

Wheezing during the first year of life in infants from low-income population: a descriptive study

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ABSTRACT

Background: Recurrent wheezing (RW) plays an important role in the morbidity and mortality of children during the first year of life in developing regions and its actual incidence in those areas is virtually unknown.

Methods and results: This study describes the occurrence of wheezing during the first year of life in a birth cohort of 188 infants followed monthly and living in a poor urban area in Santiago de Chile. This study showed that 80.3 % of the infants in the cohort had one or more wheezing episode during the first year of life, 43.1 % had RW (3 or more wheezing episodes), 44.1 % had their first wheezing within the first three months of life and 13.3 % had pneumonia (PN). Having one or more episode of wheezing in the first three months of life was the main risk factor for suffering from RW during the first year and RW was a significant risk factor for having PN.

Conclusions: This study found a high prevalence of RW in infants from a low-income population during the first year of life with the disease starting very early in their lives, progressing with more frequent episodes and being significantly associated to PN, particularly in the first 6 months of life.

Key words: Wheezing. Infants. Birth-cohort. Wheezing incidence. Recurrent wheezing.

INTRODUCTION

Recurrent wheezing (RW) in infants plays an important role in the morbidity and mortality at this age in developing regions of the world. In Latin America, about 100,000 infants under the age of one year die each year due to PN¹ and in many of them the association of wheezing and acute lower respiratory infection is consistent, representing the main cause of pediatric consultation and admission during the viral season^{1,2}. Despite this high infant mortality related to lower respiratory infections in Latin America and its common association to wheezing, there is very few information on the true occurrence of these respiratory illnesses during the first years of life in this and other developing regions of the world³.

In developed countries the figures for wheezing once or more during the first year of life ranges from 10 % to 42 %⁴⁻⁹. The variation among different reported studies may be related to locations, study population, how the occurrence of wheezing is reported and whether wheezing was assessed by questionnaires or physician diagnosed episodes.

To the best of our knowledge there is no information available from longitudinal studies on the characteristics of wheezing during the first year of life in infants from Latin America or other developing regions of the world. This study was undertaken to describe the occurrence and other characteristics of wheezing

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during the first year of life in a birth-cohort of infants from a low-income population living in a poor peripheral suburb of Santiago de Chile.

METHODS

The study was undertaken at the Department of Pediatric Respiratory Medicine, Hospital CRS El Pino, University of Santiago de Chile. The sample of mothers and infants who participated in this birth-cohort study is from a low income population living in an urban locality located at the southern area of Santiago, the capital city of Chile. The main objective of this study was to determine the incidence of wheezing during the first year of life in infants from a population with low socioeconomic status.

Subjects

A random sample of 250 mothers coursing in their third trimester of pregnancy, non-smokers and that had been monitored at the maternity outpatient clinic with otherwise normal pregnancy and fetal status (pre-natal inclusion criteria), were invited to participate in the study. Two hundred and twenty-five mothers accepted the invitation. From this group, only newborn babies with 36 or more weeks of gestation, clinically normal and with a normal respiratory condition during the following 10 days after delivery, were considered eligible and were scheduled to their first visit at our clinic at the age of 1 month (post natal inclusion criteria). Thus, the final sample of infants to be followed, that fulfilled the study inclusion criteria was 215.

Study visits were scheduled every month for 12 months. During scheduled visits, mothers were asked about their infants' health during the past 4 weeks and complete physical examination was performed on each infant. At the first visit mothers were interviewed to obtain data on anthropological, environmental, and clinical aspects considered as relevant antecedents for the study. Infants were followed up at our outpatient clinic using an easy-access system that allowed their mothers to get direct contact with the pediatricians and nurses in case of disease. Also, mothers were instructed and encouraged to attend clinic as soon as possible if their infants started with any respiratory symptom (coriza, fever, cough, wheezing) between scheduled visits to get physician examination and registration of disease.

