Werdnig-Hoffmann disease

The effects of intrauterine onset on lung growth

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SUMMARY Thoracic gas volume (TGV), resting lung volume at end expiration, was measured by the plethysmographic technique in 9 infants with Werdnig-Hoffmann disease. Five of these infants were considered to have intrauterine onset of the disease; the mother in each case had reported a pronounced reduction in fetal activity during the last trimester of pregnancy, and 4 were found to be hypotonic at birth. The remaining 4 infants appeared normal at birth and did not develop any signs of the disease until between 2 and 12 weeks postnatally. Those with intrauterine onset of disease had a significantly reduced TGV (mean 20.8 ml kg^{-1}), whereas those with postnatal onset had normal lung volumes (mean 36.1 ml kg^{-1}). The reduction in lung volume correlated only with intrauterine onset of disease, and was not related to either the degree of muscle weakness or the duration of disease. There is increasing evidence that fetal breathing movements may be one of the essential prerequisites for normal fetal lung development. It is therefore possible that diminished fetal breathing movements, resulting from weakness of the respiratory musculature *in utero*, could be responsible for the reduction in lung volume found in those infants with intrauterine onset of the disease.

Werdnig-Hoffmann disease—the acute severe infantile form of spinal muscular atrophy—often presents in the neonatal period with profound weakness and hypotonia. The disease is usually fatal by 18 months (Pearn and Wilson, 1973). In many infants a history of diminished fetal movement or the presence of large joint contractures at birth suggests intrauterine onset of disease. Although many infants have a bell-shaped chest associated with weak intercostal muscles, respiratory difficulty is rarely the presenting symptom (Byers and Banker, 1961). Two infants with Werdnig-Hoffmann disease who had respiratory failure (Mellins *et al.*, 1974) were unusual because of their severe diaphragmatic involvement. The most common cause of death is aspiration pneumonia, and here bulbar muscle weakness may be a more important factor than weakness of the respiratory muscles. Although necropsy data exist on the histological characteristics of the respiratory muscles there are no detailed reports of lung structure or function. The present study was undertaken to assess the effects of severe respiratory muscle weakness on the development of lung volume.

Subjects

Nine infants with Werdnig-Hoffmann disease were studied. In 8 of these the diagnosis had been confirmed by electromyography and muscle biopsy. One infant with a previously affected sibling did not have a biopsy. At the initial clinical assessment a questionnaire was completed by the parents. In this, 5 mothers reported reduced fetal movements, in one case this was so pronounced that an intrauterine death had been suspected at 30 weeks' gestation. The other 4 mothers had noticed a decline in movements at some stage in the last trimester of pregnancy. Although intrauterine activity is subjective unless ultrasonic monitoring is used, the lack of fetal activity in these infants was convincing, and 2 of the mothers were able to compare movements with those during previous normal pregnancies. Of these 5 infants, 4 were noted to be hypotonic at birth and neuromuscular disease was immediately suspected; these 5 infants are therefore considered to have intrauterine onset of disease. The remaining 4 infants with postnatal onset of disease had no history of reduced fetal movement and were considered to be normal at birth.

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There was considerable variation in length of history before lung function testing, both in the group with intrauterine onset of disease (Cases 1–5) and in those with postnatal onset (Cases 6–9) (Table 2). Within each group there were infants who were studied early (Cases 1, 6, and 7) and those who were studied late in the course of the disease (Cases 5 and 9).

Methods

Thoracic gas volume (TGV), resting lung volume at end expiration, was measured using an adaptation of the whole body plethysmographic technique (Stocks *et al.* 1977; Stocks and Godfrey, 1977). All measurements were made 30–60 min postprandially, after light sedation with chloral hydrate (50 mg kg⁻¹).

Results

Clinical details of the 9 infants are given in Table 1. The mean birthweight was similar in the pre- and postnatal onset groups, except that the infant in whom intrauterine death had been suspected (Case 3) was of low birthweight. The mean age of death was earlier in the prenatal onset group, but when the average length of history of diminished movements before death was calculated, it showed a similar range to that found in the postnatal onset group. Case 9 was lost to follow-up.

