Chronic lung disease in infancy following prematurity

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Survival of extremely preterm infants has improved with modern neonatal intensive care. Chronic lung disease of prematurity, however, remains an important clinical problem and this article reviews the changing presentation and discusses new concepts of its aetiology.

The care of very preterm infants in the neonatal intensive care unit has greatly improved over the last decade with significantly increased survival of even the smallest infants (Lorenz, 2001). This has been achieved largely through the routine use of antenatal steroids and postnatal exogenous surfactant (Crowley, 1995). Despite the significant reduction in mortality and the decreased incidence of the respiratory distress syndrome (RDS) following the introduction of these new treatments, chronic lung disease of prematurity (CLD) remains an important clinical problem affecting around 30% of infants born with a birthweight of less than 1200 g. The following article will review the epidemiology and pathophysiology of CLD with a particular emphasis on recent concepts regarding the role of inflammation and immune responses in the development of CLD.

CLASSICAL CLD

Manktelow et al (2001) reported the changing incidence of CLD in infants admitted to a neonatal unit at less than 32 weeks gestational age over a 10-year period (1987–1997) in the Trent region of England. Comparing three time periods there was a significant improvement in survival to 36 weeks' corrected gestation between 1987 and 1992 and also between 1992 and 1997. The incidence of CLD (oxygen requirement at 36 weeks' corrected gestational age) trebled between 1987 and 1992, however, in the time period 1992–1997, despite improved survival, there was no further increase in the rate of CLD. The reported incidence of CLD varies widely between countries and between centres (Chan et al, 2001). Marshall et al (1999) reported CLD rates between 15 and 50% for infants born less than 1500 g in the USA.

Definitions of CLD vary between reporting centres with regards to timing (oxygen dependency at 28 days after birth or at 36 weeks' corrected gestational age) and diagnostic criteria, with definite chest radiograph changes required for the diagnosis by some authors but not others. Despite these differences, studies have consistently shown the highest incidence of CLD in the smallest and most premature infants.

Historically, CLD has been defined as oxygen requirement at 28 days of postnatal life in infants born preterm with typical changes on the chest radiograph. This is sometimes also referred to as bronchopulmonary dysplasia (BPD) and the two terms unfortunately are often used synonymously (although the latter refers to the pathological findings in infants who have died). Typically the infant is born preterm, has a history of RDS after birth as a result of lung immaturity and surfactant deficiency, requires mechanical ventilation for several days and occasionally for weeks, and subsequently remains dependent on supplemental oxygen for a variable period of time. Some infants require supplemental oxygen following discharge from hospital (*Figure 1*).

This 'classic' CLD was first reported by Northway et al (1967). This was before antenatal steroids and postnatal surfactant were available as treatments. They described the severe lung injury associated with characteristic changes seen on serial chest radiographs following mechanical ventilation and treatment with high concentrations of inspired oxygen in a series of infants in the early 1960s. Before the advent of mechanical ventilation, infants either died as a result of the RDS or recovered completely by 1 week of postnatal age with a normal chest radiograph.

Four pathological stages were described by Northway et al, correlating with typical

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changes identifiable on the chest radiograph. Stage I is represented by RDS which lasts 2–3 days and is characterized by a generalized granular appearance of the lungs with air bronchograms (*Figure 2*). Histology demonstrates hyaline membranes, atelectasis and diminished lung volume. The chest radiograph in stage II (day 4–10) shows opacification of both lung fields. Necrosis of the alveolar epithelium with persistent hyaline membranes are seen histologically with some alveolar epithelial repair present. Stages III and IV are characterized by a patchy cystic pattern representing local hyperinflated and emphysematous areas and opacities as a result of fibrosis and collapse of lung tissue (*Figure 3*). With modern neonatal intensive care and the routine administration of antenatal steroids and postnatal surfactant this form of CLD has become less common.

