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Case Study

Diagnostic and Management of Hyaline Membrane Disease

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Abstract

Hyaline membrane disease (HMD), more commonly called respiratory distress syndrome (RDS), is one of the first causes of morbidity and mortality in preterm infants.

HMD is characterized by a primitive deficiency in surfactant, synthesized by type II pneumocytes. It is due to the functional insufficiency both quantitative but also qualitative (specific proteins) in surfactant. This is the first pathology to have been successfully treated by exogenous surfactant.

Surfactant which consists of phospholipids and protein is necessary for the formation of functional residual capacity (FRC), which is the key to gas exchange. The surfactant deficiency causes a hyaline material to be deposited on the surface of the alveoli that remain collapsed or unstable, causing atelectasis and shunt effect.

Its incidence is inversely proportional to gestational age, with no absolute correlation between the degree of lung maturation and gestational age.

It is characterized by respiratory distress in the early hours of life related to the increase in the elastic pulmonary retraction forces and a collapse of compliance. The radiological image is characteristic (chest retractions, alveolar syndrome with reticulogranular pattern and air bronchogram).

Its prevention uses corticosteroids.

Treatment for HMD may include:

- Mechanical breathing machine,
- Continuous positive airway pressure (CPAP) which is associated with a lower risk of the occurrence of bronchopulmonary dysplasiaor (BPD) or death in preterm infants,
- Surfactant replacement with artificial surfactant.

We propose from a literature review to take a look at the different aspects of this pathology increasingly common with the increase in the number of premature births.

Keywords: *Hyaline Membrane Disease; CPAP; Surfactant; Respiratory Distress Syndrome (RDS)*

Introduction

Hyaline membrane disease (HMD), more commonly called respiratory distress syndrome (RDS), is a major cause of respiratory morbidity and of mortality in pre-terms [1].

HMD is characterized by a primitive deficiency in surfactant, which is a multimolecular complex synthesized by type II pneumocytes. This is the first pathology to have been successfully treated by exogenous surfactant.

It is due to the functional insufficiency both quantitative but also qualitative (specific proteins) in surfactant, causing alveolar atelectasis.

It is all the more common as the child is more immature (80% before 28 weeks of amenorrhea).

It produces an acute respiratory distress syndrome.

Chest X-rays of lungs-often show typically 3 signs: alveolar syndrome with reticulogranular pattern; air bronchogram; chest retractions.

Treatment for HMD may include:

- Mechanical breathing machine,
- Continuous positive airway pressure (CPAP), associated with a lower risk of the occurrence of bronchopulmonary dysplasia or death in preterm infants,
- Surfactant replacement with artificial surfactant.

Preventing a preterm birth is the primary means of preventing HMD. When a preterm birth cannot be prevented, giving the mother medications called corticosteroids before delivery has been shown to lower the risk and severity of RDS in the baby. These steroids are often given to women between 24 and 34 weeks gestation who are at risk of early delivery.

Pathophysiology

Fetal lung [2]: Lung development begins on the 28th day of pregnancy and ends at about 18 or 24 months post-natal. It is divided into five stages.

Embryonic stage

Embryologically, the lung derives from the primitive intestine. However, there are structural differences between the intestine and the lung in relation to their innervation and endocrine cells. Pulmonary development begins on the 28th day of pregnancy as an evagination of the primitive intestine. Two buds then appear and each forms an asymmetrical division system. The whole forms the primordial lung system [3]. The buds are responsible for all the epithelial cells of the mature lung while the surrounding mesenchyme will give rise to all other cells present in lungs (fibroblasts, endothelial cells, smooth muscle cells). The ships appear in parallel. They come from the pulmonary arteries from the sixth aortic arc, from the pulmonary capillary network that develops from the mesenchyme in contact with the epithelial bud and pulmonary veins. The vascular networks connect between them from the 34th day of pregnancy.

Vascular development involves a process of "Vasculogenesis" which corresponds to the creation of new vessels from the differentiation of endothelial cells within the mesenchyme and a «angiogenesis» process that corresponds to the budding and branching of the pre-existing vessels. Two theories oppose the role of the respective of both [4]. One suggests that the vasculogenesis is the primitive phenomenon while the other suggests the coexistence of the two phenomena.

Recent studies argue for the second hypothesis with, for example, the early intervention of angiogenesis in the pulmonary veins development [5].

Pseudo-Glandular stage

During this period, the lung moves from an undifferentiated primordial system to a bronchial and respiratory system. This stage takes place between the 7th and 16th week of pregnancy.

At the beginning of the pseudo-glandular stage, the cells constitute tubules upholstered by a high and undifferentiated cylindrical epithelium scattered in abundant mesenchyme. Each of the bronchiolar extremities is at the origin of a pulmonary functional unit: the Acinus.

