Allergol Immunopathol (Madr). 2017;xxx(xx):xxx-xxx

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

REVIEW

Bronchopulmonary dysplasia as a risk factor for asthma in school children and adolescents: A systematic review

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Received 17 January 2017; accepted 18 February 2017

KEYWORDS
Bronchopulmonary dysplasia;
Prematurity;
Very low birth weight;
Asthma;
Outcome

Abstract
Background: Bronchopulmonary dysplasia (BPD) is a chronic lung disease that mainly affects extremely pre-term infants, and remains the most common complication of prematurity. Several studies have shown that prematurity predisposes to the development of asthma in school children and adolescents. Nevertheless, it is not clear to what extent a history of BPD involves an additional risk.
Methods: A systematic review of studies assessing the association between BPD and asthma in school-children and adolescents was made. A literature search was carried out in the MEDLINE and EMBASE databases to retrieve articles published between 1 January 2000 and 31 August 2016.
Results: A total of 17 studies comprising 7433 patients were included in the review. There was considerable heterogeneity in the definitions of BPD and asthma among studies. Overall, the prevalence of asthma was higher in children and adolescents with a history of prematurity and BPD compared with those who did not develop BPD. However, in only one of the studies did this difference reach statistical significance. The main limitation of this review was potential bias due to the lack of adjustment for confounding factors between exposure (BPD) and outcome (asthma) in most of the studies.
Conclusion: Based on the studies reviewed, it cannot be argued that BPD, as an independent factor of prematurity, increases the risk of asthma defined by clinical parameters in school-children and adolescents. Further studies of greater methodological quality and homogeneous diagnostic criteria of BPD and asthma are needed for improved assessment of this association.

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http://dx.doi.org/10.1016/j.aller.2017.02.004
0301-0546/

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease characteristic of pre-term infants (PTIs) with very low weight at birth (VLWB), particularly infants weighing less than 1000 g, or with extremely low weight at birth (ELWB), and constitutes the most frequent complication of prematurity.[1,2] Despite continuous advances in the care of PTIs, the prevalence of BPD still reaches 40% among infants with a gestational age (GA) of under 29 weeks.[3]

As initially described, BPD affected PTIs with a GA of over 32 weeks exposed to aggressive mechanical ventilation and high concentrations of oxygen (i.e., ''classical'' BPD).[4] With new ventilation techniques, the administration of surfactant, and corticosteroid use in pregnant women, BPD currently affects particularly extreme PTIs (GA $\leq$ 28 weeks) with lung development between the canalicular and saccular phases. In contrast to the important inflammatory and fibrotic component inherent to the classical forms of BPD, the disease in its current typical presentation is basically regarded as a consequence of the interruption of vascular and lung development[1] (i.e., ''new'' BPD).

Bronchopulmonary dysplasia can predispose to the development of obstructive pulmonary diseases as a consequence of its effect upon lung and airway growth. In nursing and pre-school infants, BPD is a cause of great respiratory morbidity, with frequent admissions to hospital and respiratory exacerbations in most cases associated to viral infections.[5] From the functional perspective, the condition typically involves important reductions in expiratory flow with air trapping.[6,7] School-children and adolescents with a history of BPD continue to experience alterations in lung function. Such patients show a persistent obstructive pattern with air trapping, bronchial hyperresponsiveness following stimulation with methacholine and after physical exercise, and a diminished carbon monoxide diffusion capacity.[7] In parallel to these findings, these subjects can be expected to exhibit a greater prevalence of asthmatic symptoms at these ages.

To date, three systematic reviews with meta-analyses have been published on the possible association between prematurity and asthma.[8–10] Although the studies included in the reviews are heterogeneous in their definition of asthma, the age of the patients (from nursing infants to adolescents), and the contemplated birth period (before or after the introduction of pre-natal surfactant and corticosteroids), all conclude that premature delivery increases the risk of asthma over the short and long term. According to the meta-analyses, the risk of asthma is inversely proportional to GA. This could suggest that patients with BPD – the immense majority of which correspond to extreme prematurity cases – are at a greater risk of suffering asthma than the rest of PTIs. However, none of the reviews have specifically analysed this issue, and at present it is not possible to affirm whether BPD is an independent risk factor for asthma in school-children and adolescents.

A systematic review has recently been published on studies of the evolution of patients with BPD from the nursing infant stage to adulthood.[11] However, most of the studies in school children and adolescents focus on lung function, with very little analysis of the prevalence of asthma from the clinical perspective.

Beyond the consequences of BPD in the first years of life, when the effects of prematurity and lung injuries are more evident, it is also important to know its clinical repercussions in later stages. At these ages the capacity to repair the damage caused may be evidenced in part while lung development and growth progresses.

The present study offers a systematic review of the publications that have investigated the possible association between BPD, as it is understood today, and asthma in school-children and adolescents, attempting to view BPD as an independent risk factor for asthma associated to prematurity.

Methods

Search strategy

A literature search was made of the MEDLINE and EMBASE databases, using combinations of the following as key words: ''bronchopulmonary dysplasia'', ''chronic lung disease'', ''asthma'', ''prematurity'', ''very low birth weight'' and ''outcomes''. We selected only those studies that included clinical information on school-children and/or adolescents and were published from the year 2000 onwards, in order to increase the likelihood that the study subjects had been born in a period when pre-natal corticosteroids and surfactants were already in use (i.e., ''new'' BPD).

Inclusion criteria and screening of studies

Only studies published in English and with access to the full text article were included. Journal editorials, congress summaries, and systematic reviews or meta-analyses were not taken into account.

We excluded all those studies that failed to specify whether the patients presented BPD (or prematurity chronic lung disease), or which did not clearly state the criteria defining the disorder. We likewise excluded those studies that failed to specify the association between BPD and asthma in some way, i.e., as the prevalence of asthma in the studied populations, or based on some risk index of one population with respect to another. Studies without at least one control group – whether full-term infants (FTIs) or PTIs – were excluded.

The existence of any of the following in the year before the study was accepted as representing a diagnosis of asthma: a medical diagnosis of asthma, asthma symptoms questionnaires addressed to the parents and/or patients, the use of anti-asthma medication and/or positive bronchodilator or bronchial provocation testing. When one same study used several of the above, priority was given to a medical diagnosis of asthma. A history of wheezing episodes at some point in time (''ever'' asthma) was not taken to represent asthma if the patient had been free of such episodes in the last year.

Following the initial search, we selected the potentially eligible studies by reading the abstracts. We subsequently reviewed the full-text version of each publication and checked compliance with the inclusion criteria for definitive selection. Lastly, we examined the literature reference lists of the selected articles in search of additional studies.

Please cite this article in press as: Pérez Tarazona S, et al. Bronchopulmonary dysplasia as a risk factor for asthma in school children and adolescents: A systematic review. Allergol Immunopathol (Madr). 2017. http://dx.doi.org/10.1016/j.aller.2017.02.004