THE CHANGING EPIDEMIOLOGY OF CLD

Two important new therapies (antenatal steroids and postnatal surfactant) were introduced into routine clinical practice during the 1990s, which have significantly improved the outcome for infants with RDS. A full course of antenatal steroids, comprising two injections, 12 hours apart, of betamethasone or dexamethasone administered to the mother threatening preterm labour before 34 weeks' gestation, has been shown to reduce the incidence of RDS, and to significantly increase survival of very preterm infants with this condition (Crowley, 1995).

The routine administration of exogenous surfactant to ventilated preterm infants, with the first dose ideally given within 30 minutes of birth, also increases survival and significantly reduces the severity of RDS (Soll, 2000). The outcome following combined treatment of antenatal steroids and postnatal surfactant is better than either treatment alone.

THE 'NEW' CLD

With the advent of modern neonatal intensive care few infants now progress to stage IV lung disease as described by Northway et al. The clinical presentation has become more variable and chest radiograph appearances more subtle (Heneghan et al, 1986). With these changes a new group of infants with CLD has emerged, who have very little lung disease initially, and are often spontaneously breathing in air for several days after which they gradually developing an increasing oxygen requirement (Rojas et al, 1995). These are a different group of infants who have not been subjected to ventilator-induced lung injury or high concentrations of inspired oxygen. It has been hypothesized that inflammation occurring in the immature lung may be the cause of lung injury in these infants (Bagchi et al, 1994). The trigger for this inflammatory process may in some cases have its origin antenatally with the development of chorioamnionitis, leading to a fetal inflammatory response (Watterberg et al, 1996).

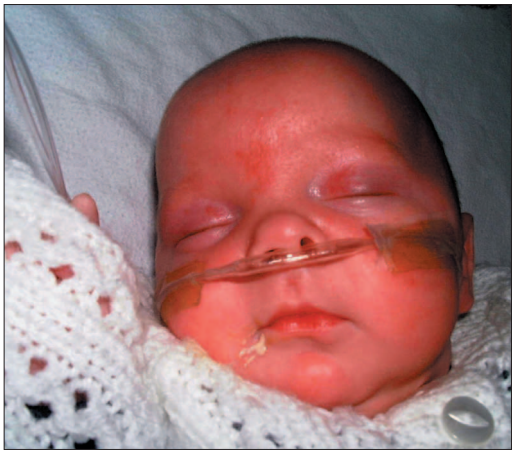

Figure 1. Infant born at 24 weeks' gestation (birth weight 595 g). Mechanical ventilation was required for 84 days and the infant was discharged home at 43 weeks' corrected gestation in 0.1 litre oxygen/minute via nasal cannulae.

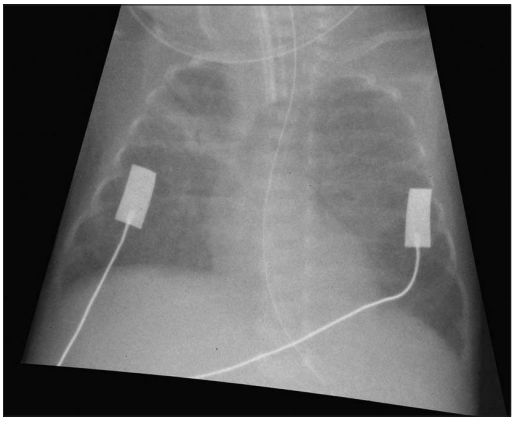

Figure 2. Chest radiograph of preterm infant (born at 23 weeks' gestation) on the first day of postnatal life showing typical appearances of respiratory distress syndrome (uniform ground glass appearance of both lung fields).

