

Recurrent Community Acquired Pneumonia in Young Children: Risk Factor for the Development of Childhood Asthma?

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Objective. To determine if recurrent community acquired pneumonia (RP) is a risk factor for developing childhood asthma (CA), compared with those children who only suffer one episode of pneumonia or non-recurrent pneumonia (NRP). To determine if patients with CA are more disposed to suffer RP.

Design. Historical cohort study.

Setting. Primary care.

Participants. A total of 80 episodes of pneumonia identified in 65 infants between the 1st of February 1996 and 30th June 1999.

Principal measurements. The relative risk (RR) and confidence interval (95% CI) of childhood asthma in the presence of recurrent pneumonia as compared to non-recurrent pneumonia, and the RR of recurrent pneumonia in the presence of childhood asthma.

Results. Of the 65 children included, 18 had RP (27.7%; 95% CI, 16.8- 38.6). The prevalence of CA was 49.2% (32 children) (95% CI, 37.1-61.4). The diagnosis of CA at any time was higher in children with RP (RR=4.1; 95% CI, 1.9-8.9). There were no differences between the incidence of RP and NRP in children previously diagnosed with CA (RR=1.28; 95% CI, 0.5-3.0).

Conclusions. A special follow-up needs to be carried out on all children diagnosed with RP in primary care, since the possibility of presenting with CA is higher in these cases.

Key words: Pneumonia. Asthma. Primary health care. Child.

NEUMONÍA RECURRENTE ADQUIRIDA EN LA COMUNIDAD EN LA EDAD PEDIÁTRICA. ¿FACTOR DE RIESGO PARA EL DESARROLLO DE ASMA INFANTIL?

Objetivo. Determinar si la neumonía recurrente adquirida en la comunidad (NR) constituye un factor de riesgo para desarrollar asma infantil (AI), comparado con los niños que padecen un sólo un episodio de neumonía o neumonía no recurrente (NNR). Determinar si los pacientes con AI están más predispuestos a padecer NR.

Diseño. Estudio de cohortes históricas.

Emplazamiento. Atención primaria.

Participantes. Un total de 80 episodios de neumonía identificados en 65 niños entre el 1 de enero de 1996 y el 30 de junio de 1999.

Mediciones principales. Riesgo relativo (RR) y su intervalo de confianza (IC del 95%) de asma infantil en presencia de neumonía recurrente frente a neumonía no recurrente, y RR de neumonía recurrente en presencia de asma infantil.

Resultados. De 65 niños incluidos, 18 niños presentaron NR (27,7%; IC del 95%, 16,8-38,6). La prevalencia de AI fue del 49,2% (32 niños) (IC del 95%, 37,1-61,4). El diagnóstico en algún momento de AI fue superior en niños con NR (RR = 4,1; IC del 95%, 1,9-8,9). No hubo diferencias entre la incidencia de NR y NNR en niños previamente diagnosticados de AI (RR = 1,28; IC del 95%, 0,5-3).

Conclusiones. Es necesario realizar un seguimiento especial a todo niño diagnosticado de NR en atención primaria, ya que las posibilidades de presentar AI en el futuro son mayores en estos casos.

Palabras clave: Neumonía. Asma. Atención primaria de salud. Niño.

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Introduction

Community acquired pneumonia (CAP) is a common illness in children.^{1,2} Its incidence in primary care (PC) has been established at 4%-6% new cases/100 susceptible/year.²

The incidence of recurrent CAP (RP) has been estimated at 8% in hospital based studies and its presence is associated with bronchial asthma, among other diseases.¹ Clark et al reported that children hospitalised due to CAP had a higher probability of subsequently developing asthma.³ After an exhaustive literature search, no studies in PC could be found which determined whether RP constituted a possible risk factor for the subsequent development of asthma, as compared to children who only have one episode of pneumonia (non-recurrent pneumonia, NRP).

Children diagnosed with asthma or wheezing episodes could have a higher probability of presenting with CAP.⁴⁻⁶ These studies, carried out in hospitals, did not look at the association between asthma and the subsequent development of RP.

