Mortality in hyaline membrane disease

by S. Sivanesan

Department of Pathology,
University of Malaya,
Kuala Lumpur

HYALINE MEMBRANE DISEASE (HMD) or the respiratory distress syndrome (RDS) is an acute condition, affecting predominantly, premature infants shortly after birth and is characterised by tachypnoea, cyanosis, inspiratory retraction of the chest wall, and expiratory grunting. Investigators in many parts of the world consider it to be the leading cause of death of premature infants[1] and despite almost three decades of intensive research, there seems to be no appreciable decline in the mortality from this disease. The pathophysiology of the condition remains imperfectly understood and its aetiology is unknown.[2,3] This predicament, should, no doubt, be a cause for distress amongst eminent students of the disorder.

A definite diagnosis of HMD can only be made by histological examination of the lungs,[4] and therefore until an unequivocal test is devised to identify the disease in life, autopsy studies will provide the only reliable means of determining its real incidence. A search of the literature in 1959 showed that HMD had not been reported outside the United States and Europe. In 1960, a study of pulmonary lesions of the newborn in Singapore revealed that HMD was the commonest cause of infants dying within the first week of life and it was demonstrated that epidemiological and ethnic factors were of little significance in its aetiology and incidence.[5] There have been other careful studies since then, [6,7,8] drawing attention to the worldwide prevalence of HMD, and also reports from this region.

The purpose of this paper is to analyse the trends in mortality from HMD in this region.

Material and Methods

The material is derived from five separate series of study, the first four being based almost exclusively on autopsies at the Kandang Kerbau Hospital (KKH) Singapore and the final series from autopsies at the University Hospital, Kuala Lumpur.

Series 1. This is based on a 1-year investigation of neonatal deaths ending in June 1960. During this period, there were 38,114 live-births, which includes a small number of births before arrival. There were 555 early neonatal (first week) deaths of which 423 were autopsied. The 'autopsy index' (per cent of early neonatal deaths autopsied) was 76.2%.

Series 2. This is a survey of stillbirths and neonatal deaths[9] over a period of 6 months, ending in December 1962. During this period there were 19,566 livebirths and 345 neonatal deaths. Autopsies were performed on 274, and of these 259 were early neonatal deaths which accounted for 75.1% of the neonatal deaths that were autopsied.

Series 3. This is derived from a perinatal mortality survey over a period of 1 year ending in March 1965.[10] There were 38,667 livebirths during this period and 618 early neonatal deaths of which 485 or 78.5% were autopsied.

Series 4. This is an analysis of neonatal mortality in KKH.[11] This is a 1-year study ending December 1966. There were 38,547 livebirths and 596 neonatal deaths, including 546 early neonatal deaths of which 399 or 73.1% were autopsied.

Series 5. This is an investigation of neonatal deaths at the University Hospital, Kuala Lumpur from January 1970 — December 1971. During this period there were 4,761 livebirths and 95 early neonatal deaths, of which 68 or 71.5% were autopsied.

The autopsies and histological examination of the lungs for the first three series were performed by three different pathologists from the Department of Pathology, University of Singapore.

Table I
Summary of the material by years

Series Concluding	1	2	3	4	5
Year of study	1960	1962	1965	1966	1971
Autopsy index	76.2%	75.1%	78.5%	73.1%	71.5%
Autopsies	423	259	485	399	68
Deaths	555	345*	618	546	95
Live births	38,114	19,566**	38,667	38,547	4,761

* Refers to all neonatal deaths
** Six months only.

In Series 1 and Series 5 of this study, the lungs were fixed in buffered formaldehyde solution (10% formalin). Representative or whole lung, paraffin embedded sections, stained with haematoxylin-eosin were then examined by the present investigator. Lungs showing varying degrees of collapse, not necessarily complete cohesion of the alveolar septa, together with the presence of eosinophilic membranes lining the alveolar ducts and/or the alveoli were diagnosed as cases of HMD. The hyaline membranes varied in thickness and length, and were diffusely distributed. Hyaline membranes were associated with focal haemorrhages, or neutrophil leucocytes within the alveoli, in a small proportion of cases.

Results

The mortality from HMD confirmed by autopsy in the five series of autopsies are compared in Table II. The number of premature infant (birth weight of 5 lbs or less) deaths, and their percentages of the total number autopsied for the same periods are also compared.

Table II
Comparison of autopsy incidence of HMD by years

Series	1	2	3	4	5
Year *	1960	1962	1965	1966	1971
HMD % Autopsies	29.8	18.2	28.4	35.8	32.3
No HMD cases confirmed	126	47	138	144	22
Prem. % Autopsies	82.2	81.9	80.7	73.4	70.5
Premature deaths	348	239	499	401	48

* Year study concluded

In addition to the data given in Table II, other findings which are considered relevant to the discussion below are:—

Series 1. Intracranial haemorrhage was the cause of death in 75 (17.7%) infants and this did not include 20 (4.7%) deaths with intraventricular, intracranial haemorrhage. Atelectasis with no hyaline membrane was found in 29 (6.3%) premature infants.

