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Hyaline membrane disease

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HYALINE MEMBRANE DISEASE

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TABLE OF CONTENTS

INTRODUCTION.....1

CLINICAL FINDINGS.....1
Clinical course.....1
Roentgenographic findings.....2
Laboratory findings.....2
Necropsy findings.....2

RELATIONSHIP TO CERTAIN FACTORS IN PREGNANCY AND DELIVERY.....3
Prematurity.....4
Diabetes mellitus.....4
Cesarean section.....4
Bleeding during pregnancy.....5
Twinning.....6
Toxemias of pregnancy.....6
Malpresentations of the fetus.....7
Sex.....7
Timing of cord ligation.....7

PATHOPHYSIOLOGY.....8
Amniotic fluid aspiration.....8
Inadequate fibrinolysin system.....9
Altered alveolo-capillary wall permeability.....10
Surfactant deficiency.....11
Pulmonary hypoperfusion.....15

SUMMARY.....16

BIBLIOGRAPHY.....17

INTRODUCTION

Hyaline membrane disease is the name usually applied to the respiratory distress syndrome of the newborn which is the world-wide leading cause of death of premature infants. It has been shown to affect 3.8 per cent of all premature newborns. Dr. Mary Ellen Avery states that it is the cause of 12,000 - 25,000 deaths per year in the United States of America (1). Gregg and Bernstein (14) report a 60 per cent crude fatality rate in dyspneic infants, half of them demonstrating pulmonary hyaline membranes at autopsy. Hyaline membrane disease is not a good name for the disease because the hyaline membranes are not always present; however, the name is well established in the literature, and will be used in this paper in view of this fact.

CLINICAL FINDINGS

Clinical course. Newborns who develop hyaline membrane disease usually have a low APGAR score, and often edema at birth; but no respiratory distress. Symptoms of dyspnea, inspiratory retractions, tachypnea of 60 or more respirations per minute, and a characteristic expiratory grunt do not appear for a few minutes to a few hours after birth. Fine crackling rales, a systolic murmur, and systemic hypotension are also frequently found. It is uncommon to develop hyaline membrane disease if the infant breaths normally for 6 - 8 hours (1). Cyanosis appears late and is relieved by oxygen until the terminal stages of the disease. Hyaline membrane disease has a relatively short duration; the infants who die, usually die within 48 hours, and rarely after 72 hours. Recovery is apparently complete in those who survive.

Roentgenographic findings. Feinberg and Goldberg report a series in which chest Roentgenographs prior to the onset of respiratory distress show only fine granularity and an increased bronchovascular pattern. The classic findings of a diffuse, reticulogranular infiltrate throughout the lung fields with an air bronchogram accompany respiratory distress. As the disease progresses, frank generalized atelectasis is found, especially in fatal cases (10).

Laboratory findings. Blood gas measurements reveal hypoxemia and respiratory acidosis. Arterial oxygen tension may fall below 40 millimeters of mercury with carbon dioxide tensions ranging from 50 - 90 millimeters mercury. Some infants may also have metabolic acidosis secondary to hypoxia with pH 7.1 to 7.3. The hematocrit is near normal which is important to note because severe blood loss can mimic hyaline membrane disease (22).

Some investigators have noted serum protein values of less than 5 grams per 100 milliliters. Dilts, in a study of cord blood proteins, found a significant decrease in globulins, but no significant decrease in Albumin (9).

Necropsy findings. The lungs always show aerated, evenly distended alveolar ducts and bronchioles, and atelectasis of alveoli which open into alveolar sacs. These are found throughout the lungs bilaterally and may be the only major findings in the lungs of newborns who die within 4 - 5 hours of the onset of the disease (3). A pulmonary hyaline membrane is usually present; it is a slightly laminated, eosinophilic membrane lining the alveolar ducts, respiratory bronchioles, and terminal bronchioles (25).

Pneumonia and pulmonary hemorrhage are frequently found, especially late in the disease. The pulmonary peri-venous lymphatics are increased in diameter and frequently filled with eosinophilic material (18).

Subarachnoid or intraventricular hemorrhage is found in a high percentage of those infants who had pulmonary hyaline membranes on necropsy. Avery reports up to a 67 per cent incidence of intra-cranial hemorrhage, which usually develops following prolonged or recurrent anoxia (16,1).