Family antecedents of atopy or other family diseases, breast feeding, type of pregnancy and delivery, among others, were registered as well as the

diseases occurring to babies during the first year of follow up i.e. URTI (viral upper respiratory infections or "colds"), PN, wheezing episodes, eczema, and also other non-respiratory diseases. Data on passive tobacco smoke exposure, crowding (defined as more than 3 persons over 2 years of age sharing the bedroom with the infant, or more than one familiar group sharing the household); level of parental education, mother's employment status, pets at home, pollutant system heating or cooking at home (gas, kerosene, wood, charcoal) among others, were also obtained from mothers as exposures. No laboratory determinations for respiratory virus or cotinine for passive tobacco smoke exposure were made due to economic reasons.

For the purpose of this study recurrent wheezing was defined as 3 or more episodes in the first 12 months of life.

Analysis of data

The data were processed by means of a statistical package and the results of descriptive analysis are expressed as proportion (%) of infants in the cohort that had URTI, wheezing episode and PN during the first, second, third and fourth trimester of life, and also as proportion of infants in the cohort who had one or more URTI, one or more wheezing episodes, recurrent wheezing and pneumonia in the first 12 months of life. Chi-square and Fisher tests were also employed when corresponding. A *p* value of < 0.05 was considered as statistically significant. The study was approved by the Hospital Ethics Committee and a written, signed and fully informed consent was obtained from parents.

RESULTS

Of the 215 infants initially enrolled, 188 (98 girls) of them finally participated in this study. Data provided in this section are those for each trimester of life and cumulatively, for the first year of life. The main reasons for loss to follow-up was families moved out of city due to father job and parental unwilling to continue with the study.

At birth, the cohort mean gestational age, birth weight and birth height were 39.0 ± 1.1 weeks, 3.359 ± 489 g and 50.3 ± 1.9 cm, respectively. The anthropometric characteristics of the 188 infants were within the range of mean gestational age (39.3 ± 1.9 weeks), birth weight (3.468 ± 563 g) and length (50.7 ± 2.1 cm) of the 3.004 normal babies who were born that year in our hospital.

The proportion of infants in the cohort who had one or more episode of URTI, WZ and PN in each of the 4 trimesters is shown in figure 1. During the first trimester 63.8 % of the infants had one or more episodes of URTI, 44.1 % had one or more episodes of wheezing, and 6.4 % had PN. There was a significant association between WZ and PN and 14.5 % of those who had WZ had PN in contrast with no PN occurring in those who did not have WZ ($p < 0.001$). Family atopy was the only independent risk factor for wheezing (OR 2.1, CI 1.01-4.35) that was statistically significant at this age. The proportion of those with wheezing in the first 3 months was larger in male infants (63.9 %) but the difference did not reach statistical significance ($p = 0.075$).

During the second trimester 65.0 % of the babies in the cohort had one or more episodes of URTI; 54 % had one or more episodes of wheezing, and 3.7 % had PN. At this age there was not a significant association between URTI and wheezing or between URTI and PN. There was a significant association between wheezing and PN and 6.9 % of those who had WZ had PN.

During the third trimester 54.3.0 % of the babies had one or more episodes of URTI, 40.3 % had one or more episodes of wheezing, and 1.67 % had PN. There was not a significant association between URTI and WZ, nor between URTI and PN. At this trimester the association between wheezing and PN did not reach statistical significance ($p = 0.06$).

During the fourth trimester of life 49.5 % of the babies in the cohort had one or more episode of URTI, 37.2 % had one or more episode of wheezing and 2.7 % had PN. There was not significant association between URTI and wheezing, nor between URTI and PN ($p = 0.19$) and as in the third trimester the association between wheezing and PN did not reach statistical significance ($p = 0.065$).

