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Pulmonary Haemorrhage in the Newborn

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The frequency of pulmonary haemorrhage in any pathological study depends on the composition of the autopsy material and the thoroughness of the postmortem examination as well as on the criteria on which the diagnosis has been based. Pulmonary haemorrhage is sometimes the sole pathological finding, but in a number of cases it is associated with other pulmonary lesions such as pneumonia, atelectasis or emphysema. It may also be found as a complication of some extrapulmonary lesions such as septicaemia, morbus haemorrhagicus neonatorum, or isoimmunization.

Unless several lobes are involved, the role and importance of pulmonary haemorrhage in perinatal mortality is not easy to determine. Particularly difficult appears the evaluation of the possible relationship between survival and several disseminated interstitial or intraalveolar haemorrhagic foci. This type of pulmonary haemorrhage should be regarded as part or a consequence of the underlying disease rather than the primary cause of death. The fact that diagnosis *in vivo* is frequently impossible does in no way diminish the clinical importance of pulmonary haemorrhage. On the contrary, the advance of neonatal pathology demands extensive pathological and clinical analysis. This is also shown by recent reports [1—4,] contributing to our present knowledge concerning neonatal pulmonary haemorrhage.

It is in the first place the detailed analysis and comparison of clinical and autopsy materials published by different authors, which may certainly help in elucidating the aetiology and pathogenesis as well as in the more exact delineation of the clinical picture of pulmonary haemorrhage. Although much uncertainty is inherent in retrospective clinical studies it appeared to be interesting to analyse certain aspects of pulmonary bleeding in our own autopsy material.

Material

The autopsy findings of infants who had died in the first 14 days of life in the period from January 1, 1960, to December, 31, 1965, have been surveyed, and cases in which pulmonary haemorrhage was reliably proved by gross and microscopic examination, have been selected for the

purposes of this study. Since most of the autopsy protocols did not clearly state whether the haemorrhage had been intra-alveolar or interstitial, and since these two types of bleeding had often occurred in combination, it was impossible to classify the material according to that criterion. By comparing the autopsy findings with the clinical picture, we also studied the possible relationship between the history of pregnancy, perinatal complications, and the clinical manifestations of pulmonary haemorrhage.

A total of 596 newborn babies died within 14 days during the examined period. The birth weight of 514 of these infants was below 2500 g.

Results

Anatomically, pulmonary haemorrhage may be classified according to its extent and site. We could, thus, distinguish focal and massive, intra-alveolar and interstitial pulmonary haemorrhage. The alveoli and bronchioles were filled with erythrocytes and frequently the interstitial spaces contained many extravasated red corpuscles in cases of "massive" haemorrhage, when at least one but often several lobes were involved. Isolated intraalveolar or interstitial bleeding was more frequent in cases of focal pulmonary haemorrhage, although mixed forms, too, have often been observed.

Table I

Year	Number of deaths within 14 days		Total	Number of histological examinations	Pulmonary haemorrhage	Incidence of pulmonary haemorrhage per cent
	< 2500 g	> 2500 g				
1960	66	14	80	42	2	2.5
1961	73	14	87	34	3	3.4
1962	97	13	110	34	1	1.0
1963	72	19	91	54	5	5.4
1964	102	6	108	102	10	9.2
1965	104	16	120	116	5	4.1
Total	514	82	596	382	26	4.3

The annual frequency of pulmonary haemorrhage, arranged according to birth weight, and the number of histological examinations are shown in Table I.

It can be seen that the 9.2% frequency of pulmonary haemorrhage observed in 1964 considerably exceeded the average 4.3% incidence for the period 1960 to 1965. Since in 1964 — in contrast to the preceding years — histological examination was performed on almost every dead newborn, it appears logical to suppose that the high frequency was mainly due to the great number of histological examinations. The fact, however, that in 1964 the

pulmonary haemorrhages, like those observed in the preceding years, were detected at gross examination and in 1965, when histological examination was likewise made in every instance, did not substantially differ from the average frequency of the years before 1964, does not support that explanation. It was the high incidence in 1964 which had directed our attention to the problem of pulmonary haemorrhage in the neonate.

