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Respiratory Distress Syndrome in Twins

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SUMMARY

Respiratory distress syndrome occurred in 77 of 1,130 liveborn twins (1 : 15) and appears to be more frequent than in singletons. This increase cannot be entirely accounted for by the higher prematurity rate of twins over singletons. In 46 twin pairs with at least one affected, there was a significantly higher concordance rate among MZ than DZ pairs, suggesting that genetic factors are of some etiologic importance in this disease.

Respiratory distress syndrome (RDS) of newborn infants is characterized by progressive pulmonary dysfunction, with tachypnea, cyanosis, expiratory grunting, sternal retraction, and episodes of apnea. The syndrome is often, but by no means always, associated with a pathologic state resulting from the formation of hyaline membrane in the lungs. The term hyaline membrane disease is often used interchangeably with respiratory distress syndrome. This usage is incorrect, for hyaline membrane disease is a pathological condition which may, or may not, be present in respiratory distress syndrome. It is important that this distinction be made. Chest X-ray may show reticular granularity of the lung field which, when present, is considered diagnostic of hyaline membrane disease.

Signs of respiratory distress appear within 8 hours postpartum and the babies either worsen and die or improve and recover within 8 days. The poor outlook for these children is compounded by the other various hazards of premature birth, since the disorder is most prevalent in prematures. The mortality rate of about 45% (Driscoll and Smith, 1962) may increase to 90% if apneic episodes develop within the first 24 hours of birth (Adamson et al, 1968).

Babies who survive apparently recover completely. Lewis (1968) and Robertson

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and Crichton (1969), who followed surviving children for many years, found no significant long-term respiratory, neurological, or developmental abnormalities, though Fisch et al (1968) reported a significant increase of neurological abnormalities in the first year of life of RDS survivers.

There are no precise figures of the birth incidence of RDS, partly because of the diagnostic problem. Estimates from various studies indicate that the disease occurs in about 25% of premature births. It is, therefore, a frequent and important perinatal complication. The occurrence of RDS in twins, and consideration of genetic factors in its etiology, have not been systematically investigated to our knowledge. An attempt to explore these two topics will be made here.

Materials and Methods

Data from the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood have been utilized for this investigation. The Collaborative Study is a cooperative effort on the part of 14 institutions throughout the United States, and the National Institute of Neurological Diseases and Stroke of the National Institutes of Health, to observe and study events which affect the parents before and during pregnancy, and to relate them to the outcome of pregnancy. Approximately 60,000 pregnant women have been followed from the first months of their pregnancy, through labor and delivery, and up to the seventh year of the Study child's life. The collection of information, medical examinations and laboratory tests are done in uniform fashion and according to preestablished protocol.

There were 615 twin pregnancies in the Collaborative Study resulting in 1,130 liveborn twin individuals. The zygosity of most pairs was established by comparison of sex, blood types using 9 systems (ABO, MNS, Rh, P, Kell, Lewis, Lutheran, Duffy, and Kidd), finger and palm prints, and gross and microscopic examination of the placenta.

Although obstetricians and pediatricians are familiar with the problem of respiratory distress syndrome, there is confusion as to precise definition and accurate diagnosis of the disorder. Criteria for diagnosis and prognosis of the disease have been proposed (Stahlman et al, 1967; Gomez et al, 1969), but these cannot always be used because clinical circumstances vary. In this study the diagnosis of respiratory distress syndrome was made on the basis of clinical signs, and the additional diagnosis of hyaline membrane disease by X-ray and pathological findings. The main criteria used to make the clinical diagnosis were respiratory rate, findings on auscultation, Apgar score, and the amplitude of respiratory excursions and sternal and costal retractions. On preliminary analysis only the respiratory excursions and retractions were found to have a high degree of reliability and consistency in arriving at the diagnosis. With respect to these two criteria, cases were scored on an ascending scale of severity from 0 to 3: for respiratory excursions, normal 0, slightly shallow 1, shallow 2, and apneic 3; for sternal and costal retractions, none 0, mild 1, moderate 2, and severe 3. Cases with a total score of 4 or more were assigned the clinical diagnosis of respiratory distress syndrome. All cases with X-ray and/or pathological diagnosis of hyaline membrane disease were accepted irrespective of their respiratory scores.

Results

In all, 77 cases with respiratory distress syndrome among twins were identified, 45 in males and 32 in females, distributed among 48 pairs; the sex difference is not significant. Hyaline membrane disease was diagnosed in 47 cases by X-ray and/or pathologic examination; the other 30 cases were identified by the respiratory score alone. The 77 RDS cases occurred among 1,130 liveborn twin individuals, an incidence of 0.068 (1 : 15 liveborn twins). The incidence of RDS in liveborn singletons in the Collaborative Study derived from cases coded on the standardized pediatric examination form ranges from 0.008 (1 : 127), if only cases coded as definite are considered, to 0.014 (1 : 71), if cases coded as definite and suspect are combined. The true incidence figure is probably between the two. A comparison, however, is not entirely appropriate, since the twin cases were selected after rigorous hand review and clinical evaluation, while singleton cases were not similarly reviewed.