RP has been associated with different diseases besides asthma, the majority severe, and whose early diagnosis is essential.¹ CAP can also have serious repercussions on the pulmonary parenchyma,⁷ particularly in RP,⁸ therefore it requires suitable treatment, as well as the identification and treatment of its predisposing factors. It is important to know the extent of RP in the community environment and establish whether it constitutes a possible risk factor for the subsequent development of childhood asthma (CA), the most prevalent chronic illness in childhood.⁹

The present study was carried out to determine if RP is a risk factor for the subsequent development of CA as compared with the presence of only 1 episode of CAP (NRP) in PC, and if patients with CA are more predisposed to present with RP.

Patients and Methods

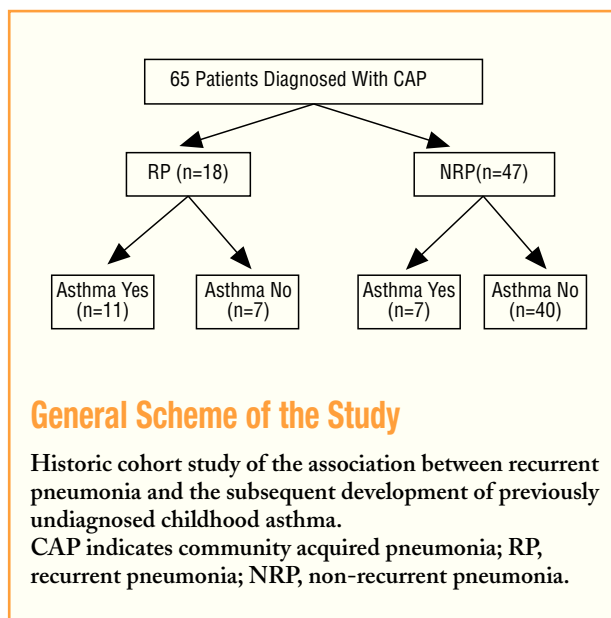
Study Design

Historical cohort study.

Population

All the episodes of CAP diagnosed in children <15 years old in the Girona Basic Health Area-4, between 1st January 1996 and 30th June 1999 were gathered (80 episodes in 65 children). The method for searching the CAP episodes has been published earlier.¹⁰

All children <15 years old who had at least one episode of CAP diagnosed and controlled in PC were included. The diagnosis was carried out by 2 radiologists, independently and blind.¹⁰



Episodes of CAP diagnosed, treated and monitored in the hospital environment and children with underlying chronic diseases (cystic fibrosis, heart disease, immunodeficiency) were excluded.

Definitions

Reviews of the computerised clinical histories were made to identify the cases according to the following definitions:

- RP: children diagnosed with more than one episode of pneumonia during the period of the study.
- NRP: children diagnosed with pneumonia on only one occasion during the period of the study.
- CA: children who comply with the criteria which defines asthma based on a medical diagnosis (clinical and/or functional), according to the criteria of the Asturia Regional Working Party on Childhood Asthma Consensus Group^{11,12} (Table 1).

Statistical Analysis

Means, standard deviations (SD), ratios, and 95% confidence intervals (95% CI) were estimated. The χ^2 and the Student-Fisher *t* test were used, along with the estimation of the relative risk (RR) and its 95% CI.

Results

During the period of the study, 65 children presented with 80 episodes of CAP. The mean age $\pm$ SD was 52.8 $\pm$ 33.8 months. Of these, 38 were girls (58.5%). There were no significant differences between the age of those affected according to sex (53.1 vs 52.6 months; *P*=.9). Of the cases identified, 18 children (27.7%; 95% CI, 16.8-38.6) had more than 1 episode of CAP (RP). The prevalence of CA in the whole sample was 49.2% (32 children) (95% CI, 37.1-61.4).

