ASTHMA AND ALLERGY: INFLUENCE OF EARLY LIFE RISK EXPOSURE

Introduction

Asthma is a developmental disease arising from abnormalities in the development of the respiratory system and immune maturation, underpinned by genetic predispositions and interactions with the environment. This article provides the clinician with insight and motivational data to reduce prenatal exposure to environmental risks, such as smoking; and the reduction of lower respiratory tract infections.

Lung function in normal healthy individuals ‘tracks’ along trajectories; lung function at birth predicts, to a certain extent, lung function for that individual throughout life. The immune system is immature at birth, with development of capacity occurring postnatally. Delayed immune maturation increases the risk of lower respiratory tract infections (LRTIs) and allergic sensitisation in early life. Together, abnormalities in lung and immune development increase risk for both asthma and allergies that is likely to persist into adult life.

At the Cipla Respiratory Symposium (Stellenbosch, March 2018), Professor Peter Sly shared insights on antenatal and postnatal risk factors for the development of asthma and allergy; and the synergistic role viruses and bacteria play in increasing the risk of disease.

KEY MESSAGES

- Abnormalities in lung and immune development increase risk for asthma and allergy
- Outcome of exposure to risk factors for acute and chronic respiratory disease is determined by the developmental stage at which exposure occurs
- Antenatal risk factor exposures impact immunity and structural development of the lung
- Postnatal risk factor exposures have structural or functional impact on the lung and immune system
- Low lung function is associated with an increased risk of both wheezing and asthma
- Wheeze may cause airway remodelling, with or without the presence of LRTIs
- There is a synergistic interaction between allergy and wheezing illnesses in risk for asthma
- The bacterial carriage of the upper airway, when infected with a virus, may determine disease outcomes.
Development of the lungs and immune system

During foetal development of the lungs, the airway branching pattern is complete by 14-16 weeks. Alveolar development occurs later, from 28 weeks gestation. At birth, 30-50% of alveoli are present and rapid alveolarisation occurs for a further 18-24 months, with lung volume doubling during this period. Lung volume doubles again by 5 years of age and again by adulthood, predominantly due to increase in size of the lung.

At birth, both the innate and adaptive immune function are immature. There is an active suppression of the Th-1 response during pregnancy (Th-1 cytokines are toxic to the placenta), resulting in a Th-2 bias in early postnatal life.¹ By 18 months, Th-1 levels have increased but full maturation of the Th-1 response does not occur until adulthood.² Postnatal maturation of the immune system is dependent on environmental exposures; a lack of appropriate stimulation increases the risk of allergy.

Risk factors for childhood asthma

Epidemiological data from long-term studies indicate that major risk factors for childhood asthma include:
- Family history (genetic predisposition)
- Low lung function
- Early allergic sensitisation
- Recurrent severe lower respiratory inflammatory (sLRI) events associated with wheeze and/or fever in first 2-3 years of life
- Environmental risk factors are maternal smoking during pregnancy, environmental tobacco smoke (ETS), traffic-related pollution and chemical exposures.

Environmental risk factors for asthma and allergy

There is a lengthy period during the maturation of the immune system and the lung where they are susceptible to environmental exposures. The outcome of exposure to risk factors for acute and chronic respiratory disease is determined by the developmental stage at which exposure occurs (Figure 1).

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“Together, abnormalities in lung and immune development increase risk for both asthma and allergies that is likely to persist into adult life.”

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Figure 1. Outcomes of prenatal and postnatal exposures to risk factors for respiratory disease.
Antenatal exposures, such as maternal smoking, impact both immunity and structural development of the lung. Postnatal exposures may have structural or functional impact on the lung and immune system. Lung growth and function is affected by ETS and pollution exposure. Postnatal immune development and function are also impacted by ETS, as well as microbial exposures.

**Maternal smoking**

The major harmful components of cigarette smoke for a foetus are nicotine and carbon monoxide, which accumulate at a higher concentration in the baby than in the mother. Intrauterine exposure results in constriction of the uteroplacental circulation, deprives the foetus of nutrients and thereby restricts growth. A single cigarette can inhibit foetal breathing movements for 30 minutes to 3 hours, thereby impacting future lung volume due to reduced mechanical stretch in utero. There is also a dose-response effect (number of cigarettes daily) on altered lung function after birth.3

Nicotine changes the way airways develop. Pregnant monkeys given nicotine infusions show increased collagen deposition in both small and large airways; and altered responsiveness of receptors.4 Professor Sly advises that nicotine replacement therapy during pregnancy is, for this reason, not necessarily safe.