Another finding of interest is pressure atrophy and ulceration of the anterior portions of the ventricular bands and vocal cords. The paired ulcerations have also been found in those patients who survive. The ulcerations are apparently not related to the use of intubation techniques (23).

RELATIONSHIP TO CERTAIN FACTORS IN PREGNANCY AND DELIVERY

Any study of the etiology of the hyaline membrane disease must include a discussion of the various factors of pregnancy and delivery which have been shown to be associated with an increased incidence of the disease. There have been literally hundreds of papers written on these associations, but very little conclusive evidence to explain the relationship of these factors to the onset of the hyaline membrane disease. It will not be possible to completely separate this section on factors in pregnancy and delivery from the following section on the pathophysiology of hyaline membrane disease; so there will be some overlapping of information.

Prematurity. A study of 26,109 infants comparing birth weights with specific death rates with and without the hyaline membrane disease by Cohen reveals a corrected death rate of 39.1 per 1,000 live births for prematures compared to 0.7 for the full-term group. The highest death rate, 140.8 per 1,000, with the hyaline membrane disease is in the 1,001 to 1,500 grams birth weight group. The death rate progressively declines with increasing birth weight (8). It should be noted that incidence rates are much higher than these figures, and all studies show increased incidence of the hyaline membrane disease in premature births. It is suggested that immaturity of certain systems is the cause of increased incidence of the hyaline membrane disease. Another hypothesis is that an inadequately functioning placenta may result in premature labor and fetal hypoxia (8).

Diabetes mellitus. It is well known that diabetic mothers have a high incidence of children with the hyaline membrane disease. It is not known exactly what the incidence really is due to difficulties in the diagnosis of diabetes and the classification of sub-clinical diabetes in pregnancy. There are several theories about the relationship of diabetes to the hyaline membrane disease. Among them are placental dysfunction, prematurity of certain systems, increased complications of pregnancy which often cause fetal distress, and infarction of the placenta which will be discussed later.

Cesarean section. Cohen's study of 26,109 live births, including 1,013 cesarean sections, reveals a four-fold increased risk of the hyaline membrane disease with cesarean section. This is more

firmly established in those infants of less than 2,500 grams birth weight than in the full-term group (8).

It must be kept in mind, however, that cesarean sections are often performed for bleeding during pregnancy or prolonged labor, both of which are associated with fetal distress and an increased risk of developing the hyaline membrane disease. Many cesarean sections are performed prior to the expected due date, in which case the infants are less mature and have a lower birth weight than if carried to term, placing them in a higher risk group. It is quite possible that cesarean section alone, in the abscence of other factors, is not associated with any increased risk.

Bleeding during pregnancy. Placenta previa, premature separation of the placenta, and other bleeding during pregnancy have been associated with the hyaline membrane disease. Cohen, in a study of 1,665 live births including 40 with placenta previa, reports 5.7 times as many deaths with the hyaline membrane disease than in the group without placenta previa. The same study reveals that premature separation of the placenta is associated with a 1.9 times higher death rate with the hyaline membrane disease than the group without placental separation. Other forms of bleeding during pregnancy are associated with a 1.6 times increased death rate with the hyaline membrane disease. These figures suggest that of the various types of bleeding during pregnancy, placenta previa is most highly associated with the hyaline membrane disease. These figures are death rates, so they are likely underestimating the true incidence of the hyaline membrane disease; however, if there were no cases other than the deaths, the figures are

significant in that the death rate is 12.5 per cent with the hyaline membrane disease in the 40 cases of placenta previa (8).

Twinning. It has been suggested that if fetal distress is a factor in the etiology of the hyaline membrane disease that the second born of twins should have an increased incidence of the disease. Rokos et. al. undertook a study of 89 sets of twins in which at least one infant died. They encountered 22 sets of twins in which both infants died of the hyaline membrane disease, in 9 cases only the first born twin died, and in 37 cases the second born twin died of the hyaline membrane disease. In total, 31 of the first born and 59 of the second born twins died of the hyaline membrane disease. Zygosity and fetal weights were not recorded, however, and a more complete study is necessary to draw any final conclusions (27).