RDS, of course, occurs almost exclusively in prematures, and twins are known to have a higher rate of prematurity than singletons. Tab. I shows that, if the conventional demarcation for prematurity by gestational age is made at 36 weeks, 11.5% of singletons born in the Collaborative Study were premature, while 45.3% of twins

Tab. I. Weeks of gestation and birth weight of liveborn singletons and twins in the Collaborative Study

Weeks of gestation	Singletons (%)	Twins (%)	Birth weight (g)	Singletons (%)	Twins (%)
			...-1500	1.3	13.5
...-32	3.6	16.5	1501-2500	9.1 (10.4)	49.0 (62.5)
33-36	7.9 (11.5)	28.8 (45.3)	2501-3000	25.0	24.2
37-...	88.5	54.7	3001-...	64.6 (89.6)	13.3 (37.5)
Total	100.0	100.0	Total	100.0	100.0

were premature. In terms of birth weight, 10.4% of singletons and 62.5% of twins weighed below 2,500 g. but this is not a meaningful way of looking at the difference, because twins at term have consistently lower weight than singletons. Thus, the increase in prematurity of twins over singletons is about fourfold and cannot entirely account for the large increase of RDS in twins. Other factors, also possibly related to intrauterine environment, may be responsible for this increase.

The importance of genetic factors in the occurrence of RDS can now be assessed by comparison of concordance in MZ and DZ twins. In 2 of the twin pairs the cotwin was stillborn, thus leaving 46 pairs with both twins liveborn for comparison. Since not all three criteria (clinical, pathological, X-ray) were used for the diagnosis of all cases, it was decided to examine the concordance of twin pairs containing RDS cases

which were diagnosed by clinical or all of the diagnostic criteria, separately from pairs containing cases diagnosed by pathology and/or X-ray only. The results are displayed in Tab. II.

In 15 of the 46 pairs the zygosity of the twins could not be established because of early death of one or both twins, so that the number of observations in either of the 2×2 tables is quite small. Even so, it is evident that concordance is much greater among MZ than DZ twins. (Since ascertainment is complete, individuals rather than pairs were counted in the calculation of the concordance rate.) Fisher's exact test yielding one-tail probability was, therefore, considered as appropriate for testing the magnitude of these differences. The results are shown in Tab. III.

Tab. II. Twins with respiratory distress syndrome

Zygosity	Concordant pairs	Discordant pairs	Concordance rate
I. Clinical, pathological, and X-ray diagnosis			
MZ	11	2	0.85
DZ	8	10	0.44
ZU *	10	5	0.67
II. Pathological and/or X-ray diagnosis, only			
MZ	8	2	0.80
DZ	3	4	0.43
ZU	5	7	0.42

* Zygosity undetermined.

Tab. III. Fisher's exact test

	P
I. Clinical, pathological, and X-ray diagnosis	
Pairs of established zygosity only	0.026
Pairs of undetermined zygosity included	0.033
II. Pathological and/or X-ray diagnosis only	
Pairs of established zygosity only	0.136
Pairs of undetermined zygosity included	0.198

Within each diagnostic category two tests were made. The first included the twin pairs whose zygosity was definitely established. For the second test the pairs of undetermined zygosity were proportionately distributed among the MZ and DZ pairs.

It will be seen that in the first diagnostic category, which includes cases diagnosed clinically and/or pathologically and/or by X-ray, the higher concordance among MZ pairs is statistically significant. This holds true when twin pairs of undetermined zygosity are included. The difference in concordance between MZ and DZ pairs in the second diagnostic category, which includes cases diagnosed pathologically and/or by X-ray only, is not significant. These cases, however, are not necessarily representative of twins with respiratory distress syndrome. X-rays were taken when circumstances permitted and autopsies were performed on those children who died. It is not possible to say how many of the clinically diagnosed cases had hyaline membrane disease, or what proportion of the whole spectrum of respiratory distress syndrome this specific diagnosis represented.

Because of the small sample and the hazards of diagnosis, it is not possible to draw definite conclusions about genetic determination of RDS from these data. Nevertheless, the significantly higher concordance of RDS in MZ than in DZ twins suggests that genetic factors are of some etiologic importance in respiratory distress syndrome of neonates.

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Riassunto

Su 1130 gemelli nati vivi, 77 sono risultati affetti da insufficienza respiratoria, la quale avrebbe dunque una frequenza (1 : 15) più elevata che nei mononati. Ciò non può essere interpretato solo alla luce del più alto tasso di prematurità nei gemelli. Infatti, in 46 coppie gemellari con almeno un gemello affetto, si è riscontrata una concordanza significativamente più elevata nei MZ che nei DZ, il che suggerisce che nell'eziologia dell'insufficienza respiratoria i fattori genetici svolgano un ruolo importante.

Résumé

L'insuffisance respiratoire aurait, chez les jumeaux, une fréquence plus élevée que dans la population générale: 77 sur 1130 jumeaux en sont résultés atteints (1 : 15). Ceci ne peut pas être simplement interprété sur la base de la fréquence de prématurés, plus élevée chez les jumeaux. Chez 46 couples avec au moins un partenaire atteint, une concordance significativement plus élevée a été remarquée chez les MZ que les DZ, ce qui suggère que les facteurs génétiques jouent un rôle important dans l'étiologie de l'insuffisance respiratoire.

Zusammenfassung

Von 1130 lebend geborenen Zwillingen litten 77 an Ateminsuffizienz, welche demnach bei diesen häufiger vorkommt (1 : 15) als bei Einlingen. Dies lässt sich nicht nur mit der grösseren Zahl von Frühgeburten unter den Zwillingen erklären. Unter 46 Zwillingspaaren mit mindestens einem kranken Paarling war die Konkordanz bei den EZ wesentlich höher als bei den ZZ, was vermuten lässt, dass beim Zustandekommen der Ateminsuffizienz die Erbfaktoren eine bedeutende Rolle spielen.

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