The proportion of infants in the cohort who had one or more episode of URTI, WZ and PN, and also RW (3 or more episodes) in their first year of life, is shown in figure 2. During the first year of life 80.3 % of the infants of the cohort had one or more episode of wheezing; 43.1 % of all infants had 3 or more episodes of wheezing (RW), 93.1 % had one or more episode of URTI and 13.3 % had PN (fig. 2). As occurred at 3 months, there was not a significant association between URTI and wheezing, or between URTI and PN during the second, third and fourth trimester of life. However, there was a significant association between WZ and PN and 15.9 % of those who had WZ had PN, in contrast with 2.6 % of PN in those who did not have WZ ($p < 0.035$). The mean number of episodes of WZ in those who had PN and those who had not PN was 4.70 ± 2.64 and 2.34 ± 2.19 , respectively ($p < 0.001$).

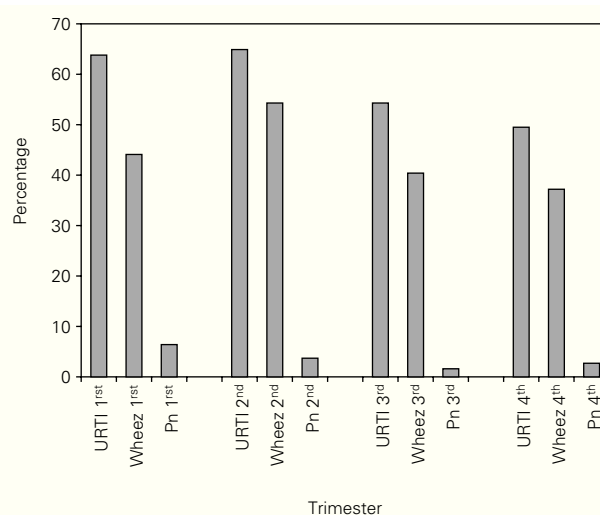


Figure 1.—Incidence of URTI, Wheezing (Wheez) and Pneumonia (Pn) at 1st, 2nd, 3rd and 4th trimester of life in a birth cohort from low income population.

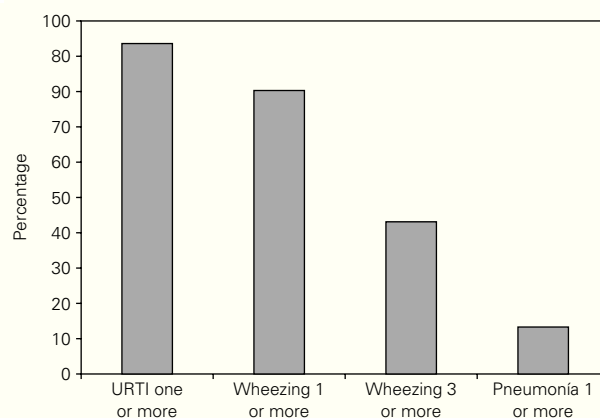


Figure 2.—Proportion of infants in the cohort (%) who had URTI, Wheezing or Pneumonia during the first year of life.

Recurrent wheezing was found to occur in 81 out of the 188 babies in the cohort; comparative information on variables from infants with and without RW in their first year of life are in table I. RW was a significant predictor for PN during the first year of life, OR = 12.9 (3.7-45.0), and wheezing at the age of three months or less was a significant predictor for recurrent wheezing during the first year, OR 23.3 (10.9-49.9). The proportion of masculine gender was significantly higher than feminine in infants who had recurrent wheezing in the first year of life (M:F = 55:26) as compared with those who had not RW (M:F = 51:56), $p = .004$. No differences was found between recurrent wheezy (RW) and non-recurrent wheezy (NRW) infants in gestational age (RW 39.04 ± 1.41 vs NRW 39.19 ± 1.33); weight at

Table I
Characteristics of infants with or without recurrent wheezing during the first year of life

	Recurrent wheezing		P
	Yes (n = 81) %	No (n = 107) %	
Caesarean delivery (%)	17.3	20.6	ns
Maternal job (out of home)	25.9	19.8	ns
Maternal instruction 8 years or less	22.5	25.5	ns
Family atopy	40.0	23.6	0.013
Crowding	57.7	47.2	ns
Kerosene combustion heating	58.8	73.3	0.027
Paved street	59.4	68.3	ns
Pets (stray dogs and cats)	61.4	56.8	ns
Indoor tobacco	55.0	49.5	ns
Breast feeding at least 4 months	76.9	85.7	ns
Eczema first year of life	30.9	32.7	ns
Wheezing first trimester	85.5	15.9	0.001
URTI first trimester	69.1	59.8	ns
PN during first trimester	14.8	0.0	0.001
PN during the first year of life	27.7	2.8	0.001

ns: difference not statistically significant.