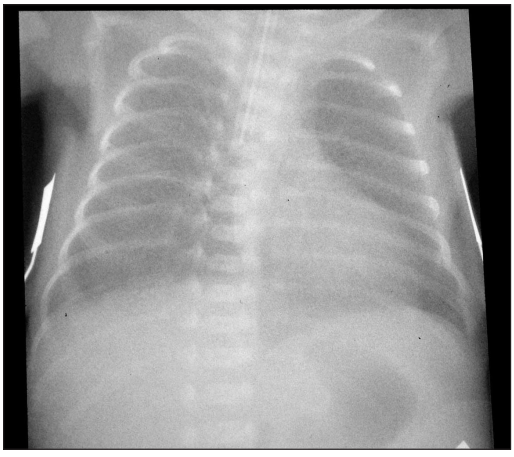

Figure 3. Chest radiograph of the same infant as in Figure 2, *still requiring mechanical ventilation at 5 weeks of postnatal age, showing typical features of chronic lung disease of prematurity. Hyperlucent areas represent patchy emphysematous changes (best seen in the left lower lobe) and areas of lung fibrosis and collapse (right upper lobe).*

INFLAMMATION AND BPD

The effect of ventilator-induced lung injury (baro- and volutrauma) and oxygen toxicity on the immature lung structures are the main factors leading to CLD (Davis et al, 1991). Parallel to this an initial exudative inflammatory phase in the lung is followed by one of repair and resolution, and finally a chronic fibroproliferative phase with lung growth and remodelling (Speer, 2001).

The number of inflammatory cells, particularly neutrophils and macrophages, recovered from bronchoalveolar lavage (BAL) fluid of very preterm ventilated neonates has been shown to rise in the days following birth (Groneck et al, 1994). In infants who do not develop CLD the number of neutrophils in BAL fluid gradually falls again towards the second week of postnatal life, whereas high numbers persist in those who go on to develop CLD. It has been suggested that these neutrophils are stimulated to release toxic oxygen metabolites and elastase which cause the parenchymal injury responsible for the development of CLD (Speer, 2001).

Attraction of inflammatory cells into the lung is mediated through cytokines and chemokines. These are the messenger proteins of the immune system and play a critical role in the modulation of the host immune response. Increased levels of interleukin-8, the most important chemoattractant within the lung, have been found in BAL fluid of ventilated preterm infants. Interleukin-8 is locally produced by alveolar macrophages, neutrophils, fibroblasts and type II alveolar and endothelial cells. Interleukin-10, thought to be an anti-inflammatory cytokine, has been shown to rise later. Several other proinflammatory cytokines have been found to be elevated in ventilated preterm infants that went on to develop CLD, including interleukin-1β, interleukin-6 and transforming growth factor-β (Bagchi et al, 1994; Kotecha et al, 1996). The exact mechanism which initiates this inflammatory cascade is not well understood and it remains contentious as to whether this inflammatory response is the cause of the lung injury or merely represents a repair mechanism.

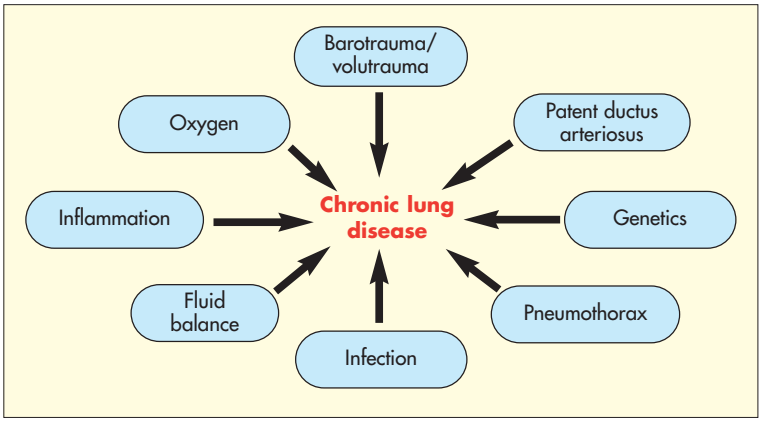

Figure 4. Factors contributing to the development of chronic lung disease of prematurity.

FETO–MATERNAL INFLAMMATION

Interest has focused on inflammation preceding birth. This has been termed feto–maternal inflammation and it has been suggested that the inflammatory process, which eventually leads to the development of CLD, may start antenatally in some infants following chorioamnionitis (Watterberg et al, 1996). This may trigger a fetal inflammatory response, which is present before birth and may subsequently be amplified by the development of RDS.

