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Pulmonary hyaline membrane disease

by

Professor Wong Hock Boon MBBS, FRCP(Ed.), FRFPS(G), DCH(Lond.)

DEPARTMENT OF PAEDIATRICS, UNIVERSITY OF SINGAPORE.

Pulmonary hyaline membrane disease of newborns is a fascinating pulmonary condition affecting chiefly premature infants who are severely dyspnoeic with cyanosis, marked intercostal retraction and with a high mortality rate. At autopsy, the lungs are airless, purple with a liver-like appearance, and histology shows extensive atelectasis together with the presence of an eosinophilic membrane adjacent to the aerated portions of the lung. It is fascinating because after half a century since the condition was first recognised, the aetiology is still unknown. This lack of knowledge is not due to want of research. In fact, there is a plethora of ideas and theories put forward to explain the aetiology and at this stage it shows very clearly the manner in which medical research inches its way to the final truth, but before the end of the road is reached, various approaches will have to be made and often many of them are totally different and even diametrically opposite. We are now in the midst of this stage of evolution and there is no doubt that the answer will be available in the future but for the present it is interesting to study the various theories advanced and to speculate on the relative importance of each of these theories. Before considering the aetiological factors, a few definite facts about the disease will now be enumerated.

Clinical Features

The infant is almost premature and some time within the first six or eight hours, the infant shows respiratory difficulty, consisting of increase in respiratory rate with soft tissue retraction during inspiration. Respiratory grunts and sighs are conspicuously audible and cyanosis easily seen. Auscultation reveals poor air entry and crepitations occasionally heard, and a systolic murmur may be heard. There is systemic hypotension with tachycardia, but with impending death, the infant is shocked, cold, with gasping respirations and increasing cyanosis and bradycardia.

X-rays reveal a diffuse uniform granular opacity in both lung fields and with associated obstructive emphysema, the air-filled bronchial tree stands out in marked contrast against the opacity to give an air-bronchogram effect.

Various ECG patterns have been described in this disease, the significance of which are still in the process of being evaluated. Some of them are secondary to electrolyte changes such as hyperkalaemia or acidosis, while others have mentioned that a right-heart pattern is associated with a better prognosis than a left-heart pattern.

Pathologic Criteria

Pathologists may differ in their acceptance of histological criteria for the disease. Generally most agree that the lungs are airless with the appearance of liver tissue. Microscopically, the widespread atelectasis is striking with the presence of the eosinophilic membrane adjacent to the aerated portions of the lung. This hyaline membrane consists of fibrin and it is the consensus that it is derived from the blood. There is evidence of epithelial necrosis in the terminal bronchioles underlying the membranes. There is associated vascular engorgement and sometimes frank pulmonary haemorrhage.

The idea that the membrane is derived from aspirated material is now not accepted and all evidence points to its origin from the circulation.

Pathogenesis

The multiplicity of theories forwarded for the aetiology of hyaline membrane disease is

itself a testimony to the fact that the truth is not yet known.

1. Possibility of a common mechanism:

The pathological picture of hyaline membrane disease in the newborn is also seen in other clinical states not necessarily limited to the infant age group. The rather differing clinical states which may produce this common pathological picture seems to suggest a common mechanism. The condition in which hyaline membrane may be demonstrated in the lungs include:—

a. **Gaseous inhalation:** Inhalation of war gases such as phosgene, or mercury vapour may be followed by hyaline membrane formation. Similarly, animals exposed to high concentrations of oxygen or carbon dioxide for prolonged periods may also end up with pulmonary hyaline membranes.

b. **Aspiration:** Aspiration of milk and kerosene have been known to produce hyaline membranes.

c. **Pneumonitis:** Viral or rheumatic pneumonitis similarly may be associated with formation of hyaline membranes.

d. **Miscellaneous diseases:** Such widely differing pathologies as Hodgkins disease, bronchogenic carcinoma and hepatic insufficiency have all produced hyaline membranes on occasion.

