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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
inflammatory cells and causing the release of other cytokines (including itself). It also activates endothelial cells for an increased expression of adhesion molecules such as intercellular adhesion molecule. During the first days of life there is an increase of IL-1 in the lungs of ventilated preterm infants. Increased levels of IL-1 and IL-1β have been demonstrated in bronchoalveolar fluid from infants who developed CLD [27].

Interleukin-6

IL-6, another pro-inflammatory cytokine, may have potent local and systemic effects by induction of hepatic acute-phase reactant proteins and immunomodulatory effects which include stimulation of B-cell differentiation and T-cell activation [25]. This cytokine has been demonstrated in high concentrations in the bronchoalveolar secretions of infants with RDS and CLD [34]. It can be detected as early as day 1 of life in lung lavage fluids from preterm infants who progressed to CLD [26]. In a study by Bagchi et al. [3], IL-6 concentrations in lung lavage fluids were compared between infants with CLD or RDS and a control group. IL-6 activity was signifi-

cant higher in lung lavage of infants who developed CLD compared with activities in lavage from control and RDS infants. This finding is explained by suggesting that pathways for inactivating or inhibiting IL-6 may be present in the lungs of RDS and control patients but may be deficient in infants with CLD. The activity of IL-6 remained high in the lavage of the CLD patients during the first 2 weeks of life and declined to low levels by day 28.

IL-6 can also be found in amniotic fluid and this might be a reflection of the host response to intrauterine infection [40]. In a study by Tsuda et al. [51], amniotic fluid IL-6 levels in patients with preterm labour were analysed. They concluded that determining IL-6 levels in amniotic fluid of patients in preterm labour may be of

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**Table 1** A time-frame of the elevation of cytokine levels in lung lavage fluid from infants who developed CLD (adapted from [3])

| Cytokine | Level and time in lung lavage fluid |
|----------|------------------------------------|
| TNF-α    | Low levels on the first day, subsequently increasing with a peak activity on day 14 |
| IL-1     | High levels during the 1st week of life |
| IL-6     | High levels during the 1st week of life |
| IL-8     | Low levels at birth, high levels from day 10–14 |
| IL-12    | No data |
| IL-10    | Low levels or absent during first weeks of life |
clinical value in establishing the severity of chorioamnionitis and its early diagnosis.

Interleukin-8

IL-8 is probably one of the most important chemotactic factors in the lung [22]. It is most likely produced by alveolar macrophages, fibroblasts, type II pneumocytes and endothelial cells. Hypoxia, hyperoxia and endotoxins stimulate production of IL-8. Additional upregulation of IL-8 is caused by other pro-inflammatory cytokines such as IL-1β. IL-8 is found in high concentrations in the airway samples of infants with CLD [33]. Early increase in IL-8 and IL-6 in tracheal aspirate (TA) precedes a significant neutrophil influx into the airways of the lung in preterm infants who develop CLD. The presence of IL-8 and IL-6 in TA from these infants suggests that these cytokines either initiate the acute inflammatory cascade in the lungs or that they are early markers of the inflammatory process, putting preterm infants at high risk for CLD [33].

Interleukin-10

IL-10 is an anti-inflammatory cytokine produced by macrophages, T-cells and B-cells [14]. In conditions of lung inflammation, IL-10 is not detectable in the lungs of preterm newborns whereas precursors of IL-10 and in some cases IL-10 itself are expressed in those of term newborns [21]. This suggests that preterm newborns with lung inflammation may be unable to activate expression of IL-10 as compared to term newborns with a similar profile of lung inflammation. Jones et al. [21] concluded that this can be explained by the fact that IL-10 gene expression is developmentally regulated. The susceptibility of the preterm newborn to CLD may in part reflect an inability to regulate inflammation through the expression of the anti-inflammatory cytokine IL-10 [21].

Nevertheless, the influence of IL-10 on the pathogenesis of CLD remains to be elucidated. At present, there are no published data that examine this issue directly. McCollm et al. [31] stated that infants of comparable gestational age who have good clinical outcomes differ in their IL-10 production. Further studies are needed to examine the role of IL-10 in the development of CLD.

Interleukin 12

This cytokine promotes Th1-type immune responses (cellular immunity), while inhibiting Th2-type (humoral immunity) immune responses. It has been increasingly recognised for its central role in antimicrobial immunity [4]. To our knowledge, no studies have been done on IL-12 in endotracheal fluids.