Chorioamnionitis is characterized by the presence of inflammatory cells in the placenta and fetal membranes and/or the presence of polymorphonuclear leukocytes in amniotic fluid. Clinically this is often associated with a raised maternal white cell count and C-reactive protein, low grade fever and uterine tenderness.

Watterberg et al (1996) found a significant association between the presence of chorioamnionitis, levels of proinflammatory cytokines in BAL fluid of ventilated preterm infants (born <2000 g) and the development of CLD in a study preceding the use of antenatal steroids and postnatal surfactant. Interestingly chorioamnionitis was more common in infants presenting without RDS, some of whom later developed an increasing oxygen requirement.

An association between proinflammatory cytokines in amniotic fluid or cord blood at delivery and subsequent CLD has also been reported by two other studies. Ghezzi et al (1998) found significantly elevated interleukin-8 concentrations (a potent neutrophil attractant chemokine) in amniotic fluid of infants born between 24 and 28 weeks' gestation who went on to develop CLD, and increased concentrations of amniotic interleukin-6 and tumour necrosis factor-α were reported in infants born less than 33 weeks' gestation who developed CLD (Yoon et al, 1997).

OTHER FACTORS CONTRIBUTING TO CLD

In addition to prematurity and very low birth weight other important risk factors for the development of CLD have been described (*Figure 4*).

Several studies found an increased risk of CLD in white preterm infants compared to African American infants (Horbar et al, 1988; Palta et al, 1991), and male gender has also been shown to be an independent risk factor for the development of CLD (Palta et al, 1991). The reasons for this are not clear.

An association between patent ductus arteriosus (PDA) and CLD has been demonstrated by several authors (Palta et al, 1991; Rojas et al, 1995; Marshall et al, 1999). It had been hypothesized that the PDA contributes to the interstitial and alveolar oedema observed in the lungs of infants with RDS/CLD. However, early closure of PDA either medically (with indomethacin) or surgically only reduced the incidence of CLD in three studies of 12 which were reviewed by Knight (1992). The risk factors for PDA are similar to those of CLD and PDA may therefore only be a marker for the development of CLD.

A link between postnatal nosocomial infection and CLD has been described (Rojas et al, 1995; Marshall et al, 1999). Although infection is an independent risk factor for CLD the highest incidence of CLD has been described in infants with combined nosocomial infection and PDA (Marshall et al, 1999). This synergistic association may be explained by infection delaying ductus closure or even reopening a previously closed PDA.

CONCLUSION

Survival of the smallest and most immature infants has significantly increased over the last decade, while the incidence of CLD has remained largely unaffected. This is partly explained by the fact that increasing numbers of extremely premature infants survive to discharge, and it is those infants who are most at risk of developing CLD.

Pulmonary inflammation associated with CLD has been an important focus of research, and more recently inflammation occurring before birth has been found to be associated with the subsequent development of CLD. No causal link has been proved, however, and the pathophysiological mechanism leading to CLD remains speculative. It will be important to further refine our knowledge of the molecular mechanisms leading to this condition.

Whether infants with the 'new BPD' have different long-term outcomes and pulmonary morbidity remains to be determined. HM

Conflict of interest: none.

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KEY POINTS

- Survival of very preterm infants has significantly improved over the last decade.
- The introduction of new treatments, particularly antenatal steroids and postnatal surfactant, has been largely responsible for this improved survival.
- Despite wide variation reported between centres the incidence of chronic lung disease of prematurity (CLD) has probably remained unchanged over this period.
- Fewer infants now develop the clinical and chest radiograph picture of severe CLD.
- A new form of CLD is observed more frequently, involving infants with only mild or no respiratory distress syndrome at birth.
- Pulmonary inflammation and amniotic inflammation before birth has been found to be associated with the development of CLD in preterm infants.