Authors relying on quantitatively and qualitatively different material [1, 2, 5, 9, 16, 17], claimed the occurrence of neonatal pulmonary haemorrhage to vary from 1 to 10% of the number of deaths. The wide range of frequency is also emphasized by a recent communication [9] reporting a frequency of 17.8% in 758 liveborn infants who died within 14 days after birth. The variable incidence is mainly explained by the fact that the autopsy material of different authors is not strictly comparable with regard to the complications of pregnancy, delivery, birth weight, neonatal disturbances and postnatal age.

The distribution of pulmonary haemorrhage according to weight categories is shown in Table II.

It can be seen that the incidence in infants weighing less than 2500 g was 3.3%, whereas in infants weighing more than 2500 g it amounted to 11%. A similar increase in incidence with the birth weight has been reported by ESTERLY and OPPENHEIMER [9].

TABLE II

Birth weight	Number of deaths	Pulmonary haemorrhage		Weight groups				Birth weight	Number of deaths	Pulmonary haemorrhage	
		Number of cases	Incidence, per cent	<1000	1000—1500	1501—2000	2001—2500			Number of cases	Incidence, per cent
<2500 g	514	17	3.3	2	4	7	4	>2500 g	82	9	11

The most important data concerning the history of pregnancy, perinatal complications, the concomitant findings at autopsy as well as bleeding from the airways in the 26 infants with pulmonary haemorrhage are seen in Table III where the serial number of the individual cases is the same as in Fig. 1.

As can be seen, 8 babies had undoubtedly been suffering from chronic intrauterine or acute perinatal hypoxia; in 4 infants no pertinent data were available concerning the history of pregnancy and delivery while in 12 cases no notable disorders or complications were observed. There were 4 mature and 5 premature infants in whom pulmonary haemorrhage was not associated with other

TABLE III

Case No.	Birth weight	History of pregnancy and birth	Autopsy finding apart from pulmonary haemorrhage	Haemorrhagic manifestation
1	1800 g	Twisting of umbilical cord around neck	Atelectasia subtotalis pulmonum	—
2	2670 g	Toxaemia. Livid asphyxia	Ruptura falcis cerebri inde haemorrhagia intermenigealis	+
3	970 g	Algid asphyxia	—	+
4	2600 g	Threatening intrauterine asphyxia. Algid asphyxia	Ruptura tentorii cerebelli inde haemorrhagia intermeningealis	+
5	2400 g	Intrauterin asphyxia. Caesarean section	Labium leporinum, faux lupina	+
6	1250 g	Negative history	Haemorrhagia intermeningealis. Cheilo-gnato-palatoschisis	—
7	1400 g	Negative history	Haemorrhagia intermeningealis. Sepsis enteralis	+
8	3150 g	Negative history	—	+
9	3050 g	Toxaemia. Extensive infarcts on placenta. Livid asphyxia	—	—
10	980 g	Negative history	—	+
11	2450 g	Negative history	Kernicterus. Sepsis enteralis	+
12	1800 g	Negative history	—	+
13	1800 g	Hydramnion. Premature birth	Haemorrhagia intermeningealis. Enterocolitis.	+
14	2200 g	Negative history	Dislaceratio tentorii cerebelli. Atelectasia subtotalis pulmonum	—
15	1450 g	Premature rupture of foetal membranes. Caesarean section	Haematocephalus internus	—
16	1850 g	—	—	+
17	3150 g	—	Multiple malformations	+
18	1800 g	Negative history	Kernicterus	+
19	3600 g	Toxaemia. Threatening intrauterine asphyxia. Livid asphyxia	Haemorrhagia intermeningealis	+
20	3900 g	Negative history	Haemorrhagia intermeningealis	+
21	2400 g	Breech presentation	Haematoma subarachnoideale	—
22	2750 g	Negative history	—	—
23	1800 g	—	—	—
24	1150 g	Negative history	Haemorrhagia intermeningealis. Haematoma subcapsulare hepatis	—
25	1900 g	—	Enterocolitis	—
26	2900 g	Negative history	—	—

