The role of inflammation in the development of chronic lung disease in neonates

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Abstract Chronic lung disease (CLD) has been associated with chorioamnionitis and upper respiratory tract colonisation with Ureaplasma urealyticum. The aim of this review is to describe the increasing evidence that inflammation plays a critical role in the early stages of CLD of the neonate. Ongoing lung damage in the premature infant may be caused by failure to downregulate and control this inflammatory response. Tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and IL-8 are important pro-inflammatory cytokines of which IL-8 is an important chemotactic factor in the lung. Data suggest that preterm newborns with lung inflammation may be unable to activate the anti-inflammatory cytokine IL-10. Therefore, early post-natal anti-inflammatory therapy could help in preventing development of CLD. Prophylactic dexamethasone therapy cannot yet be recommended. There are a number of potential interactions between surfactant and cytokine effects on the preterm lung which have not been evaluated. Surfactant protein A may be an important modulator of the immune response to lung injury. The role of high-frequency ventilation in the prevention of CLD still remains unclear.

Conclusion Many aspects of the pathogenesis of the inflammatory response in the development of chronic lung disease remain to be elucidated. Further research to identify preterm infants at highest risk for the development of this multifactorial and complex disease is needed.

Key words Chronic lung disease · Cytokines · Inflammation · Neonate · Pathogenesis

Abbreviations CLD chronic lung disease · IL interleukin · RDS respiratory distress syndrome · SP surfactant protein · TA tracheal aspirate · TNF-α tumour necrosis factor-alpha

Introduction

Chronic lung disease (CLD) is a persisting problem among the survivors of preterm delivery who required assisted ventilation. Its incidence has changed little despite improvement in perinatal care, including the use of prenatal corticosteroids, post-natal surfactant treatment and improved ventilation strategies [11]. In this review, we summarise the multifactorial causes and their potential role in early inflammation as an intermediate step in the pathogenesis of CLD in neonates. We also examine the current point of view concerning the possible effects of post-natal treatment on lung inflammation.

Definition

Two definitions of CLD are used: (1) the need for supplemental oxygen at the post-natal age of 28 days [2, 38] and (2) the need for supplemental oxygen at the post-menstrual age of 36 weeks [44]. To confirm the
diagnosis, additional radiological findings on chest X-ray, compatible with CLD are required. Several radiological patterns have been identified as being associated with CLD [8, 35]. The classification developed by Hyde et al. [17] is frequently used to diagnose CLD on chest X-ray: type 1 consists of normal lung inflation with densities homogeneously spread over the lung fields while type 2 is characterised by lung hyperinflation, emphysematous bullae and streaky densities.

**Chorioamnionitis**

The presence of chorioamnionitis has been associated with preterm onset of labour and an increased risk of neonatal infection [16]. The commonest cause of chorioamnionitis is ascending infection by *Ureaplasma urealyticum* [28]. Several studies have shown that microbial invasion of the amniotic cavity with *U. urealyticum* is a risk factor for impending preterm delivery and adverse perinatal outcome [24]. Other pathogens associated with chorioamnionitis are *Escherichia coli* [49], *Group B Streptococcus* [23] and rarely *Candida albicans* [12]. Amniotic fluid culture is an unreliable method for early diagnosis, detecting only 6–24% of patients with chorioamnionitis [39]. Elimian et al. [10] recently studied the perinatal effects of histological chorioamnionitis on preterm neonates and the effectiveness of antenatal corticosteroids in the presence of histological chorioamnionitis. In accordance with other studies, they found that histological chorioamnionitis increases major perinatal morbidity, such as neurological damage [30], via its association with preterm birth. Therapy with antenatal corticosteroids in the presence of histological chorioamnionitis significantly decreased perinatal morbidity including respiratory distress syndrome (RDS).

**Tracheal colonisation**

Prenatal acquired infections of the lung and/or trachea may play a role in the development of CLD. Upper respiratory colonisation or infection with *U. urealyticum* in premature neonates has been linked to the development of CLD [37]. Colonisation of neonatal airways by gram-negative bacilli has not yet been studied extensively in relation to respiratory diseases. Although associated with severe CLD, further studies are necessary before therapeutic efforts to eradicate gram-negative bacilli from the airways should be undertaken [5]. Viral agents have also been reported to play a role in the development of CLD. It is thought that the lung pathology is due to host immune response (e.g. cytokine production, induction of apoptosis) rather than direct damage to the cells resulting from virus replication [7]. Colonisation of the lungs with cytomegalovirus has been reported to be associated with an increased risk of developing CLD. However, cytomegalovirus infections in infants who developed CLD were believed to have occurred postnatally [41]. In the case of other viruses such as enterovirus and parvovirus, the association with the development of CLD has not been investigated. However, one study demonstrated a significant association between adenovirus infection and the development of CLD [6].

**Cytokines as mediators of pulmonary host defence**

The inflammatory response to an infectious challenge is a complex, dynamic process involving a balance between pro- and anti-inflammatory cytokines. Other contributory factors in this inflammatory process are lipid mediators including leukotrienes, prostacyclin and platelet activating factor. They exert various effects on the airways and the vascular system by increasing the microvascular permeability [46]. Chemotactic cytokines are necessary for leucocyte recruitment and activation, but this cytokine expression must be controlled to prevent excessive tissue injury and possible damaging systemic effects [47]. In infants who subsequently develop CLD, raised concentrations of pro-inflammatory cytokines have been detected in the amniotic fluid [13] and in bronchoalveolar lavage samples within hours after birth [34]. In the latter, these values remain high at 2–3 weeks of age [34]. In addition, a rapid influx of large numbers of activated neutrophils has been found in the airspaces within hours after birth [1]. Ongoing lung damage may be caused by the failure of the premature baby to downregulate and control this inflammatory response [3]. All these findings indicate that the injury responsible for CLD in a subset of infants may begin before birth. Some important cytokines are discussed below and Fig. 1 gives a schematic representation of the different pathways that may be involved in the pathogenesis of CLD. Table 1 shows a timeframe of the elevation of cytokine levels in lung lavage fluids.

**Tumour necrosis factor-alpha**

Tumour necrosis factor-alpha (TNF-α) appears to be one of the most important components of cytokine-mediated host defence against bacteria, mycobacteria, fungi, and parasites. It activates both neutrophils and macrophages leading to enhanced leucocyte phagocytic and microbicidal activity and causing the release of other cytokines. Although not directly chemotactic by itself, TNF-α can mediate the influx of leucocytes (both neutrophils and monocytes) by stimulating the expression of adhesion molecules on the surface of leucocytes and vascular endothelial cells [29]. This finding was demonstrated in bronchoalveolar fluid from infants who developed CLD [27].

**Interleukin-1**

Interleukin-1 (IL-1) is an important mediator in the early inflammatory response by recruiting and activating