The results of lung function tests are shown in Table 2. Expected values of TGV were calculated for each infant from the appropriate regression equations obtained from data on normal infants during the 1st year of life, using the same plethysmographic technique (Stocks and Godfrey, 1977). The correlation coefficients found in this study of normal infants were 0.99 for the relationship between TGV and body weight (normal values of TGV = 33 ± 0.8 (SEM) ml kg⁻¹), and 0.95 for the relationship between TGV and body length.

Table 2 *Details at time of lung function testing*

Case no.	Postnatal age (weeks)	Duration of disease (weeks)	Body weight		TGV ml kg ⁻¹
			kg	Centile	
1	2	2	3.8	75	22.4
2	6	12	3.2	3	22.9
3	7	19	2.7	< 3	12.3
4	8	18	4.9	50	21.0
5	24	28	6.2	10	25.4
6	6	4	4.2	25	32.0
7	8	6	4.1	10	36.6
8	17	9	5.8	25	31.7
9	48	4	6.3	≤ 3	44.1

TGV normal value = $33 \text{ ml kg}^{-1} \pm 0.8$ (SEM).

In the present study the only infants with normal lung volumes (Cases 6, 7, and 8) were those with postnatal onset of disease. All 5 infants with prenatal onset showed pronounced reduction in TGV. Of the 5 infants whose history suggested intrauterine onset, Case 3 showed the most striking reduction in TGV. In the postnatal onset group, Case 9 had an increased ratio of TGV to body weight, but he was extremely underweight ($\leq 3\%$), and his lung volume was appropriate for his body length. Case 3, who was also underweight at the time of study, had a lung volume which was abnormally small even for his low body weight.

The relationship between lung size and time of onset of diminished movements can be seen in Fig. 1, where TGV is expressed as a percentage of that expected for body weight (except in Case 9, in whom TGV is expressed as percentage expected for body length). Using the same data, Fig. 2 shows that there is no relationship between the duration of muscle weakness and diminished movement and TGV.

Measurements of frequency, tidal volume, and minute volume were also made at the time of lung function testing (Table 3). Cases 1–4 all breathed with an increased frequency but tidal volume was significantly reduced only in Case 1, so that of the group of 5 infants with intrauterine onset of disease only Case 1 had a reduced minute volume. In the

Table 1 *Clinical data*

Case no.	Birthweight (kg)	Gestational age† (weeks)	Postconceptional age at onset	Postnatal age at death (weeks)	Length of history (weeks)
<i>Prenatal</i>					
1	3.6	38	38	13	13
2	3.0	40	34	14	20
3	2.5	40	28	10	22
4	3.5	42	32	15	25
5	3.2	41	37	31	35
<i>Postnatal</i>					
6	3.7	40	42	22	20
7	2.9	38	42	16	12
8	3.5	40	48	40	32
9	3.3	40*	52	—†	—

*Date of last menstrual period uncertain; †lost to follow up; ‡based on last menstrual period.

Fig. 1 Relationship between TGV (expressed as a percentage of normal), and postconceptional age (PCA) at the onset of diminished movements in 9 infants with Werdnig-Hoffmann disease. Hatched area represents the normal range.

Fig. 2 Lack of relationship between TGV and duration of illness before testing. Hatched area represents the normal range for TGV.

postnatal onset group none of the infants breathed with a frequency above that expected, and where minute volume was above expected this was achieved with an increase in tidal volume. Thus the pattern of breathing in 4 out of 5 of the infants with intrauterine onset of disease showed an increased frequency, but as blood gases were not examined routinely it is impossible to say whether the drive to breathe more rapidly was because of a raised PCO_2 . The tendency towards tachypnoea, noted in the group of intrauterine onset babies, may be associated with their small lung volumes as tachypnoea has been one of the major presenting symptoms in infants who have had hypoplastic lungs due to other causes (J. Stocks, unpublished data).

Discussion

The results suggest that the growth of the lung is critically affected by the time of onset of Werdnig-Hoffmann disease, but that the duration of disease *per se* does not affect lung size. In all the infants in whom there was evidence for intrauterine onset of disease, lung volumes were reduced; this was particularly so in Case 3 who had the earliest intrauterine onset of diminished fetal movements. Infants with postnatal onset of disease had normal lung volumes.

Muscle weakness affects lung mechanics and results in a restrictive defect. In adults this is reflected by a proportionate reduction in vital capacity and forced expiratory volume, but functional residual capacity (FRC) may not be affected (Gibson *et al.*, 1977). This suggests that TGV (which is equivalent to FRC in the absence of gas trapping), is not a sensitive index of muscle weakness.