TABLE 1 Diagnostic Criteria for Childhood Asthma According to the Asturias Working Group on Childhood Asthma in Primary Care

Criteria	Validity of the Condition	Criteria
<i>0 to 24 months</i>		
Three episodes of wheezing	Criteria sufficient to accept as confirmed asthma	
<i>2 to 5 years</i>		
Three episodes of dyspnoea or wheezing or 2 in the last year, with a response to bronchodilator treatment	Criteria sufficient to accept as confirmed asthma	
<i>Over 5 years where pulmonary function might not be evaluated (due to lack of collaboration or non-availability of spirometer)</i>		
Three episodes of dyspnoea or wheezing or 2 in the last year, with a response to bronchodilator treatment	Criteria sufficient to accept as confirmed asthma	
<i>Over 5 years where pulmonary function has been carried out</i>		
Three episodes of dyspnoea or wheezing or 2 in the last year, with a response to bronchodilator treatment	Criteria pointing towards asthma. Requires complying with condition: if complied with: asthma confirmed	Bronchodilator test with positive reversibility in at least 1 of the episodes
Continuous symptoms (nocturnal cough, morning cough, wheezing, nocturnal dyspnoea, fatigue with cough, on exercise, the cold or emotions), or symptoms with exercise	Criteria pointing towards asthma. Requires complying with condition: if complied with: asthma confirmed	At least one abnormal function test: bronchodilator test with positive reversibility and/or positive variability recorded in MEF

RP was associated with the development of previously undiagnosed CA (Table 2). The risk of CA was greater in children with RP than in those who had NRP (RR=4.1; 95% CI, 1.9-8.9; $P=.0002$). The prevalence of CA among children with RP was 64.7% versus 15.4% in those who had NRP.

There were no significant differences between the percentages of RP and NRP in children previously diagnosed with CA who had not presented with any previous episode of CAP (Table 3); 26% had 1 episode of CAP and 33.3% more than 1 episode (RR=1.28; 95% CI, 0.5-3.0; $P=.6$).

Of the 18 children with RP, 15 were previously diagnosed or were subsequently diagnosed with CA ($P=.0007$).

Discussion

This study has some limitations. The definition of RP which has been used was less strict than that found in the literature (at least 2 episodes in 1 year or more than 3 episodes throughout life¹³), whilst in the present study RP was considered when more than 1 episode was presented during the period of the study (approximately 3,5 years). Despite this fact, the definition of RP in this study has been sufficiently sensitive to be able to demonstrate significant and clinically relevant differences as regards the subsequent development of asthma after presenting with RP as compared to children diagnosed with NRP. Another important limitation of this work is its small sample size, a fact which prompts caution in the interpretation of the

TABLE 2 Association Between Recurrent Pneumonia and Subsequent Development of Previously Undiagnosed Childhood Asthma*

	Bronchial Asthma		<i>P</i>	RR (95% CI)
	Yes n (%)	No, n (%)		
RP	11 (61.1)	7 (38.9)	.00019	4.1 (1.9-8.9)
NRP	7 (14.9)	40 (85.1)		
Total	18 (27.7)	47 (72.3)		

*RP indicates recurrent pneumonia; NRP, non-recurrent pneumonia; RR, relative risk; CI, confidence interval.

TABLE 3 Association Between Previously Diagnosed Childhood Asthma and Subsequent RP or NRP*

Childhood asthma	CAP		<i>P</i>	RR (95% CI)
	RP, n (%)	NRP, n (%)		
Yes	5 (33.3)	10 (66.7)	.58	1.28 (0.5-3)
No	13 (26)	37 (74)		
Total	18 (27.7)	47 (72.3)		

*CAP indicates community acquired pneumonia; RP, recurrent pneumonia; NRP, non-recurrent pneumonia; RR, relative risk; CI, confidence interval.

statistically non-significant associations, since this can happen in a beta type error. The 95% CI are too wide for the same reason. The sample size was not determined beforehand, but was arrived at by the number of patients who were detected with RP during the period of the study.

What Is Known About the Subject

- In hospital based studies asthma is considered a predisposing factor for presenting with recurrent pneumonia in the paediatric population. The opposite hypothesis has hardly been studied.
- The incidence of recurrent childhood pneumonia in primary care is unknown.
- There are no community based studies to determine if there is an association between recurrent pneumonia and the subsequent development of asthma.

What This Study Contributes

- Recurrent childhood pneumonia seems to be a risk factor for the subsequent development of bronchial asthma.
- The percentage of recurrent pneumonia is not significantly higher than the percentage of non-recurrent pneumonia in children previously diagnosed with bronchial asthma.
- There is a strong association between bronchial asthma and recurrent childhood pneumonia in primary care: 15 out of 18 children (83.3%) with recurrent pneumonia developed asthma or suffered from it previously.