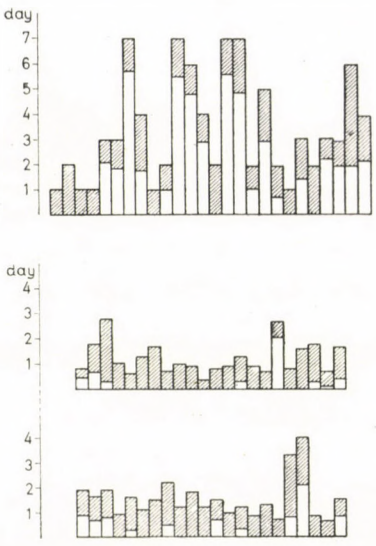

FIG. 1. The height of the upper and lower columns indicates the survival time of infants in whom autopsy revealed pulmonary haemorrhage and hyaline membrane disease, respectively. The empty part of the columns shows the length of the symptomless period in both groups of infants

pathological findings which could have played some immediate role in death. Among the rest of the infants, intracranial haemorrhage was frequently revealed as a concomitant lesion at autopsy. In 12 cases out of 17, pulmonary haemorrhage was associated with complications (intracranial haemorrhage, atelectasis, pneumonia) giving rise directly or indirectly to hypoxia.

It is well-known that bleeding from the nostrils and mouth is a frequent occurre ce in neonatal pulmonary haemorrhage. In the present material (Table III) it occurred in 15 infants (57.6%); in 9 infants, in whom pulmonary haemorrhage was not associated with any other significant pathological lesion, the incidence of haemoptysis was identical with that in the whole material.

Most of the infants died on the 3rd or 4th postnatal day (average survival, 3.4 days). The survival time of infants showing pulmonary haemorrhage as a single pathological finding was approximately the same, i.e. 3.3 days. The height of the column in Fig. 1 indicates the time of death of the individual cases shown in Table III. The unshaded part of the column represents the length of the symptomless period in relation to the time elapsed from the first clinical symptom to the time of death (shaded part of the columns).

In order to delineate the clinical picture of pulmonary haemorrhage [1, 6, 16, 17], the symptomatology has also been analysed. The sudden development of respiratory distress (dyspnoea, cyanosis, preterminal haemoptysis, blood-tinged mucus from the nasopharynx) is regarded by most authors as characteristic of pulmonary haemorrhage. In 110 of 135 retrospectively analysed cases [11] dyspnoea and cyanosis supervened immediately, or in the three hours after delivery. In 8 infants of the present material dyspnoea and cyanosis appeared immediately after birth and then became more and more pronounced.

It can be seen from Table III that in three of these infants (Nos 3, 9, and 22) pulmonary haemorrhage was the only pathological finding at autopsy, while in the remainer addi-

tional lesions such as atelectasis or intracranial haemorrhage could also be observed.

As mentioned above, in altogether 9 out of 26 newborns autopsy did not reveal concomitant pathological findings and in three (Nos 3, 9 and 22) respiratory distress appeared immediately after birth. The clinical picture in these cases showed no sign pointing to pulmonary haemorrhage. Since the symptoms of the remaining six infants appeared to be characteristic of neonatal pulmonary haemorrhage, a short description is given of the clinical picture.

Case No. 8. This full term infant showed no symptoms until the age of two days, when severe respiratory distress developed. On the third day convulsions and preterminal bleeding from mouth and nose occurred.

Case No. 10. On the second day of extrauterine life, this premature infant became suddenly grey and apnoeic. Haemoptysis was noted terminally.

Case No. 12. After a symptomless period of 5 days apnoeic attacks occurred and the general condition deteriorated rapidly. Before death bleeding from nostrils and mouth was observed.

Case No. 16. This infant appeared to be healthy until the age of 3 days when slight epistaxis occurred repeatedly and the infant became increasingly lethargic. Death soon ensued amidst signs of massive pulmonary haemorrhage.