2. The nature of the common mechanism:

If there is a common mechanism, what could the nature be? Since the membrane is now known to be derivative product from the blood, a logical assumption could therefore be that somehow or other blood elements have exuded out from the pulmonary capillaries into the alveoli and later converted into hyaline membranes. Various workers have tried to prove this by means of certain observations:—

a. **Low serum protein:** If this is low, the osmotic pressure in the pulmonary circulation would be less and hence there is a greater tendency for exudation into the alveoli. Cooke (1960) showed that the prognosis was better in inafnts with hyaline membrane disease if the serum protein was more than 5 Gm% than if it was less than 5 Gm%.

b. **Left ventricular failure:** To substantiate this there is sometimes evidence of systolic murmur, enlarged heart and evidence of a left to right shunt. Left heart failure would therefore lead to pulmonary oedema and hence hyaline membrane formation. However, many infants with cardiac failure due to congenital cardiac malformations do not form hyaline membranes, and the exhibition of digitalis does not seem to help.

c. **Decreased pulmonary perfusion:** If less blood is delivered to the pulmonary vessels, then there may be the possibility of capillary damage with exudation. Tooley et al (1961) have discovered hyaline membranes in patients in the post-operative period after cardiac pulmonary bypass.

d. **Lack of fibrinolytic enzymes:** Plasminogen is the precursor of certain fibrinolytic enzymes and has been found to be low in prematures and since the membrane is composed of fibrin it is postulated that the membrane formed because of lack of fibrinolytic enzymes. It is also known that the placenta produces a substance which inhibits plasminogen activator and contributes further to the low fibrinolytic activity.

e. **Lack of alveolar lining layer:** Clements (1962) showed that certain cells lining the alveolar membrane produce a lipoprotein which has the property of lowering the surface tension of the air-liquid interface in the alveoli. If the lung is immature, these cells would be unable to produce sufficient amounts of this "detergent" substance so that the alveoli will not expand and hence the atelectasis. How lack of this substance would produce the membrane is another matter. It is postulated by those who believe in this mechanism that this "immaturity" of the alveolar lining membrane allows of transudation of blood into the alveoli.

f. **Asphyxia:** There are some who think that these premature infants have had anoxia at delivery and that this anoxia damaged the capillary lining with exudation and formation of the hyaline membrane. However, there are many premature infants who also had asphyxia but do not suffer from the disease.

g. **Aspiration:** This as stated above, was the cause originally thought of, especially the aspiration of amniotic fluid and that the membrane was derived from this fluid. This is untenable now as it is known that the membrane is derived from the blood. Also if intrauterine aspiration had occurred then it would be possible to see the membrane in the first few hours of life, which is not so. However, the proponents of this aspiration theory suggest that the aspirated amniotic fluid could damage the alveolar lining and set the conditions for exudation and subsequent hyaline membrane formation.

h. **Disturbed autonomic regulation:** Certain clinical observations seem to suggest that there is gross imbalance of the autonomic nervous system such as the hypotension, oedema and coldness of the extremities. Pulmonary oedema can be produced by bilateral vagotomy in experimental animals. Although there is evidence of autonomic imbalance, the cause of this and the way in which this produces the final disease picture are unknown.

3. Miscellaneous considerations

There are 3 observations relevant to the problem of pulmonary hyaline membrane disease, *viz*:—

a. **Caesarian section:** Hyaline membrane disease is about 9 times as common in babies delivered by caesarian section compared to vaginal deliveries, other things being equal. However, it was later discovered that if caesarian section was done because of maternal bleeding then the increased incidence was true, but if maternal bleeding was excluded then the incidence after caesarean and after vaginal delivery were the same. Therefore elective caesarean per se does not predispose to hyaline membrane disease.

b. **Maternal diabetes:** It has also been observed that infants of diabetic mothers are more prone to hyaline membrane disease, and yet their birth weights are much more than those of premature infants. But it should be realised that many of these large babies who succumb to hyaline membrane disease are indeed premature by gestational age. In other words, the propensity of these infants to develop hyaline membrane disease is due to a combination of immaturity and the peculiar circumstances attendant on an infant born of a diabetic mother.