birth (RW 3.389 ± 499 vs NRW 3.330 ± 452); height at birth (RW 50.3 ± 2.3 vs NRW 50.0 ± 2.1) and cranial perimeter (RW 34.71 ± 1.52 vs NRW 34.61 ± 1.50).

Fifty-two percent of infants in this cohort was exposed to intra-domiciliary tobacco smoke, 82.2 % exposed to some type of contaminant heating or cooking (mainly kerosene, gas), 38.5 % had unpaved street in front their houses, 58.9 % had "pets" at home (stray dogs and cats), 12 % of mothers and 24.5 % of fathers referred they smoked at home and 24.2 % of mothers had just basic scholar education (8 years or less of continuous school attendance).

Having URTI or wheezing in the first trimester of life were significant independent predictors for having one or more episodes of wheezing and to suffer from RW during the first year of life. Family atopy or asthma, heating with kerosene, PN at 3 months and male gender were also significant independent predictors for RW during the first year of life.

PN at 6 months was significantly associated with passive exposure to tobacco smoke ($p < 0.04$), one or more wheezing episode during the first and second trimester of life. The main predictors of PN during the first year of life were wheezing in the first 2 trimesters and recurrent wheezing. Breast feeding during the first 4 months of life acted as a protective factor for PN ($p < 0.003$) OR 0.274 95 %CI 0.142-0.525 but not for RW.

Family atopy was not associated with having one or more episode of wheezing during the first year but it was present in 40 % of those infants who had recurrent wheezing during the first year of life and in 26 % of those who had not RW ($p < 0.013$). Allergic dermatitis was not associated with RW in the first year of life and was present in 30.9 % and 32.7 % of those with or without RW, respectively.

Having URTI in the first 3 months of life was significantly associated with having one or more wheezing episode in the first year of life ($p < 0.012$) and 68.2 % of those who had one or more episode of wheezing in the first year also had URTI in the first trimester of life. However, having URTI in the first 3 months of life was unrelated to recurrent wheezing (3 or more episodes of wheezing) and 69.1 % of those with RW had URTI in the first trimester versus 59.8 % of those without RW ($p = 0.22$).

DISCUSSION

This descriptive study found that 80.3 % of infants from a poor urban area had one or more episode of wheezing during the first year of life. In addition, 44.1 % of infants in the cohort started with the disease at the age of 3 months or earlier and 43.1 % suffered from recurrent wheezing (3 or more episodes of wheezing) in their first year of life. Of the 188 infants in this cohort, 13.3 % had PN mainly before the age of 6 months and 80 % of those who had PN had had one or more previous episodes of wheezing. In this cohort, RW wheezing was the main risk factor for PN in infants from our cohort with those beginning wheezing under the age of 3 months having the higher risk for PN.

The clear relationship found between starting with wheezing before the age of 3 months and having PN before the age of 6 months, and suffering from recurrent wheezing during the first year of life suggests that wheezing illness in these infants from underprivileged populations may be more severe than phenotypes described in infants from developed areas where the prevalence of recurrent wheezing and PN is notoriously lower during the first year of age⁴⁻⁹. In Tucson, Martinez et al⁴ have reported that about 34 % of children under the age of 3 years had one or more episode of wheezing related to viral respiratory infections. Sporik et al⁵, in a birth-cohort study of 67 children from UK, found a 31 % of yearly period cumulative incidence of wheezing before the age of 2 years, and a 16.4 % during the first year of life. In London, Dezateux et al⁶ in a cohort of 101 Caucasian infants found that about 10 % of them had more than one episode of