It is important that prospective studies are carried out in the future with sufficient statistical power to be able to provide more accurate data.

This study suggests that RP can be a risk factor for the subsequent development of CA, as compared to the presence of only 1 episode. There are no PC studies carried out to be able to compare these results. In the hospital environment, it has been shown that children admitted due to CAP have a higher prevalence of CA (45%) in subsequent years³. However, the repercussions of RP on the subsequent incidence of CA have not been studied separately. In our study, the prevalence of CA among patients with RP was unusually high. This fact should serve as a warning to the PC paediatrician, since the probability of being confronted with a still undiagnosed asthmatic child, as such, is very high. In the present study, the prevalence of CA in our sample group was very high. There was no patient control group without CAP to be able to establish more accurate comparisons. However, epidemiological population studies carried out in Spain are available, and

using the same definition of CA, have reported a prevalence of CA in the general paediatric population which varies between 10.1% and 11.5%.^{11,12}. The percentages found in our study are much higher than these.

The hypothesis of CA as a predisposing factor for presenting with CAP has been the subject of more studies, the majority in hospital situations, case-controlled and carried out in developing countries. All have established, to a greater or lesser extent, the association of the previous existence of asthma episodes or wheezing with a higher probability of presenting with a CAP. In one study carried out in the community, it also confirmed this association.¹⁴ Uniquely, 1 study carried out in a hospital which had as its objective to determine whether the pre-existence of CA was associated with a higher risk of presenting with RP and/or persistent pneumonia, confirmed this association in hospitalised patients.¹⁵ In our study, the percentage of children with RP was very high in comparison with children who only had one episode of CAP. The difference between both groups was not statistically different, perhaps owing to the small sample size. It cannot be ruled out that CA, besides being a risk factor for the development of CAP,⁴⁻⁶ also increases the probability of presenting with RP. Future prospective studies with a larger sample and in the community should help to resolve the problem.

In the present work, the strong association between CA and RP in our area is obvious. In the absence of larger studies which could confirm this data, the association between the 2 clinical entities, reported in hospital studies, also appears to be confirmed in the PC environment.

This study is the first to analyse the relationship between RP and childhood asthma in PC. Despite the limitations already mentioned, its results are relevant to the PC paediatrician: it is necessary to be alert and make a special follow-up on every child diagnosed with RP (at least 2 episodes of CAP), since the possibility of developing CA is multiplied by four; more studies in the community are needed to accurately determine the prevalence of CA in children previously diagnosed with CAP, to study whether the incidence of RP is higher than that of NRP in children previously diagnosed with CAP and to confirm if RP is a risk factor in PC for the subsequent development of asthma.

References

1. Owayed AF, Campbell DM, Wang EEL. Underlying causes of recurrent pneumonia in children. *Arch Pediatr Adolesc Med.* 2000;154:190-4.
2. Buñuel JC, Vila C, Tresserras E, Viñas A, Ferrero MJ, Rubio ML, et al. Estudio descriptivo de la neumonía adquirida en la comunidad en la edad pediátrica. Una perspectiva desde atención primaria. *Aten Primaria.* 1999;23:397-402.