Case No. 23. Episodes of dyspnoea and apnoea appeared on the third day of life. Aspiration was diagnosed which seemed to be supported by the X-rays. Autopsy revealed pulmonary haemorrhage.

Case No. 26. The infant was admitted at the age of 3 days because of repeated apnoea and cyanosis. Six hours later death occurred amidst convulsions. Terminally no epistaxis or haemoptysis was observed.

As it can be seen from Fig. 1, six infants died comparatively late, i.e. on 6th or 7th day. Two of them (Nos 12, 16) were fed through gastric tube and before autopsy the possibility of a traumatic bleeding from the nasopharynx with consequent aspiration of blood could not be excluded. Postmortem examination, however, revealed primary pulmonary haemorrhage. In the other infants who died on the 6th or 7th postnatal day (Nos 7, 11, 15, 25), pulmonary haemorrhage occurred in association with septicaemia or other severe pathological lesions (intracranial, haemorrhage, kernicterus).

Bleeding or discharge of blood-stained mucus from the mouth or nostrils is one of the most reliable signs of pulmonary haemorrhage. These signs were observed in 15 newborn infants (57.6%), including 5 of those 9 cases in which pulmonary haemorrhage was associated with other disorders (Table III).

Discussion

Opinions are divided concerning the aetiology and pathogenesis of neonatal pulmonary haemorrhage. On the basis of histological examinations carried out in 125 infants who had died within seven days of birth, Landing [11] concluded that neonatal pulmonary haemorrhage was usually accompanied

by pneumonia. Other authors [6, 8, 12] attributed a decisive role to perinatal hypoxia, and suggested that pulmonary haemorrhage was an independent entity which usually manifests itself suddenly a few days after birth. On the basis of a retrospective analysis of 105 cases ROWE and AVERY [15] inferred that hypoxia and asphyxia played an essential role in the pathomechanism of neonatal pulmonary haemorrhage. They relatively often observed the concomitant occurrence of congenital heart disease which fact pointed to the possible significance of changes taking place in pulmonary circulation. It is known that pulmonary haemorrhage may also occur in hyaline membrane disease of the newborn: its incidence varied between 11 and 50% in the material of different authors [1, 4, 6, 10], a fact which raises the possibility of a common aetiology and pathogenesis of the two syndromes.

ROBERTS *et al.* [14] examined the possible role of coagulopathies but failed to demonstrate any defect in blood coagulation. It should, however, be noted that CELANDER [7] demonstrated reduced capillary resistance in hypoxic newborns. Prolonged fibrinolysin and prothrombin time in association with respiratory distress has been reported by MARKARIAN *et al.* [13].

It is evident from the foregoing short survey of the literature that the majority of authors regard perinatal hypoxia as the most common factor contributing to pulmonary haemorrhage. Our present material is not large enough to justify any definite conclusions in respect of pathogenesis, but is nevertheless sufficient to allow — at least as far as conditions in Hungary are concerned — certain statements which may confirm or complete our present state of knowledge.

The average incidence of pulmonary haemorrhage in the present material was 4.3%. The annual frequency varied between 1.0 and 9.2% during a period of six years, which is in accordance with the wide range of fluctations in the material of different authors.

According to the present findings, neonatal pulmonary haemorrhage is seldom an independent entity and its clinical picture is far from being uniform. In the absence of terminal or preterminal bleeding from the airways it is almost impossible to diagnose the condition, particularly if the clinical picture is dominated by the signs of intracranial bleeding, respiratory distress, septicaemia or some other disturbance. Haemorrhage from nostrils or mouth may occur under other conditions as well, and therefore bleeding or blood-tinged mucus in the mouth or nasopharynx does not justify the diagnosis of pulmonary haemorrhage. In the newborn infant fed through a gastric tube, lesions of the pharynx, the oesophagus or the gastric mucosa may easily occur, and in such cases aspiration of blood should carefully be distinguished from intraalveolar haemorrhage.