Vascular development continues with the appearance of pre-acinar arteries and veins. The cells located in the aerial conduction pathways begin to differentiate at this stage in hair cells and in goblet cells. The mesenchyme differs in smooth muscle from 7 weeks. The cartilage appears at this stage and develops on the same pattern [6].

Respiratory units develop at the late pseudo-glandular, canalicular, saccular and alveolar stages.

Canalicular stage

It takes place between the 16th and 26th weeks. Terminal bronchioles give rise during this stage to Canaliculi, tubules, and pulmonary parenchyma.

The salient element of this stage is the modification of the epithelium and the surrounding mesenchyme with the appearance of a very clear demarcation between the cells of the future airways which retain a cylindrical appearance and the cells of the regions of gas exchange that acquire an cuboidal epithelium.

The first lamellar inclusions appear around 19 weeks. The lumen of the tubules widens and part of the epithelial cells flattens. From 24 weeks, more or less mature type I or II pneumocytes can be distinguished [7] with cubic type II pneumocytes that differentiate into squamous type I pneumocytes.

Another major change in this period is the development of distal pulmonary circulation. A capillary network forms around the distal air passages. Some capillaries protrude through the epithelium separated by a layer of basal lamina.

The gas exchange surface becomes increasingly fine with a thickness of 0.2 µm at the end of the canalicular stage. The vascular bed continues to grow by angiogenesis.

Saccular stage (26th to 36th Week)

Clusters of alveolar bags are formed at the terminal parts of the respiratory tree.

At the distal end of each terminal division are these smooth-walled alveolar bags upholstered by type I and II pneumocytes. The septa between the alveolar bags are still thick at this stage and contain the capillary networks of the two neighboring bags.

The Septas matrix is composed of collagen fibers and elastic fibers that are still rare. It plays a key role in the growth and differentiation of the overlying epithelium.

At the end of this stage, interstitial fibroblasts begin to produce extracellular material in the inter-saccular space. The epithelium initially cuboidal thins to become squamous. Surfactant secretion is increasing. Vascular development continues.

Alveolar stage

In the last few weeks of pregnancy, new alveolar bags are formed simultaneously giving birth to the first alveoli. The parenchyma forming the primary septa between the alveolar bags consists of a double thickness of capillaries. The formation of mature alveoli consists of two successive phases: the secondary septation and microvascular maturation. The secondary septation corresponds to the subdivision

of primitive saccules by the appearance of new inter alveolar partitions. Elastin deposits, synthesized by myofibroblasts, accumulate in the thickness of the primary septa between the two capillary networks and «drag» the wall to form perpendicularly the secondary septa, the elastin being then found at the apex septa. The second phase, which marks the end of the alveolisation process, is characterized by the thinning of the *p*rimary and secondary septa (by apoptosis of fibroblasts and reduced volume of interstitial tissue), and by the fusion of the double capillary network into a single network (microvascular maturation).

This stage allows both to significantly increase the surface of gas exchanges and to optimize the diffusion of gases on both sides of the air/blood barrier. The process of alveolisation is essentially a postnatal phenomenon in humans and probably ends between 18 and 24 months [8,9].

However, the formation of new alveoli can occur later in childhood or even in adults, so it is called "late alveolization» [10]. Similarly, the formation of new alveoli was observed after lung resection in mice, evidence of possible compensatory growth by increasing the number of alveoli and not by increasing the volume of the pre-existing alveoli; we speak in this case of «neoalveolisation» [11].

Pulmonary surfactant

Surfactant is a multimolecular complex synthesized by pneumocytes II from the 20th Week of gestation [12,13]. It consists mainly of phospholipids and specific proteins (6 phospholipids and 4 apoproteins). It has three main functions:

1. The decrease of the alveolar surface tension, established from the first minutes of postnatal life with the establishment of the water-air interface. The decrease of the alveolar surface tension, adjacent to 0 MN/m at the end of expiration, stabilizes the alveoli, reduces respiratory work, optimizes gas exchanges and ensures the maintenance of a functional residual capacity;
2. An anti-edematous action;
3. An anti-infectious defense function.

HMD is characterized by a primitive surfactant deficiency. This is the first pathology to have been successfully treated by exogenous surfactant.

It is due to the functional insufficiency both quantitative but also qualitative (specific proteins) in surfactant, causing alveolar atelectasis. This produce unventilated but infused areas creating an intra-pulmonary right-left shunt and hypoxemia.