3. Clark CE, Coote JM, Silver DAT, Halpin DMG. Asthma after childhood pneumonia: six year follow up study. *BMJ*. 2000;320: 1514-6.
4. Mahalnabi D, Gupta S, Paul D, Gupta A, Lahiri M, Khaled MA. Risk factors for pneumonia in infants and young children and the role of solid fuel cooking: a case-control study. *Epidemiol Infect*. 2002;129:65-71.
5. Pereira JC, Escuder MM. Susceptibility of asthmatic children to respiratory infection. *Rev Saude Publica*. 1997;31: 441-7.
6. Fonseca W, Kirkwood BR, Victoria CG, Fuchs SR, Flores JA, Misago C. Risk factors for childhood pneumonia among the urban poor in Fortaleza, Brazil: a case-control study. *Bull World Health Organ*. 1996;74:199-208.
7. Kim CK, Chung Y, Kim JS, Kim WS, Park Y, Koh YY. Late abnormal findings on high resolution computed tomography after *Mycoplasma pneumoniae*. *Pediatrics*. 2000;105:372-8.
8. Singleton R, Morris A, Redding G, Poll J, Holck P, Martínez P, et al. Bronchiectasis in Alaska Native children: causes and clinical courses. *Pediatr Pulmonol*. 2000;29:182-7.
9. Fernández C, Alba F, Bamonde L, Montón JL. La importancia del asma en niños y adolescents. In: Cano A, Díaz CA, Montón JL, editors. *Asma en el niño y adolescente. Aspectos fundamentales para el pediatra de atención primaria*. Madrid: Exlibris Ediciones, S.L.; 2001.
10. Buñuel JC, Vila C, Heredia J, Lloveras M, Basurto X, Gómez E, et al. Utilidad de la exploración física para el diagnóstico de neumonía infantil adquirida en la comunidad en un centro de atención primaria. *Aten Primaria*. 2003;32:349-54.
11. Grupo Regional de Trabajo sobre el Asma Infantil en Atención Primaria de Asturias. Prevalencia de Asma diagnosticada en la población infantil de Asturias. *An Esp Pediatr*. 1999;51:479-84.
12. Morell JJ, Cuervo J. Estudio de situación del asma pediátrico en Extremadura. I. Prevalencia de asma diagnosticado [on line]. Available from en: <http://www.spapex.org/spapex/asmaprev.htm>.
13. Wald E. Recurrent and non-resolving pneumonia in children. *Semin Respir Infect*. 1993;8:46-58.
14. Heiskanen-Kosma T, Korppi M, Jokinen C, Heinonen K. Risk factors for community-acquired pneumonia in children: a population-based case-control study. *Scand J Infect Dis*. 1997;29:281-5.
15. Eigen H, Laughlin JJ, Homrighausen J. Recurrent pneumonia in children and its relationship to bronchial hyperreactivity. *Pediatrics*. 1982;70:698-704.

COMMENTARY

Recurrent Pneumonia. A Risk Factor for Developing Childhood Asthma?

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Pneumonia is defined as the presence of fever and respiratory symptoms together with radiological evidence of parenchymal infiltrate. It is a problem of great magnitude in paediatrics, as it preferentially affects children less than 5 years old. It causes more than 4 million deaths per year, particularly in developing countries. In Spain, community acquired pneumonia (CAP) has an incidence of 4%-6% per year in children.¹ In other areas and incidence of CAP of 6.7%-7.4% has been reported in pre-school age children, of which 6.9%-8.2% had recurrent pneumonia (RP).² According to other authors, up to 8% of children with pneumonia can present with RP.³

RP is defined as 2 or more episodes of pneumonia in 1 year or a total of 3 or more episodes throughout life, with normal radiology between episodes.⁴ An aetiological study should be started on any child who presents with acquired

Key Points

- Recurrent pneumonia in paediatrics is present in 1 out every 8 children with community acquired pneumonia.
- In 85% of cases an underlying cause can be identified.
- Asthma is the most common associated factor in children without a previously known disease.
- Children with 2 or more episodes of pneumonia are at risk of developing asthma.

RP, to identify underlying causes which might not be known at the time of the diagnosis.

Most of the studies which look at the causes of RP come from series of hospitalised children, and the diseases most frequently found differ, depending on the authors consulted. On many occasions, the underlying disease, previous to the pneumonia, is known (80.9%), in others it is discovered during the first episode (11.4%), and less frequently the causal diagnosis is made after the RP (7.7%). The disease processes which tend to be present before the first pneumonia are: bronchial aspiration, immunodeficiency, and congenital cardiac disease, while asthma, abnormalities of the respiratory tract and gastroesophageal reflux are those which are discovered after the first pneumonia or in RP.³

In another series of patients studied for RP, the most frequently found underlying disease processes were: asthma in 32%, gastro-oesophagus reflux in 15%, disease of the immunological system in 9%, lung and thoracic abnormalities in 6% and bronchopulmonary dysplasia in 4%, cystic fibrosis in 3%, tuberculosis in 3%, aspiration syndrome in 3%, and 15% with no identifiable cause. In children less than 1 year, gastroesophageal reflux is the most frequent underlying process and in those over 2 years old, asthma.⁵ As a conclusion it could be pointed out that after an appropriate investigation the causal diagnosis of RP can be arrived at in 85% of cases. When there is no previous diagnosis, asthma and gastroesophageal reflux should be actively investigated.