When the two groups of infants were compared at time of lung function testing there were similar degrees of generalised muscle weakness, particularly in the lower limbs. Consequently if muscle weakness alone was responsible for a reduction in TGV, one would expect all infants to be affected and the size of the lungs to be related to the duration of the disease and degree of muscle weakness. However,

Table 3 Frequency, tidal volume, and minute volume at time of lung function testing

Case no.	Frequency (per min)		Tidal volume (ml)		Minute volume (ml/min)	
	Observed	Expected	Observed	Expected	Observed	Expected
1	65	50	17	30	1105	1500
2	96	50	26	30	2496	1500
3	87	55	32	21	2784	1155
4	55	48	47	39	2585	1872
5	24	45	76	41	1824	1845
6	38	40	37	38	1406	1520
7	47	45	47	32	2209	1440
8	47	45	51	41	2397	1845
9	27	35	97	54	2619	1876

among the infants studied, the only factor which related to the reduction in lung volume was that of intrauterine onset of the disease, with the severest reduction in lung size being seen in the infant who had the earliest onset of diminished fetal activity.

Fetal lung growth is influenced both by the presence and amount of amniotic fluid and by the state of the placenta. Small hypoplastic lungs are known to occur when the volume of amniotic fluid is reduced (Fantel and Shepard, 1975). The 3 cardinal features of Potter's syndrome are renal agenesis, oligohydramnios, and a characteristic facies, but pulmonary hypoplasia is usually also present (Potter, 1946, 1974). Perlman and Levin (1974) and Thomas and Smith (1974) reviewed clinical and pathological data on infants with renal agenesis and hypoplastic lungs and they concluded that oligohydramnios was a common feature. In our patients, however, there was no evidence of either oligohydramnios or renal agenesis to account for their small lungs.

Chronic placental insufficiency, as seen in prolonged maternal pre-eclampsia, results in generalised fetal growth retardation, but growth of the lungs is often more impaired than that of other organs (Brans and Cassady, 1975). There was however, no anxiety about maternal health during any of these 9 pregnancies, and there was no delay in onset of respiration at birth.

Conditions which restrict fetal thoracic volume—such as congenital diaphragmatic hernia—are also associated with small lungs (Areechon and Reid, 1963; Kitagawa *et al.*, 1971). Landau *et al.* (1977) have shown reduced values for TGV in some infants with congenital diaphragmatic hernia who were studied neonatally. Necropsy data analysed in detail by Blackburn *et al.* (1977) have shown marked hypocellularity in the ipsilateral lung (i.e. on the side of the hernia). It appears likely that lung growth may be similarly inhibited in Werdnig-Hoffmann disease if thoracic movement is reduced as a result of muscle weakness *in utero*. We were unable to obtain necropsies in any of the 8 infants who died, but post-mortem data are available on one other infant with intrauterine onset of disease, and this showed severely hypoplastic lungs in which the proportion of alveoli to bronchi and bronchioles was markedly reduced (J. S. Wigglesworth, personal communication).

The reduction in TGV in the 5 infants with intrauterine onset is more likely to be due to failure of lung development than to any direct effects of muscle weakness.

Wigglesworth *et al.* (1977) suggested that normal fetal lung growth is dependent not only on adequate lung liquid but also on respiratory movements. Boddy and Dawes (1975) showed that fetal breathing movements can be recorded by ultrasound as early

as 11 weeks. Experiments on fetal lambs showed that although the respiratory movements may be insufficient to clear the tracheal dead space, they produce significant changes in intrathoracic pressure. It is reasonable to suppose that in the human fetus, respiratory movements, although of small amplitude, will exert considerable pressure changes within the lungs, and these could influence development. Wigglesworth was able to produce cessation of respiratory movements in the rabbit, by selective destruction of the upper cervical cord, without interrupting the spinal reflex arc. This resulted in arrested lung development, and as there was no evidence of impaired fetal lung liquid secretion, the small lung volumes could be related directly to reduced fetal respiratory activity.

We suggest that in infants affected *in utero* with Werdnig-Hoffmann disease, the reduced activity also involves the respiratory muscles, and the consequent reduction in fetal breathing movements inhibits normal lung growth. The importance of fetal breathing for normal lung development may have wider implications.

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