Respiratory distress syndrome develops because of impaired surfactant synthesis and secretion leading to atelectasis, ventilation-perfusion (V/Q) inequality, and hypoventilation with hypoxemia and hypercarbia. Blood gases show respiratory and metabolic acidosis that cause pulmonary vasoconstriction, resulting in impaired endothelial and epithelial integrity with leakage of proteinaceous exudate and formation of hyaline membranes.

Epidemiology

Respiratory distress syndrome, also known as hyaline membrane disease, occurs almost exclusively in premature infants. The incidence and severity of respiratory distress syndrome are related inversely to the gestational age of the newborn infant.

In the absence of prenatal corticosteroid administration, its incidence is in the order of 60% in newborn of gestational age less than 30 weeks, reaching nearly 100% of premature infants under 26SA. Female sex has a protective role, while maternal diabetes is a predisposing factor. Intra-uterine growth retardation of vascular origin has a role discussed, aggravating for some [14], neutral [15] and even protector [16] for others. Some see the two effects according to the term [17].

Clinical Signs

From a functional point of view, the forces of elastic pulmonary retraction are increased, resulting in a collapse of the compliance. The newborn adapts to this disturbance by increasing its respiratory frequency to compensate for the low current volume he can mobilize.

The hyaline membrane disease will then manifest clinically by:

- The occurrence of secondary respiratory distress a few minutes after birth that gets progressively worse with:
    - A lowering of the pulmonary compliance,
    - A decreased alveolar ventilation,
    - A decrease in functional residual capacity,
    - A right-left intra-pulmonary Shunt,
    - A decrease in capillary perfusion,
    - Reduced oxygen supply
    - The presence of signs of struggle: grunting, nasal flaring, chest retractions, xiphoid retraction.
    - A tachypnea
    - A cyanosis
    - Decreased vesicular murmur
- The symptoms of RDS usually peak by the third day.
- A Gradual improvement.

Radiological signs

In this respiratory distress syndrome (RDS), the classic chest radiographic findings consist of pronounced hypoaeration, bilateral fine granular opacities in the pulmonary parenchyma, and peripherally extending air bronchograms.

The radiologic spectrum of RDS ranges from mild to severe and is generally correlated with the severity of the clinical findings.

Radiologically, there are 4 stages in the HMD:

1. **Stage 1:** Slight reticular (slight granular) decrease in transparency of the lung, no certain difference to normal findings.
2. **Stage 2:** Soft decrease in transparency with an aerobronchogram, which overlaps the heart (a sign of an alveolar lung reaction).
3. **Stage 3:** Like stage 2, but with gradual stronger decrease in transparency, as well as a blurry diaphragm and heart.
4. **Stage 4:** White lung: practically homogenic lung opacity.

Biological signs

Biologically, blood gases often show lowered amounts of oxygen and increased carbon dioxide:

- Initially, a pure hypoxemia directly related to intra-pulmonary shunt.
- And in the severe forms immediately, or when the child runs out in spontaneous ventilation appears a hypercapnia.

Complications

The complications of the HMD are associated with hypoxemia, hypercapnia, hypotension, instability of blood pressure, and lowered cerebral perfusion.

Complications of respiratory distress syndrome include:

- Intraventricular hemorrhage (IVH),

- Lesions of the white substance (Leukomalacia),
- Pneumothorax,
- Patent ductus arteriosus (PDA),
- Pulmonary hemorrhage,
- Bronchopulmonary dysplasia (BPD) (consequence of immaturity and aggressive treatment on an immature lung),
- Sepsis,
- Apnea/bradycardia,
- Necrotizing enterocolitis (NEC),
- Retinopathy of prematurity (ROP),
- Death in the neonatal period.

Treatment

Prevention

Prenatal steroids

Glucocorticoids have a modulating effect on pulmonary maturation. At the end of gestation, glucocorticoid increases the biosynthesis of phosphatidylcholine and thus the amount of phosphatidylcholine in the lung, as well as the activity of choline phosphate cytidylyltransferase, a key enzyme in the metabolism of the surfactant.

Their effect on biosynthesis and transcriptional activation of the genes of surfactant-specific proteins is important (SP-B and SP-C). The production of surfactant by Pneumocytes II is thus facilitated.

Glucocorticoids improve the biomechanical characteristics of the animal's lung.

Dexamethasone and Betamethasone that easily pass the placental barrier in active form and are poorly inactivated by 11 beta-hydroxysteroid dehydrogenase are indicated in the prevention of HMD.

Corticosteroids therefore accelerate lung maturation and reduce the incidence of respiratory morbidity.

The use of prenatal corticosteroids is currently recommended at 24 - 33 weeks gestation in women at risk of preterm delivery [18].

Post Natal treatment

Respiratory Support

CPAP (Continuous Positive Airways Pressure)

CPAP has multiple physiological advantages.

