Smokers at home				F= 2.96
Mean nº of people	.84	1.10	.59	p= . 05
•Bedroom crowding				F= 7.46
Mean nº of people	4.02	3.80	2.92	p= .00
Economic & Social status				
•Family income				
Monthly averege (US$)	269.15	341.52	952.40	F= 12.93 p= .00
•Parental education				
Illiterate father	10	6	1	x^2= 31.60 p= .00
Illiterate mother	12	7	3	x^2= 31.18 p= .00
Personal medical history				
•History of laryngitis	23	7	12	x^2= 12.43 p = .00
•Previous diagnosis of asthma	19	7	11	x^2= 7.93 p = .01
•Current wheezer	23	10	8	x^2= 13.17 p = .00

* Kruskal-Wallis or ANOVA, as applicable.

Table 3 - Results of logistic regression.

Variables	Initial model			Final model		
	Odds ratio	95% CI	Signif. Level	Odds ratio	95% CI	Signif. level
Illiterate mother (contrast=university educated)	5.05	000.11 - 222.50	0.40			
Illiterate father (contrast=university educated)	1.54	000.01 - 157.59	0.73			
Environ. pollution	1.66	0.70-3.92	0.24			
Nº asthmat. relatives	1.66	0.34-8.16	0.52			
Atopic child	1.29	0.35-4.74	0.70			
Age in months	0.98	0.95-1.01	0.36			
Nº smokers at home	0.81	0.45-1.46	0.48			
Sex (if male)	0.68	0.19-2.40	0.55			
Nº Atopic relatives	0.57	0.21-1.56	0.27			
Toilette outside (contrast=inside)	0.56	0.11-2.72	0.47			
Hist. laryngitis	0.48	0.06-3.47	0.47			
Collective lodgings (contrast=individual)	0.29	0.05-1.62	0.16			
Family income (contrast-high)			0.17			0.04
Low	6.36	0.87-46.28	0.06	5.59	1.38-22.63	0.01
Intermediate	2.36	0.40-13.90	0.34	2.44	0.59-9.98	0.21
Bedroom crowding	1.68	0.88-3.21	0.11	1.49	0.95-2.32	0.07
Current wheezer	17.22	2.26-21.47	0.00	7.07	2.34-21.36	0.00

as an indicator of its frequency in the population, a tentative estimate of attributable risk of 51.42% may be calculated[1], this being roughly the expected reduction in the incidence of pneumonia if wheezing disease effects are withheld.

COMMENTS AND CONCLUSION

The present study has found that wheezing diseases are a major risk factor for the development of pneumonia which stands side by side with other known risk factors such as crowding and low family income. Moreover, the multivariate analysis provided evidence that its effects on the development of pneumonia are independent of and have a multiplicative action on the effects of these known risk factors: a wheezing child has a 7 times greater chance of developing pneumonia than a non-wheezing child under the same conditions of family income and bedroom crowding, and the chances of pneumonia for a wheezing child with low family income who sleeps in a room with another person are 58.8 (5.59 X 1.49 X 7.07) times greater than they are for a non-wheezing child of high family income who sleeps alone.

Even though it could be argued that not all wheezing children are asthmatics[4], as the study design excluded infectious causes of wheezing it is likely that the wheezers identified are either asthmatics in the strict sense of bronchohyperreactivity and atopy[26], or are cases of similar pathological conditions whose clinical presentations receive different clinical labels. Most of these cases would benefit from a prompt and straightforward recognition of the asthmatic condition as they would get better with anti-asthmatic therapy[28].

The calculated attributable risk of 51.42% might not be a fair assessment of the possible impact of the control of the wheezing diseases on the incidence of pneumonia because it was not drawn from a random population sample but from a hospital based study. Nonetheless, the community assisted by the Teaching Hospital of the University of S. Paulo was fairly represented in the sample studied and one would not expect this community to differ very greathy from the general population of S. Paulo City as a whole. Indeed, as a general hospital, the University Hospital is spared the selection bias common to specialised hospitals and yet, having a defined catchment area for general medical assistance, it is likely to faithfully to represent at least this latter community. Possible differences between this community and the rest of the population would be mainly of a geographical nature as the gamut of the occurrence of all the independent variables was duly covered by the enlarged range provided by the two control strategy.

The present findings should not only advise clinical practice, recommending surveillance of asthmatics with regard to the possible development of pneumonia, but they also suggest the need for a review of the current World Health Organization's guidelines for the control of acute respiratory infections in children, a major world-wide challenge to public health. These guidelines[33] focus on screening and case management of pneumonia while the present findings suggest that comprehensive care able to assist chronic illnesses such as wheezing diseases could contribute with a considerable reduction of the incidence of pneumonia, in some same places achieving levels of up to 50%.

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