Tracheal aspirate cytology

Cytological findings in TAs are representative of epithelial morphology in more peripheral airways and provide information on epithelial abnormalities and ongoing inflammation in the airways [32]. The start of CLD in ventilated preterm infants is characterised by an exudative phase and a proliferative phase beginning within 1 week after initial lung injury in RDS. Defective healing of the regenerating airway epithelium leads to a chronic oxygen or ventilation dependency and may exhibit varying degrees of hyperplasia and squamous metaplasia. Moreover, very preterm infants with CLD seem to be unable to develop alveoli, resulting in lungs with fewer and larger alveoli. Pro-inflammatory mediators probably interfere with the presently unknown signalling pathways that are important for lung maturation and alveolarisation [20]. A study by Smets et al. [45] demonstrated that the presence of squamous metaplasia in very low birth weight infants during the 1st week of life predicts development of CLD with a specificity of 94%. However, a sensitivity of only 45% was achieved and therefore it was suggested that further studies on the predictive value of combination of cytological parameters with other markers in the TA or blood are needed. In a recent study, it was found that during re-epithelialisation after alveolar injury, alveolar type 2 cells proliferate, cover the injured surface, and differentiate into type 1 cells. The regenerating type 2 cells strongly express KL-6 antigen. KL-6, a mucinous glycoprotein, was found to be elevated in the blood of infants with CLD soon after birth, indicating more severe alveolar damage [36].

White blood cell counts in TA from preterm infants are significantly correlated with IL-6, IL-8 an IL-10 levels. Similarly, correlations were found between neutrophil counts and cytokines [43]. Todd et al. [50] demonstrated that cytological changes consistent with bronchial epithelial and pulmonary damage followed by an inflammatory response were found in the TA of a group of infants clinically diagnosed with CLD. However, their results were not predictive for CLD.

Possible effect of early post-natal treatment on lung inflammation

Dexamethasone therapy

Due to their strong anti-inflammatory properties, corticosteroids are an attractive intervention strategy. However, there are growing concerns regarding the short- and long-term effects, such as gastrointestinal perforation and decreased growth, of systemic corticosteroids [48]. Theoretically, administration of inhaled corticosteroids may provide beneficial effects on the pulmonary system with a lower risk of undesirable systemic side-effects. In a meta-analysis by Shah et al. [42],
there is no evidence from the trials reviewed that early administration (in the first 2 weeks of life) of inhaled steroids to ventilated preterm neonates was effective in reducing the incidence of CLD; however, there was a reduction in the need for systemic steroids. Currently, use of inhaled steroids in this population cannot be recommended. Studies are needed to identify the risk/benefit ratio of different delivery techniques and dosing schedules for the administration of corticosteroids with particular attention to neurodevelopmental outcome.

Effect of ventilation on inflammation

Mechanical ventilation can injure the preterm lungs and multiple ventilation strategies have been tried to reduce injury and improve outcomes. The best is avoidance of mechanical ventilation with the use of nasopharyngeal continuous positive airway pressure whenever possible. Barotrauma, volutrauma and oxygen toxicity during intermittent positive pressure ventilation are thought to be important factors in the pathogenesis of CLD since they cause lung injury resulting in a release of multiple pro-inflammatory cytokines and production of extracellular matrix components and growth factors [9]. Although not strictly validated by randomised-controlled trials, the liberal use of continuous positive airway pressure has been associated with less CLD [2]. High-frequency oscillatory ventilation using a high lung volume strategy also can decrease the incidence of CLD. The use of mean airway pressures somewhat higher for high-frequency oscillatory ventilation than for conventional ventilation probably assures that lungs will not be ventilated in the low lung volume injury zone, and oscillation seems to result in more uniform lung inflation which will add lung volume to minimise the risk of lung overdistention [18].

Surfactant therapy

Although surfactant therapy has become an effective standard for infants with RDS, preterm infants with and without RDS remain at high risk of developing CLD. There are a number of potential interactions between surfactant and cytokine effects on the preterm lung, which have not been evaluated. Furthermore, cytokines may be regulators of surfactant metabolism in the preterm infant [52]. The use of prophylactic surfactant before the first breath has been shown to reduce acute lung damage in animals but not yet in humans. This reduction in lung injury may reduce the incidence or severity of CLD [18]. Surfactant proteins A (SP-A) and D (SP-D) are important in the innate host defence against pathogenic microorganisms. They are known to interact with carbohydrate structures on the surfaces of a wide range of pathogens and enhance phagocytosis and killing by neutrophils and macrophages. A deficit in these proteins in premature infants, either because of immaturity or as a consequence of superimposed CLD, could increase their susceptibility to infection [53]. A study by Hallman et al. [15] proved that levels of SP-A could appropriately predict CLD and death in preterm infants. Although SP-A may not be involved in the biophysical function of surfactant, it may be an important modulator of acute inflammation, delayed injury and immune responses to lung injury [53]. Therefore, recombinant SP-A might be a useful component of surfactant treatment in cytokine-exposed infants without RDS to prevent CLD [19]. These surfactant proteins vary in different commercialised exogenous surfactant products.

Conclusion

It is clear that inflammation in the early stages plays a critical role in the development of CLD in neonates. Although evidence for immunological determinants has been accumulated through extensive research over the past decades, many aspects of the pathogenesis of this early inflammatory response and subsequent CLD remain to be elucidated. Unravelling the specific mechanisms involved may be critical in finding the key to effective prophylactic and therapeutic approaches. It is therefore very crucial to identify as early as possible preterm infants at highest risk for CLD. Development of prediction models for CLD should make it possible to select high risk neonates for randomised intervention studies.

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