Hypoxia, asphyxia and acidosis often precede pulmonary haemorrhage. In about one third of the present material a disturbance of intrauterine or perinatal oxygen supply could be assumed, while in half of the cases pulmonary haemorrhage was accompanied by lesions which themselves could have been either the cause or the consequence of hypoxia. The pathogenetic importance of a deficient oxygen supply is supported by the observation that pulmonary haemorrhage is frequently found in stillborn foetuses. Hypoxia, asphyxia and acidosis may affect or modify neonatal pulmonary circulation both anatomically and functionally, and under certain conditions this may manifest itself in the form of pulmonary haemorrhage, an assumption that has yet to be proved. In contrast to the observations of ROWE and AVERY [15] in our material no congenital heart defect associated with pulmonary haemorrhage was observed. Vigorous resuscitation or intermittent positive pressure breathing, which also might give rise to pulmonary haemorrhage, had not occurred in our cases.

The fact that in the majority of pulmorrhagic infants neither clinical nor pathological signs or changes attributable to hypoxia or asphyxia could be observed, appears to be important with respect to pathogenesis. Beside hypoxia the aetiological role of other factors such as infection, septicaemia, etc. should also be considered. Thus, in the present material it was in four cases that severe enteritis had preceded pulmonary haemorrhage. Profound and protracted hypothermia may also cause haemmorhagic lesions in the lung [3]: in our material, however, no such case was encountered. ROWE and AVERY [15] suggested that in some infants pulmonary haemorrhage may have a common pathogenesis with hyaline membrane disease; atelectasis, formation of hyaline membrane and pulmonary haemorrhage, the three conspicuous manifestations of the respiratory distress syndrome, might have a common origin in the deficiency of the pulmonary surfactant which ensures the stability of the lung. Indeed, in the material reported by ROWE and AVERY [15] the clinical picture and the radiological changes showed features characteristic of the respiratory distress syndrome. Whereas the assumption of a close relationship between the two syndromes is quite logical in infants dying of respiratory distress within the first 24 or 48 hours, the majority of cases does not fit in the framework of hyaline membrane disease. 12 infants out of the total of 26 presented in this paper could clearly be separated from those who succumbed within 48 hours, and whose clinical picture fitted into the respiratory distress syndrome.

Beside the clinical symptoms, the concomitant occurrence of hyaline membrane and haemorrhage appears to support the common pathogenesis of the two syndromes. The incidence of hyaline membrane formation varied from 11 to 50% in the ma-

terial of different authors. Although histological examinations in our own material did not reveal hyaline membrane formation, a relationship between pulmonary haemorrhage and respiratory distress syndrome could not be excluded.

Among 44 newborn infants who died of hyaline membrane disease, histological examination revealed interstitial pulmonary haemorrhage in one single case. The average survival of these infants did not exceed two days, in accordance with the general observation that 85% of such infants die within 48 hours. This also demonstrates that this group of infants, in contrast to the 26 cases of pulmonary haemorrhage, was much more homogeneous as far as the factors influencing survival are concerned. Although the present material does not justify definite conclusions concerning the possible relationship of pulmonary haemorrhage and the respiratory distress syndrome, it appears that in a number of cases the clinical course of neonatal pulmonary haemorrhage is quite different from that of hyaline membrane disease.

Summary

The clinical course, manifestations and certain aspects of aetiology and pathogenesis of neonatal pulmonary haemorrhage have been studied in 596 infants surviving two weeks or less. It has been found that

(i) the incidence of pulmonary haemorrhage was 4.3%;

(ii) intrauterine or neonatal hypoxia occurred in about one third of the cases;

(iii) in 12 out of 26 infants pulmonary haemorrhage was accompanied by lesions which themselves could have been the result or the cause of hypoxia;

(iv) the majority of deaths occurred on the 3rd or 4th postnatal day;

(v) in some infants respiratory distress syndrome appeared immediately after birth, which seems to support the suggestion that pulmonary haemorrhage may have a common pathogenesis with hyaline membrane disease; in the majority of the cases, however, respiratory distress was preceded by a symptomless interval of a few days and pulmonary haemorrhage was usually associated with infection or septicaemia.

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