From the studies mentioned the great importance of asthma emerges as a background disease in the child with RP. However the role of recurrent pneumonia as a risk factor for the development of childhood asthma has not been sufficiently studied. The work of Picas et al⁶ makes an interesting contribution in this direction, since it tries to determine if acquired RP in the community is a risk factor for the development of childhood asthma (CA) as compared to the presence of only one episode of pneumonia, non-recurrent pneumonia (NRP), as well as determining if patients with CA are more predisposed to present with RP.

It must be emphasised that this study deals with children studied as out-patients of a health centre and that none of them required hospitalisation, while the majority of studies on RP come from hospital series. They recorded 80 episodes of CAP in 65 children <15 years old (mean age, 52.8 months) over a period of 3 and a half years.¹ It excluded hospitalised children and those with previously known diseases. It should be pointed out that the definition criteria for RP has been less strict than that used by other authors,⁴ since it has considered that RP is present in all children diagnosed with more than one episode of pneumonia during the period of the study.

The frequency of RP found among children who had a previous CAP is 27.7%, a figure higher than that reported

by other authors (6.7%–7.4% and 8%)^{2,3}; this fact can be explained by several factors; the diagnostic criteria to define RP is less strict than that used in other publications, the fact that they were out-patients, considering that only 10% of children with pneumonia require hospitalisation, as well as the sample size.

The present study has been able to detect that RP was associated with previously undiagnosed CA, as compared to the presence of NRP (RR=4.1; 95% CI, 1.9–8.9; $P=0.002$), while no significant differences were found between RP and NRP in children previously diagnosed with CA (RR=1.28; 95% CI, 0.5–3.0; $P=0.6$).

This data is of special interest, since it demonstrates the strong association between RP and CA in children <15 years in primary care, while no association was found between previously diagnosed CA and RP.

Up until now, the factors associated with the prevalence of bronchial asthma in children and adolescents are: to be male, family history of asthma, rhinitis symptoms, respiratory infections, need to exclude any food from the diet, and wheezing or cough with exercise.⁷

In primary care, the direct application of these findings is that children who present with RP, without previously known diseases, are a “high risk population” for the subsequent development of CA.

It is essential to concentrate diagnostic efforts, treatment and prevention directed at all children who present with acquired RP in the community, without previously known underlying diseases, due to the risk of subsequently developing CA.

It would be of great value to perform future prospective, multi-centred studies, carried out from primary care, to obtain more accurate data which could increase the value of the strength of association described.

References

1. Buñuel JC, Vila C, Tresserras E, Viñas A, Ferrero MJ, Rubio ML, et al. Estudio descriptivo de la neumonía adquirida en la comunidad en la edad pediátrica. Una perspectiva desde atención primaria. *Aten Primaria*. 1999;23:397–402.
2. Weigl JA, Bader HM, Everding A, Schmitt HJ. Population-based burden of pneumonia before school entry in Schleswig-Holstein, Germany. *Eur J Pediatr*. 2003;162:309–16.
3. Owayed AF, Campbell DM, Wang EEL. Underlying causes of recurrent pneumonia in children. *Arch Pediatr Adolesc Med*. 2000;154:190–4.
4. Wald ER. Recurrent and non-resolving pneumonia in children. *Semin Respir Infect*. 1993;8:46–58.
5. Ciftci E, Gunes M, Koksali Y, Ince F, Dogru U. Underlying causes of recurrent pneumonia in Turkish children in a university hospital. *J Trop Pediatr*. 2003;49:212–5.
6. Picas A, Lladó A, Buñuel JC, Vila C. Neumonía recurrente adquirida en la comunidad en la edad pediátrica. ¿Factor de riesgo para el desarrollo del asma infantil? *Aten Primaria*. 2006;37:127–31.
7. Fernández-Benítez M, Esteve C, Guillén M. Factores asociados a la prevalencia del asma bronquial en la infancia y adolescencia. *Acta Pediatr Esp*. 2005;63:232–40.