wheezing diagnosed by a physician in their first year of life. Gold et al⁷ in a birth-cohort of 499 children with family atopy in Boston, USA, found that 42 % of them wheezed once or more before their first birthday and 8 % of all the cohort infants were reported to experienced 3 or more episodes of wheezing during their first year of life. Recently, Guerra et al⁸, also in a birth cohort of 238 children that participate in the Infant Immune Study, in Arizona, USA, have reported that during the first year of life 39.5 % of their infants experienced wheezing episodes and 17.2 % had recurrent wheezing. Copenhaver et al⁹ in the Childhood Origins of Asthma Project in Madison, USA, found that among their cohort of 285 infants, 25 % of children had one or more viral-associated wheezing during the first year of life.

Taking into account the differences regarding methodology between studies, in the cohort of Gold et al⁷, the percentage of infants that had one or more episode of wheezing in the first 3 months was similar to what we found in this study (42 %) however, the incidence of recurrent wheezing in the first year of life was five times less than ours and no PN episode was reported. Similarly, the study of Guerra et al⁸ reported the half of our figures for wheezing once or more and 2.5 times less for recurrent wheezing and no PN reported during the first year age.

It is likely that the early beginning and more frequent and severe progression of wheezing in our infants may have been determined by the high rate of respiratory viral infections in the first 3 months of life and early exposure to harmful inhaled environmental agents (tobacco, contaminant heating, ozone, PM_{2.5}) present in their houses and in Santiago's smog. The sustained action of these agents on the respiratory system might "set up" the airways to more intense reactions against inhaled irritants and viral respiratory infections, with higher possibilities of wheezing recurrence and severe concurrent complications as PN.

There is recent evidence suggesting that the first three months of life may be a particularly susceptible immunological moment where potent environmental stimuli may alter the innate immune response resulting in more frequent and severe episodes of bronchial obstruction during the first years of life. In fact it has been recently reported that levels of interferon gamma, soluble CD14 and IL 10 in early life predict RW during the first year of life⁸⁻¹⁰. The reported role of these and perhaps other mediators to determine higher rates of RW may be directly related with the magnitude of early exposures to harmful environmental agents as endotoxin, respiratory virus, tobacco smoke and other chemicals present in the inhaled air.

This birth-cohort may not be representative of all the many different underprivileged populations in the Third World but it is illustrative for populations similar to what we surveyed, which are commonly present in several of the big capitals in Latin America and other developing continents in the world. It has been showed that low socioeconomic status is an important risk for both, persistent respiratory symptoms in infants and morbidity attributable to infant wheezing illness^{11,12}.

Although we found that just 40 % of the infants with RW had family atopy, this antecedent was clearly related to RW suggesting a parallel but important role of atopy inheritance as predictor for RW in an important group of infants. In Britain, Wilson et al¹³ in a group of children aged 3 years with at least one hospital admission due to acute wheezing episode in the previous years found that the number of wheezing episodes in the first 3 years, associated with colds, was independent of the finding of atopy but the tendency to wheeze between viral infections was associated with atopy. The relationship of acute lower respiratory infections and wheezing is frequently present in hospitalized infants from developing areas. Murtagh et al¹⁴ in a study on acute lower respiratory infections in Argentinean children found a 71 % incidence of associated bronchial obstruction (wheezing and/or prolonged expiration) either in hospitalized patients as in outpatients. Our cohort study demonstrated that this association is longitudinally present all through the first year of life and that early wheezing (first trimester of life) is a main risk for PN and recurrent wheezing during the following months. This study also support the growing evidence about the importance of the type and magnitude of airway injuries occurring in the first months as determinants for recurrent wheezing and probably the type of wheezing phenotypes during the first years of life^{3-9,15}. However, the relationship between early exposures, altered innate immunity, inflammation, bronchial responsiveness, lung function and types of clinical expressions, remains to be defined by future studies that also include epidemiological aspects of recurrent wheezing in different world localities with distinct socioeconomic development.