Toxemias of pregnancy. Good figures relating the toxemias of pregnancy to the incidence of the hyaline membrane disease are difficult to find. Cohen, in a study of 1,623 live births, including 80 cases of pre-eclampsia, eclampsia, nephritis, or hypertension, reports 3 neonatal deaths secondary to the hyaline membrane disease in those 80 cases, and 42 deaths in the 1,543 births without that history. He calculated from these figures a 1.6 times increase in the death rate due to the hyaline membrane disease with a history of toxemia of pregnancy (8). It is generally accepted that toxemia of pregnancy increases the risk of developing the disease. It is probable that the increased risk is related to fetal distress and low birth weight, since toxemic mothers often deliver early.

Malpresentation of the fetus. It is doubtful that fetal presentation alone has any effect on the incidence of the hyaline membrane disease. However, since fetal malpositions are often associated with placenta previa and prematurity it is probable that there is an increased incidence due to those factors. It is possible that an often associated prolonged labor, which may lead to fetal distress, could be related. I am not aware of any studies to support this hypothesis.

Sex. It has often been observed that males comprise a large share of the cases of the hyaline membrane disease. Miller et. al. conducted a study of 1,066 premature Negro infants considering birth weights and sex. He used a standard set of criteria for diagnosis and found the overall incidence rate to be twice as large in males than in females. He showed that males and females had equal incidence rates in the under 1,250 grams group. The greatest difference is in the 2,001 - 2,500 grams group, being nearly 4 times as great in males than in females (23).

Timing of cord ligation. Early cord ligation has been in vogue as an explanation for neonatal distress for a number of years. In 1801, Erasmus Darwin wrote:

> "Another thing very injurious to the child is the tying and cutting of the naval string too soon, which should always be left till the child has not only repeatedly breathed, but till all pulsation in the cord ceases. As otherwise the child is much weaker than it ought to be, a part of the blood being left in the placenta which ought to have been in the child." (11)

Frank and Gabriel made a prospective study of 190 premature infants weighing 1,000 to 2,500 grams, comparing early and late

ligation of the cord. Early ligation was defined as that before 2 breaths of the infant and late ligation as that after 2 breaths. All other factors were equal and the infants were all held at the level of the mothers' abdomens until the cords were ligated. There were 61 in the early ligation group and 129 in the late ligation group. They found that 31 per cent of the early and 27 per cent of the late ligation group developed symptoms of respiratory distress (11). The difference of figures is not statistically significant.

PATHOPHYSIOLOGY

The pathophysiology of a disease must account for all the symptoms and signs of the disease, the pathological findings, and explain the association of the disease to factors apparently related to the etiology of the disease. There have been a number of attempts to do this with the hyaline membrane disease, and a large amount of work has been done studying individual aspects of the disease. Some of the information is well-established, some of it is disproven, some of it is presently being researched quite extensively, and certainly many factors are not yet known. One of the unknown factors of the hyaline membrane disease is whether there is a single causative factor, or are there multiple causative factors. An explanation of a number of theories follows.

Amniotic fluid aspiration. The theory of amniotic fluid aspiration as the etiologic agent in the hyaline membrane disease is an old one which has lost most of its followers in recent years. The theory is that the hyaline membrane forms from squames in

the amniotic fluid on aspiration. Atelectasis of the alveoli is explained as a result of obstruction secondary to the formation of the hyaline membranes. Obstruction causes trapping of air in the alveoli, which is absorbed into the circulation leaving collapsed alveoli (7).

This theory was partially disproved by Gitlin and Craig (13) using fluorescein-labeled antibody to demonstrate that the hyaline membrane has a basically fibrin composition. It is possible, however, that amniotic fluid aspiration results in fibrin deposits being formed, possibly acting as a tissue thromboplastin. Most investigators do not believe that this theory is the most likely to explain the etiology.

Inadequate fibrinolysin system. The pulmonary hyaline membrane was shown earlier to be composed basically of fibrin (13). Some investigators have postulated that in normal infants the fibrin hyaline membrane is lysed by tissue fibrinolytic activity so that the membrane does not develop clinical significance.

Lieberman (19) studied the tissue fibrinolytic activity in the lungs of 49 fetuses and infants including 8 with hyaline membranes. He found an absence of plasminogen-activator activity in 8 of the 41 without hyaline membranes and in all of the 8 with hyaline membranes. Plasminogen (profibrinolysin) was found to be present in all subjects. The defect was not well correlated to gestational age.

Lieberman later studied the absence of plasminogen-activator activity in more detail (20). He demonstrated in those subject with the defect the presence of a potent inhibitor characterized by its ability to adhere to the particular matter containing the enzyme.