Series 2. Intracranial haemorrhage was the cause of death in 92 (35.5%) early neonatal deaths and included 37 (14.2%) cases of intraventricular haemorrhage. In 17 (6.6%) infants, the cause of death was attributed to prematurity itself.

Series 3 & 4. Intracranial haemorrhages accounted for 25.0% and 14.3% of deaths respectively; prematurity itself was the cause of death in 3.7% and 2.0% respectively in each of these series.

Discussion

An analysis of the results shows a decline in mortality from HMD in 1962 as shown in Table II and an increased mortality in 1966. An increase has also been a cause for comment in the past elsewhere.[12]

The changes in the lungs in an infant who develops RDS consist of progressive collapse of the air sacs leading to atelectasis, and this has been confirmed by radiologic studies.[18] The hyaline membranes are rarely found if the baby dies before within 7 or 8 hours,[14, 15] and the classical appearance of the lungs is seen only in infants dying after 8 to 10 hours.[16] It is unlikely that a diagnosis of HMD in the absence of pulmonary hyaline

membranes was made by any of the pathologists connected with these series. There is no doubt that different investigators might show minor differences in pathologic criteria, (Avery 1968) and also when haemorrhages or inflammatory changes are present, strands of fibrin may resemble hyaline membranes, presenting difficulties in diagnosis and classification.

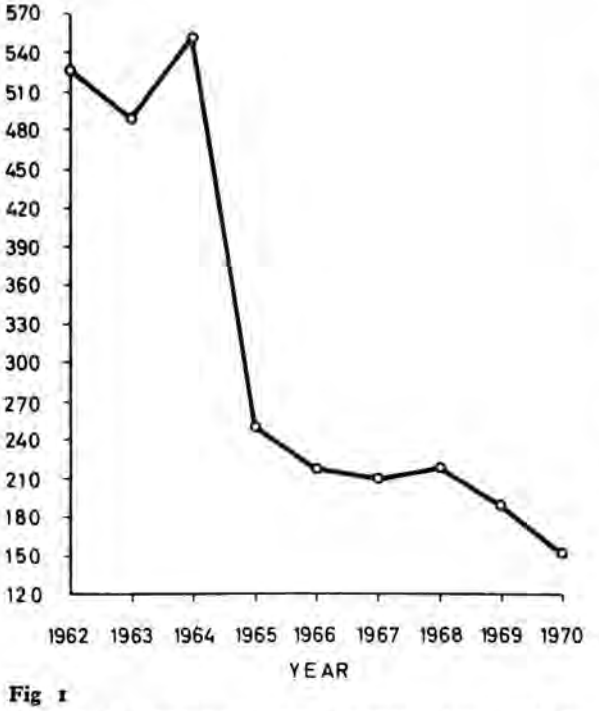

Fig 1

Decline in premature infant mortality from 1962-70 (except 1963) in Kandang Kerbau Maternity Hospital

The increasing survival of premature infants at KKH[17], except for an inexplicable rise in 1964, is shown in Fig. 1. Apart from reduction of deaths due to infection, increased survival is probably attributable to improving standards of paediatric and nursing care, themselves consequences of better understanding of the problems of the premature newborn, more rational and improved methods of oxygen administration, and thermal protection in incubators. In 1970, there were only 120 deaths per 1,000 premature livebirths at the KKH. This improvement is highly suggestive of at least longer survival of ill-fated infants with RDS, allowing time for hyaline membranes to form, and this most probably accounts for the apparent increase in deaths from HMD in 1966.

It will also be noted in Table II, that, throughout the period 1960 to 1966, there has been a steady decline in the proportion of premature infants examined post-mortem. At the University Hospital, Kuala Lumpur the figure was 70.5%. There are also reasons to believe that in spite of the lack of any established specific therapy for RDS, general supportive measures enable a greater proportion of infants who develop the condition to survive.

Intraventricular haemorrhage is due to anoxia and this has recently been emphasised again.[18] HMD was found in 42% of babies with intraventricular haemorrhage in a perinatal survey.[19] When hyaline membrane is present in a lesser degree, it will be a matter of opinion whether the case should be so classified,[20] and it is therefore reasonable to presume that many infants in Series 2 died of HMD rather than intraventricular haemorrhage which is one of the complications of the disease. An unexpectedly low mortality from HMD in Series 2 may be due to some extent at least to accepting intraventricular haemorrhage instead of HMD as a primary cause of death in 14.2% of cases. Furthermore, in Series 2 prematurity itself has been attributed as a cause of death in 6.6% compared to 3.7% and 2.0% in Series 3 & 4. In premature infants that are autopsied, there will be a substantial number of cases of atelectasis, 6.3% in Series 1, and a few of these would be due to RDS in its early phase.

Summary and Conclusion

1. An analysis of 5 separate series of consecutive autopsies on newborn infants, with special reference to hyaline membrane disease is presented.
2. Despite the improved survival of premature infants as shown in Fig. 1, no comparable reduction in mortality from HMD as disclosed at autopsy was noted.
3. Nevertheless, it is very likely, that in these series, where the presence of hyaline membranes at autopsy was the main criterion used, the comparable reduction to be expected was not disclosed.
4. To some extent this finding may be due to the fact that hyaline membrane formation does not occur unless the infant lives for 8 hours or more.

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