This study also showed that infants from our cohort were markedly exposed since birth to several well known airway irritants present as indoor pollution (tobacco smoke, kerosene and gas for cooking and heating) and in atmospheric pollution (PM, gases), endotoxin, together with a burden of respiratory viral disease in the first 6 months of life. It has been demonstrated in infants that airway responsiveness after viral infection of the lower respiratory tract remains elevated several months after the acute

episode¹⁶ suggesting viral-induced changes on airway response not just on clinical progression but also on lung function. It might be that the summatory effect of early and subsequent viral respiratory infections together with a sustained inhalation of environmental irritants may alter innate immunity resulting in airways inflammation and hyperresponsiveness expressed as more frequent and severe wheezing episodes in exposed infants.

Regarding airway inflammation, it has been reported that infants with recurrent wheezing have elevated levels of exhaled nitric oxide during exacerbations that rapidly decrease after steroid therapy suggesting an underlying airways inflammation in those patients¹⁷. It has also been found that lower production of interferon gamma during bronchiolitis would be related with lower pulmonary function, increased reactivity to histamine and asthma several months after viral respiratory infection¹⁸, suggesting some link between immunological and functional responses of airways in these infants. Studies employing direct examination of bronchial alveolar lavage fluid (BAL) fluid from infants with recurrent wheezing^{19,20} have demonstrated that infants with persistent wheezing have airways inflammation and predominating cells are epithelial cells, macrophages and neutrophils but not eosinophils as found in older asthmatic children and adults. Furthermore, non-atopic mechanisms would be involved in the recurrence and severity of wheezing episodes in infants after RSV and those patients whose monocytes produced higher levels of IL-10 during RSV infection had more episodes of wheezing after bronchiolitis¹⁰. Thus, not only allergen-driven Th2 cytokine responses can lead to asthmatic symptoms²¹ but also and maybe more important in infants, virus-induced changes in cytokine responses and also other non-biological environmental exposures.

The morbidity and mortality due to PN in the first year of life is one of the most important public health issues in the developing world. The strong and significant association found in this study between recurrent wheezing and PN since the first months of life also suggests that recurrent wheezing under the age of 1 year may be a potentially preventable and treatable risk factor for PN deaths and sequels in infants from underprivileged populations. The findings of the present study suggests that different and effective strategies for the management of RW should be implemented for these populations in developing areas, considering the higher risk of PN, repeated consultations to emergency rooms, admissions, high demand on primary care system, etc., all of that resulting in a serious risk for infants' health and a remarkable increase of health expenses. At the same

time, randomized controlled trials need to be undertaken in developing countries to determine whether current treatment modalities for asthma, initiated very early in infants with recurrent wheezing may decrease the prevalence and severity of wheezing episodes, PN, and death due to PN, at least during their first years of life, the time when the greatest risk of death occurs.

Furthermore, our results indicate that data on prevalence of wheezing during the first year of life from developed countries are not suitable for extrapolations to developing ones because it is quite probably that as found in the international study on asthma (ISAAC), there are true differences in the prevalence and characteristics of wheezing within and between countries that would be mainly determined by environmental issues^{22,23}.

The surprising lack of information on the several aspects of RW strongly demands multicentric comparative studies on wheezing in infants during their first years of life, using standardized methodology and involving developed and developing areas of the world. Such an initiative appears as necessary at present in order to test the extension of current hypothesis on asthma and set basis for collaborative studies on etiology, prevention and early therapeutic interventions on this disease.

CONCLUSION

This birth-cohort study demonstrates that the prevalence of recurrent wheezing is high in infants living in poor urban suburb, with an important percentage of them starting with wheezing episodes before the age of 3 months. Although the reasons for the much lower prevalence of wheezing in infants reported in studies from developed countries are unknown, the difference may suggest that early and sustained exposure to a large burden of environmental risk factors, mainly related to low socioeconomic status, may "setup" the airway for more frequent and severe episodes of wheezing in these infants from underprivileged populations. In our infants having one or more episodes of wheezing during the first 3 months of age was the main risk factor for RW during the first year, and RW was the main risk factor for PN, particularly in the first 6 months of life.

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