In spontaneously breathing premature, it facilitates respiratory efforts by synchronizing the airways and the diaphragm. It keeps the alveoli open, increases the functional residual capacity of the lung and optimizes the adaptation of the ventilation to the perfusion.

Compared to mechanical ventilation and tracheal intubation, CPAP minimizes the volutrauma and subsequent barotrauma. CPAP induces a stimulation of lung growth when administered to animals for an extended period of time [19].

Meta-analyses have demonstrated these benefits of the CPAP and its role in reducing the incidence of bronchopulmonary dysplasia (BPD) [20,21].

In addition, these tests have shown that nasal CPAP is a safe and effective alternative to intubation and mechanical ventilation in premature with HMD.

These results led the European Association of Perinatal Medicine and the American Academy of Pediatrics to recommend the use of non-invasive ventilation for first-line respiratory support in preterm infants with respiratory distress [22,23].

More recent studies have shown that the use of CPAP is associated with a lower risk of BPD or death in preterm infants.

In addition, the successful use of CPAP may reduce the risk of severe IVH, persistent ductus arteriosus (PDA) requiring surgical ligation, mechanical ventilation days and the number of infants discharging with oxygen at home [24].

NIPPV (Nasal intermittent positive pressure ventilation)

It is non-invasive nasal ventilation with intermittent positive pressure.

Compared to nasal CPAP its benefits are uncertain to prevent exposure to mechanical ventilation.

The various studies were made predominantly in the less than 32 weeks.

High flow nasal (HFN) oxygen delivery

The High flow nasal (HFN) oxygen delivery should be used only if the CPAP is not available.

There is currently no tangible data on the level of respiratory support actually received by the patient.

Mechanical Ventilation

It is only used if non-invasive ventilation fails.

Pulmonary injuries (barotrauma, volutrauma, activation of an inflammatory complex cascade) induced by the use of mechanical ventilation play an important role in the pathogenesis of BPD [24].

Surfactant

It is now certain that the surfactant leads to:

- A reduction in mortality,
- A decreased risk of pneumothorax, pulmonary emphysema and chronic lung disease.

The surfactant also allows:

- The prevention of short-term complications in the presence of moderate to severe symptomatology,
- To prevent pneumothorax and the respiratory failure,
- To reduce the duration and intensity of respiratory symptoms,
- The reduction of the duration of respiratory support and oxygen therapy,
- The reduction of hospitalization duration.

In the medium and long term, the surfactant administration is not associated with an improvement in the neurological and developmental outcome.

The methods of surfactant administration have been the subject of many studies in recent years:

- Intubation and IN-SUR-E (intubation- surfactant- extubation).
- The surfactant administration by minimally invasive method using a small bore probe (Caliber ≤ 5 French); the patient remains in spontaneous respiration during the administration.

This strategy avoids the mechanical ventilation and the administration of positive invasive ventilation pressure. There are several methods:

- MIST: Minimally invasive surfactant therapy.
- LISA: Less invasive surfactant administration.
- LIST: Less invasive surfactant therapy.

The objectives are:

- To minimize the duration of symptoms of respiratory distress syndrome,
- To minimize the risk of complication,
- To minimize the use of mechanical ventilation,
- To minimize the risk of BPD,
- To minimize the use of postnatal steroids,
- To promote a more homogeneous distribution of the surfactant,
- To avoid the short period of invasive ventilation associated with the in-SUR-E method.

These techniques also have disadvantages such as desaturations, bradycardia, and surfactant reflux. There are several methods (Cologne method, Hobart method).

Unfortunately sedation remains an aspect of the technique that needs improvement.

Olivier F [25], in a controlled randomized study including 3 centers in North America showed that the use of MIST for the management of respiratory distress syndrome in moderate and late newborn infants was associated with a significant reduction in use of mechanical ventilation and the occurrence of pneumothorax.

Conclusion

The preterm newborn is characterized by the immaturity of all its physiological functions, causing specific pathologies, especially respiratory (HMD, BPD) and neurosensory (intraventricular hemorrhage (IVH), leukomalacia and retinopathy of prematurity).

Antenatal corticosteroid therapy indicated in the case of a threat of premature delivery up to 34 weeks of gestation is a major factor in preventing complications of prematurity.

The early CPAP is the best management method for HMD.

The use of CPAP is associated with a lower risk of BPD or death in preterm infants.

In addition, the successful use of CPAP may reduce the risk of severe IVH, PDA requiring surgical ligation, mechanical ventilation duration and the number of infants discharging with oxygen.

The surfactant replacement therapy should be considered in patients with moderate/severe symptoms or with a fast evolution in the first hours of life.

Conflict of Interest

No conflict of interest.

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