c. **Acid-base disturbances:** Normal newborn infants have an arterial pH of 7.25 to 7.30, with PCO_2 of 50-70 mm.Hg and bicarbonate values of 18 to 22 mEq./litre. This degree of acidosis which is both respiratory and metabolic is corrected by the normal newborn infant when he begins to breathe and blows off the excess CO_2 and within a few hours has retained enough bicarbonate to counteract against the metabolic acidosis. However, in infants with hyaline membrane disease both these compensatory measures are inadequate so that the

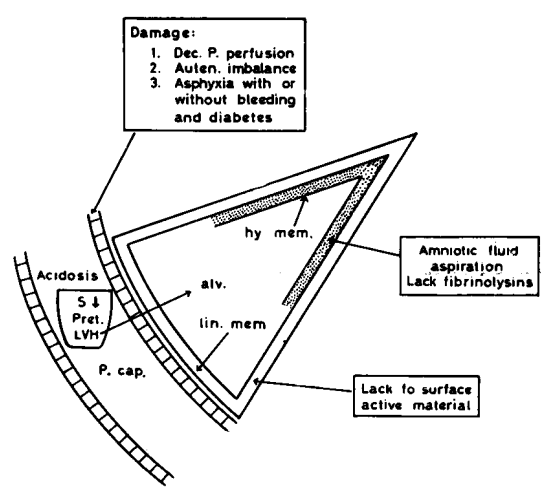

Fig 1. Summary of theories offered for causation of pulmonary hyaline membrane disease (for explanation, see text).

arterial pH may be as low as 7.0 and pCO_2 levels of over 60mm.Hg. Usher (1961) felt that a venous pH of less than 7.15, or pCO_2 of more than 70mm.Hg. and bicarboate values of less than 18mEq/litre are usually ethal in the infant with hyaline membrane disease unless electrolyte therapy is instituted.

Summarising then the various theories which have been postulated for the pathogenesis of hyaline membrane disease, the following is a highly-simplified diagram of the possible mechanisms. (Fig. 1)

Therapy

Since the actual aetiological factors and the mechanisms are unknown, various regimens of therapy have been devised. It is almost impossible to assess the efficacy of each of these measures for various reasons. One of these is that often a worker trying out a new regime of treatment would pay more attention and provide almost continuous observations to assess the response and in this way unconsciously the patients would have had more care than previous cases. Also, these prematures are already extremely feeble and although they may have responded to the new regime died as a result of prematurity or complications arising therefrom. Furthermore, it is not always possible to try the regime on sufficient patients in any one centre in order to gather statistical evidence which may be valid. All these attendant factors must be taken into consideration when evaluating the results of any one form of treatment.

Arising from the various theories put forward for the aetiology and pathogenesis of the disease, the following have been tried:—

1. **Low serum protein:** Use of 25% serum albumin at a dose of 4mg/lb.
2. **Left ventricular failure:** Use of digitalis.
3. **Decreased pulmonary perfusion:** Delivery of premature infants below the level of the placenta and delayed cord clamping till pulsations have ceased, usually 3-5mins. This would allow an extra volume of 30-100ml. of placental transfusion.
4. **Asphyxia:** Breathing of high concentrations of oxygen.
5. **Aspiration of amniotic fluid:** Gastric aspiration of all prematures immediately after delivery.
6. **Lack of fibrinolysins:** Urokinase-activated human plasma given i/v and by aerosol.
7. **Lack of surface active substance:** Use of surface active substances given by aerosol.
8. **Electrolyte disturbances:** Use of sodium bicarbonate in 10% glucose at rate of 65ml/kg/day.

References

Avery, M.E. (1964). The lung and its disorders in the newborn infant. W.B. Saunders Co., Philadelphia & London.

Clements, J.A. (1962). Physiologist, 5, 11.

Cooke, W.D.D. (1960). Med. J. Austr. June 4th, 887.

Tooley, W.H., Gardner, R; Thung, N. and Finky, T. (1961). Fed. Proc. 20, 428.