He also demonstrated high levels of the inhibitor in placental tissue.

The theory of an inadequate fibrinolysis system, in view of the demonstration of a potent inhibitor to the plasminogen-activator system offers a very attractive explanation to many cases of the hyaline membrane disease. It is possible that placenta previa and premature separation of the placenta are related to the release of the inhibitor into the fetal circulation. Placental infarction is a possible mechanism of release of the inhibitor into the fetal circulation in cases of toxemia and maternal diabetes.

Altered alveolo-capillary wall permeability. It is well established that the hyaline membrane is derived from the proteins of the blood, including fibrin (13). As stated previously, the lymphatics are frequently filled with an eosinophilic material which reflects increased pick-up of fluid and proteins by lymphatics (18). It has been proposed that the transudate is drawn from the blood by surface-tension forces when the alveoli are held open by inspiratory effort (24).

Most investigators believe that there is a state of altered alveolo-capillary wall permeability which allows more transudate to pass from the capillaries into the air-spaces to form a hyaline membrane. Indeed, electron microscope studies reveal damage to alveolar epithelial cells and discontinuities in the basement membrane (24). The mechanism of damage is not fully established as yet. It was previously felt to be secondary to oxygen therapy, but this has largely been abandoned. It is most likely that the

damage is caused by cellular hypoxia secondary to pulmonary hypoperfusion (6). It has been suggested that the maintenance of correct alveolo-capillary wall permeability requires lipoprotein synthesis, which may be decreased due to pulmonary hypoperfusion (26).

An altered alveolo-capillary wall permeability state is probably responsible for the formation of the hyaline membrane, but it does not explain the respiratory distress in those infants who die before the membrane is present. It is an important factor of the hyaline membrane disease, but it probably is not the cause of the onset of the hyaline membrane disease, nor is it the entire explanation for respiratory distress.

Surfactant deficiency. A review of the normal physiology of the lung is necessary to understand the theory of surfactant deficiency. The Laplace relationship,

$$\text{Pressure} = \frac{2T}{\text{Radius}} \qquad T = \text{surface tension}$$

describes the relationship of pressure within a bubble to its radius. The Laplace relationship shows that the pressure in a bubble is inversely proportional to the radius if the surface tension is constant; that is, the smaller the bubble, the higher the pressure. Two bubbles of equal size with a communication allowing free movement of air from one to the other would remain of equal size. Two bubbles of unequal size with a communication allowing free movement of air would not remain the same size. The smaller bubble, having a higher pressure, would force air into the larger. This would leave a collapsed bubble, and an overdistended bubble. Alveoli are basically bubbles with free communication which would follow the

same rule with the collapse of some alveoli and the overdistension of others if it were not for surfactant.

Surfactant is another term for surface active material which alters the Laplace relationship. Surfactant causes the pressure within the alveoli to remain constant or even decrease with reduction in the radius of the alveoli, thus preventing collapse of some alveoli and overdistension of others. The surface tension is increased as the radius is increased, and decreased as the radius is decreased.

Surfactant has been identified in lung tissue. It was first described as lecithin (phosphatidyl choline) in beef (17). Later it was shown to be dipalmityl lecithin (4). Recently it has been described as lecithin, phosphatidyl ethanolamine, sphingomyelin, and lysolecithin plus neutral lipids and relatively large quantities of complex polysaccharides. No proteins have been identified. Lecithin is the major component (28).

Lecithin is produced in the lung itself, possibly in the lining layer of the alveoli. The current hypothesis is that alveolar cells take up plasma fatty acids, and synthesize surfactant. The alveolar cells probably synthesize phosphatidyl ethanolamine and release it into the lining layer of the alveolus where it is methylated to form lecithin. Periodic compression and expansion of the alveolus may be necessary to complete the conversion to lecithin (28).

At birth the lung is filled with tracheal fluid. Lecithin has been identified in the tracheal fluid. This lecithin probably maintains the proper stability of expansion of the alveoli until the fluid is cleared from the lung and the alveolar cells release

lecithin precursor (phosphatidyl ethanolamine) and the respiratory movements drive the conversion to lecithin in the lining layer of the alveoli.