Maternal smoking also delays immune development. Levels of interleukin-4 and interferon-γ are highest after birth in babies whose mothers have never smoked and lowest in mothers who are currently smoking. However, these levels are also reduced in babies whose mothers had given up smoking before pregnancy. These children have an increased risk of asthma and allergy at the age of 6 years, despite lack of intrauterine exposure to maternal smoking (Figure 2).5

**Low lung function**

Low lung function is associated with an increased risk of developing both wheezing and asthma. Longitudinal cohort studies show asthmatics to always have lower lung function from early life, suggesting that low lung function is one of the primary risk factors for asthma.6
Wheeze in infants and young children

In mechanical terms, wheeze implies expiratory flow limitations. If the airways are smaller to begin with, the individual is more likely to wheeze due to airway damage from repeated episodes of viral-induced inflammation and fever. Lung growth may be reduced by severe lower respiratory infection (sLRI) episodes; and low lung function increases the risk of further sLRI episodes and chronic lung disease.7

Some data indicate that wheeze itself can damage the airways and increase asthma risk, although this view is controversial. Adult atopic asthmatics without additional inflammation show bronchoconstriction-induced remodelling (increased collagen deposition in the airways and increased profibrotic cytokines).8

Allergens and viruses

There is a synergistic interaction between allergy and wheezing illnesses in risk for asthma. General community data from a cohort study in Perth show that if a child was allergic at age 6 years but had no wheezing in the first year of life, risk of asthma was doubled. If there was wheezing in the first year of life and allergic sensitisation, risk of asthma increased more than 9-fold.9 It was found in a high-risk cohort group (parents having asthma and/or allergy) that the risk for asthma at age 5 years and 10 years was only seen in those sensitised by the age of 2 years, no matter which phenotype of wheezing with sLRI occurred in the first year of life.10-12 Allergic sensitisation in combination with the way the immune system responds to the environment (allergen-specific IgE/IgG balance) determines risk of asthma.13

Bacteria

Alloiococcus, Corynebacterium and Staphylococcus are the predominant species in the upper airway microbiome of a healthy baby. With acute respiratory infections, the bacterial carriage alters so that Streptococcus, Haemophilus and Moraxella are the dominant species.14

The Copenhagen Prospective Study on Asthma in Childhood followed a high-risk cohort of infants born to mothers with asthma. Hypopharyngeal swabs were performed at the age of 1 month and the children were monitored thereafter. It was found that early bacterial colonisation in the hypopharyngeal region with Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis (or a combination of these organisms) increased risk of wheeze, hospitalisation for wheeze, and asthma outcomes by the age of 5 years.15

It is likely that sLRI risk is associated with those who cannot re-establish a healthy microbiome after a viral infection. When LRTIs are associated with fever, the risk for respiratory disease is then increased. If the child develops allergic sensitisation, the risk is magnified further for development of chronic wheeze and/or asthma (Figure 3).10,11,14 The bacterial carriage of the upper airway when infected with a virus may determine disease outcome, with specific combinations of viruses and bacteria that may be more damaging than others.

Potential mechanisms of viral-bacterial interactions in acute disease

There are numerous proposed mechanisms by which respiratory syncytial virus (RSV) and S. pneumoniae interact. Direct binding between the two may enable RSV to pull Streptococcus into the epithelium, allowing for more effective infection. Other potential mechanisms include viral glycoproteins acting as bacterial ‘receptors’; an increase in surface expression of bacterial binding proteins due to viral infection; and viral epithelial damage exposing the basement membrane.16
Prenatal exposure to environmental risk can result in low lung function at birth and delayed maturation of both innate and adaptive immunity. Repeated early life episodes of sLRI are more likely in this milieu, with further potential consequences of reduced lung growth, primary atopic sensitisation and persistent inflammation. These risk factors for the development of asthma and allergy are further aggravated by postnatal environmental risk exposure.

References

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