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SERIES: CHILDHOOD ORIGINS OF ADULT RESPIRATORY DISEASE

Some chronic obstructive pulmonary disease will originate in neonatal intensive care units

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Summary Chronic lung disease is the most common adverse outcome in survivors of prematurity. These infants experience frequent hospitalisation because of respiratory-related illness in their first year, as well as persistent cough, wheeze and oxygen dependence. Although the severity of respiratory illness decreases and supplemental oxygen is needed less as their lungs mature, childhood is still complicated by persistent wheeze, cough and reduced exercise tolerance in comparison with their peers. Although there is little longitudinal follow-up data beyond adolescence, imaging studies suggest that these infants are highly likely to suffer with respiratory problems akin to chronic obstructive pulmonary disease in later adulthood. The nature of their long-term respiratory problems, the impact of cigarette smoking and the effect on life expectancy are all unanswered questions that need addressing as these infants grow up.

INTRODUCTION

Respiratory illness accounts for most admissions to neonatal intensive care units (NICUs). Among the many causes in term infants are transient tachypnoea of the newborn, meconium aspiration syndrome and congenital diaphragmatic hernia. Follow-up studies in children who have had these conditions have shown an increased risk of wheezing.[1–4] In premature infants, chronic lung disease (CLD) or chronic oxygen dependency is the most common adverse respiratory outcome. It has been suggested that there is a spectrum of respiratory sequelae in preterm infants ranging from asymptomatic infants with physiologically detectable lung disease, through those with mild respiratory symptoms who may have chest radiograph abnormalities, to infants with severe respiratory disease with features on the chest radiograph typical of CLD. These features include bilateral hazy opacification, areas of over-inflation and indistinct heart borders.[5,6]

ASSOCIATION OF NEONATAL LUNG DAMAGE WITH SUBSEQUENT RESPIRATORY MORBIDITY

Predisposition to respiratory problems in infants admitted to NICUs is linked to increased long-term respiratory morbidity. One study identified prematurity as the cause of wheeze and other respiratory symptoms, showing that the lower the birth weight, the lower the functional vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). It was calculated that the risk of wheeze decreased by 10% for every additional week of gestation. These results came from a cohort of 5573 infants, the majority of whom were born near to term. In follow-up at 5–11 years of age, all of these children were assessed for respiratory symptoms and 2036 had lung function assessed.[7]

AETIOLOGY OF CLD

CLD of prematurity is characterised by an inflammatory process in the lung involving release of numerous cytokines (interleukin 1, interleukin 6 and interleukin 8). Neutrophil

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migration into the alveolar space is facilitated by soluble intracellular adhesion molecules and the release of oxygen free radicals by these neutrophils results in lipid peroxidation and cellular damage. The presence of transforming growth factor-beta suggests an ensuing fibrotic process as the inflammation resolves. Interleukin 10, which may inhibit the inflammatory cascade, may be absent or may rise late and be ineffective.[8–11] Clinical factors that may predispose to the inflammatory process are barotrauma, oxygen toxicity, lung fluid overload, infection and probably even genetic polymorphisms. Poor lung growth and a deficiency in antioxidant enzymes and their cofactors may compound lung damage. Until recently, CLD was thought to occur mainly in preterm infants with severe respiratory distress syndrome, with barotrauma being the main predisposing factor. However, an increasing number of very-low-birthweight infants who have minimal respiratory disease postnatally develop CLD. Probable key factors predisposing this group to CLD are poor alveolar growth and impaired postnatal remodelling, together with infection and the presence of a patent ductus arteriosus.[12]

SHORT-TERM MORBIDITY IN CLD SURVIVORS

Infants with the severe form of CLD may be oxygen dependent for months and require home oxygen therapy, oral and inhaled steroids and bronchodilators for episodes of wheezing. Optimal nutrition, prevention of infection and immunisation are all important issues in the management of these children after discharge.[13] Among infants who receive home oxygen therapy, there may be an increased risk of sudden infant death and up to two-thirds may be hospitalised within the first year, mainly as a result of respiratory infection or airway obstruction.[14–18] The median time that oxygen is given in these children is approximately 4–6 months. The financial burden of caring for these children, both in the community and in hospital, is considerable, particularly in the first 2 years.[19]

CHILDHOOD RESPIRATORY MORBIDITY IN CLD SURVIVORS

Chan *et al*. followed-up 130 preterm infants of birth weight under 2 kg with age-matched controls to between 7 and 9 years of age.[20] Lung function testing showed that low birth weight was associated not only with physiological evidence of obstructive airway disease but also with symptoms of wheeze and cough. Cough occurred more frequently in infants receiving intensive care in the neonatal period. Other studies of children with CLD to school age (4–11 years) have reported increased wheeze, cough, exercise intolerance and bronchial hyperactivity compared with controls.[21–25] FEV_1 was generally lower although this appeared to improve with time.[26,27] The chest radiograph demonstrated air trapping and there was a fall in oxygen saturation on exertion.[21] There have been a number of radiographic follow-up studies of the older child with CLD which have shown air trapping, linear shadows and interstitial thickening of the chest radiograph. Some of these findings improved with age, though one-third of children have slight residual changes. Computerised tomographic (CT) scanning may reveal worse parenchymal lung disease than plain radiographs suggest.[28,29] More unusual findings include persistent lobar over-inflation and isolated cysts occurring in infants with CLD. The medium- to long-term outcome of these abnormalities is not known.

ADULT RESPIRATORY MORBIDITY IN CLD SURVIVORS

A subgroup of the 7–9-year-old, low-birthweight NICU graduates studied by Chan *et al*. have been followed-up to the age of 21 years.[20,30] Of these, 10% had mild-to-moderate airway hyper-responsiveness as opposed to none in the control group and 13% had persistent cough compared with 2% in the control group. There was no difference in FEV_1 and FVC. The authors concluded that although lung function testing shows evidence of catch-up lung growth, the symptoms in these adults reveal residual functional impairment. It is unfortunate that the cohort included few infants who originally had CLD. Of these, fewer still were followed-up into adulthood. Northway *et al*., the first to describe bronchopulmonary dysplasia (BPD) in 1967, followed-up a group of infants born between 1964 and 1973 to a median age of 18 years.[31,32] Born at an average of 33 weeks' gestation, this cohort represents a slightly preterm group by current practice and follow-up findings may not reflect potential abnormalities and problems in the extremely-low-birthweight group. Northway *et al*. also studied a group of 26 preterm controls without BPD and 53 adults of the same age who were born at term.[32] Wheeze and reduced exercise tolerance was not uncommon and pectus excavatum was discovered in a number of adults. The family history of atopy was the same in all groups. Adults with previous BPD were of shorter and lighter build and, in some cases, had impaired neurodevelopment. Notably, three of the adults who had suffered from BPD were smokers. The effect of smoking on already impaired lung function in adults with previous BPD at the age of 21 years can only be detrimental. Lung function in these adults revealed a low FEV_1:FVC ratio and increased residual volume reflecting air trapping and a reduced transfer factor. A particularly disturbing finding was that one-quarter of the young adults had fixed airways obstruction not responding to bronchodilators or steroids, which must be considered to be chronic obstructive pulmonary disease (COPD).

COPD IN CLD SURVIVORS

CT scanning in young adults with previous CLD and BPD has shown evidence of decreased bronchi:bronchial artery