The theory of surfactant deficiency is that without sufficient surfactant, more work in necessary to expand the alveoli. The end result is atelectasis of most alveoli with overdistension of some. The increased work of respiration attempting to open the collapsed alveoli, and decreased oxygenation of blood are the causes of respiratory distress. The volume of atelectasis causes an increased pulmonary blood volume leading to pulmonary congestion which results in more transudation. The increased transudation is the explanation of the hyaline membrane (2).

Many studies have been conducted to determine the relationship of decreased surfactant to the hyaline membrane disease (15,26,12,2). Many techniques have been used to determine how much surfactant is present. Most have used a measurement of surface activity. Stability of bubbles expressed from a fragment of lung and pressure-volume relations of air-inflated lung tissue have been used with good results.

Avery and Mead (2) demonstrated a deficiency of surfactant activity in most infants under 1,200 grams, and in those infants who died of the hyaline membrane disease. An exception to this is in those infants who survived 48 hours, even with the hyaline membrane disease. Surfactant activity was uniformly found in those infants who weighed greater than 3,000 grams.

Gandy et. al. (12), in a study of 315 perinatal deaths related to respiratory distress, report that most who die within 6 hours of birth have decreased surfactant without pulmonary hyaline membranes.

Those infants who die at 6 - 24 hours after delivery have decreased surfactant activity and pulmonary hyaline membranes. If the infants survive longer than 24 hours they usually have pulmonary hyaline membranes, and normal surfactant activity at the time of death. In another study of 90 perinatal deaths it was observed that those with decreased surfactant activity developed pulmonary hyaline membranes if they survived longer than 2 hours.

Most studies indicate that usually by the 24th week of gestation there is functionally significant surfactant activity, and a large reserve by term (26). The theory of surfactant deficiency is that those infants who have adequate surfactant activity should not develop the hyaline membrane disease, and those who have deficient surfactant activity should develop the disease.

Many different mechanisms could explain inadequate surfactant activity at birth. Immaturity of the system which produces or releases surfactant is logical in the extremely premature, that is, 1,200 or less birth weight. It is logical that immaturity of that system is a variant of normal in some infants weighing more than 1,200 grams.

There are many explanations why those who survive a few days develop surfactant activity. Scarpelli (28) suggests that decreased lecithin in the tracheal fluid prevents adequate expansion of the alveoli the first few minutes after birth so the conversion of phosphatidyl ethanolamine to lecithin is inhibited.

Most observers explain that hypoxia prior to delivery may cause a temporary failure of production of surfactant. If oxygenation can be restored, surfactant is again produced (12).

Another possibility is that plasma fatty acids with fetal or maternal distress or maternal diabetes mellitus are decreased. Since plasma fatty acids are the precursors to surfactant, synthesis is decreased (28).

Pulmonary hypoperfusion. The pulmonary hypoperfusion theory has recently gained many followers. One group of investigators (6) have recently suggested renaming the disease the pulmonary hypoperfusion syndrome.

The reasoning of the pulmonary hypoperfusion theory is that there is a reflex vasoconstriction when the newborn is subjected to one or more of several stresses, such as hypoxemia, acidemia, hypothermia, and hypovolemia. Vasoconstriction in the lung should cause a right to left shunt through the ductus arteriosus. Indeed, there is evidence that there is a large right to left shunt (29).

Chu et. al. (6) studied the lungs of 49 infants, 19 of which died of the hyaline membrane disease and reported that the average pulmonary vascular conductance in the group with the hyaline membrane disease was one-twelfth that of the controls. Histologic examination suggested that the site of obstruction was in the arterioles.

Chu reasoned that if pulmonary arteriolar constriction caused pulmonary hypoperfusion, acetyl choline might improve their condition. Eleven of the twelve he treated responded rapidly and favorably. Five of the twelve died, however, four of those five received acetyl choline late in the disease.

Surfactant deficiency and increased alveolo-capillary wall permeability are explained by decreased anabolism in the alveolar cells secondary to hypoxemia. There is also indirect evidence in the

literature that uptake of plasma fatty acids by tissues is directly proportional to blood flow (5). This would also explain decreased synthesis of surfactant.

SUMMARY

The hyaline membrane disease is a complex syndrome which is difficult to explain with a single step by step progression of the development of the disease. Indeed, it is not possible to do so with the present knowledge of the disease. I have attempted to explain the reasons each risk group is more prone to develop the disease than the infants not in that group. The various theories of pathophysiology have been discussed with some emphasis on their merits and deficiencies.

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