

Aetiological factors in rickets of prematurity

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SUMMARY Six very preterm (<32 weeks' gestation) infants who developed late-onset respiratory distress were each matched for sex and gestation with 2 control preterm infants. Radiologically and biochemically the diagnosis of rickets and rachitic respiratory distress seemed clear and the pattern conformed with other reports of the syndrome. The control infants were of similar gestational ages but there was a significantly higher incidence of pre-eclampsia in the pregnancies of index cases. Also significant was a prolonged illness of several weeks' duration in the index cases; this illness was either heart failure due to patent ductus arteriosus or prolonged ventilation in the early weeks of life for apnoeic attacks. Awareness of these 2 aetiological factors shows the necessity of monitoring such infants for evidence of rickets. The use of water-soluble antirachitic prophylaxis such as 1 α -hydroxy-vitamin D or 1,25-dihydroxy-vitamin D is sometimes indicated.

It is well-established that preterm infants have a tendency to develop rickets.¹⁻² Glasgow and Thomas³ described a syndrome of late-onset respiratory distress due to rachitic softening of the chest wall occurring in very preterm infants. There are other reports and accounts of preterm babies with bone disease in which the disease seemed to conform to a similar pattern and would appear to be rickets.⁴⁻⁸

We have seen 6 such infants in Cardiff, and we feel

that they had rickets. Each was extremely preterm and had a similar biochemical and radiological pattern. Details are summarised in the Table and sample x-rays are shown (Figs 1, 2, 3, and 4). Three of them developed late-onset respiratory distress of a severe form interfering with their ability to feed. One had profound hypocalcaemia, a very high alkaline phosphatase concentration, and clinically gross tetany (unresponsive to oral supplements). In this infant (Case 1) the respiratory distress occurred

Table Details of 6 infants who developed late-onset rachitic respiratory distress

Case	Gestation (weeks)	Birthweight (g)	Complications of pregnancy	Delivery	Complications in early infancy	Vitamin D dosage (IU/day)	Respiratory distress		Features of the rachitic respiratory distress
							Severity	Age at onset (weeks)	
1	30	850	Severe pre-eclampsia	Caesarean section	Patent ductus weeks 4-10 with failure	200	+++	12	Tetany; rib fractures; pulmonary 'infiltrates'
2	30	1030	Severe pre-eclampsia	Caesarean section	Ventilated for 5 weeks for apnoea and pneumonia	200	++	7	Rib fractures; pulmonary changes
3	30	1350	Severe pre-eclampsia	Vaginal	Patent ductus with failure weeks 3-9	400	++	12	Rib fractures; pulmonary changes
4	30	1475	Severe pre-eclampsia	Vaginal	Apnoeic attacks in first 2 weeks of life	400	+	12	Rib fractures; pulmonary changes
5	27.5	750	Recurrent antepartum haemorrhage	Vaginal	Recurrent apnoea, ventilated for 4½ weeks	800	+++	6	Pulmonary changes marked
6	30	1030	Recurrent antepartum haemorrhage	Vaginal	Diabetes mellitus weeks 2-10. Required insulin	200	+++	12	Rib fractures; gross pulmonary changes

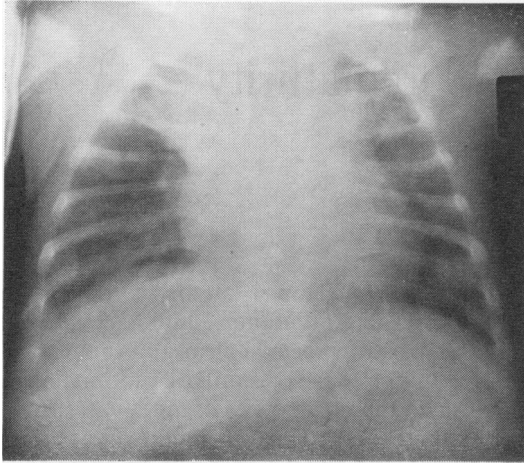


Fig. 1 (Case 1.) Chest x-ray at age 12 weeks.



Fig. 3 (Case 1.) X-ray of right wrist at age 14 weeks.



Fig. 2 (Case 1.) X-ray of right knee at age 14 weeks.

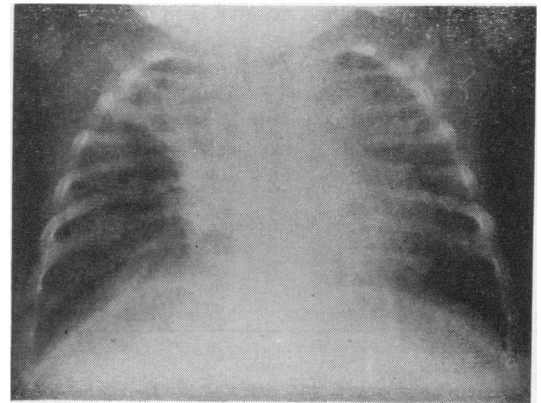


Fig. 4 (Case 6.) Chest x-ray at age 12 weeks.

at age 12 weeks and persisted for 4 weeks, as did the hypocalcaemia and tetany. There was no neutropenia to suggest copper deficiency⁹ and magnesium levels were normal (0.9 mmol/l; 2.2 mg/100 ml). X-rays of this child's chest showed rib fractures, osteoporosis and pulmonary collapse, and lung infiltrates similar to those described by Glasgow and Thomas.³

This syndrome is in our experience occasionally seen in preterm infants despite routine vitamin prophylaxis, and yet no aetiological factors have

been defined. We have used our index cases to try to identify aetiological factors. Each case was matched for gestational age, sex, and period of delivery with 2 controls (for twins, two sets of twins, or if one survivor of twins, then similarly with a single survivor of twins). Possible aetiological factors were compared in the two groups using Pike's method¹⁰ and Student's *t* test.

Results

Six index cases were matched with 12 control preterm infants born in the same period March 1977–May 1978 in the same units. The mean gestational age of the index cases was 29.5 (SD±1.02) weeks, and that of the controls 29.8 (±0.83) weeks. The mean birthweight of the index cases was 1080 (±256.8) g, and that of the controls 1267 (±232.5) g. The difference in mean birthweights was not significant ($P>0.25$).

In the two groups, index cases and controls, the following factors were compared: severe pre-eclampsia (albuminuria, oedema, and diastolic blood pressure >100 mmHg), recurrent antepartum haemorrhage, initial respiratory illness (respiratory distress or recurrent apnoea), prolonged illness, initial serum calcium, and initial vitamin D prophylaxis. The prolonged illnesses were heart failure from patent ductus arteriosus (3 infants), ventilation for >4 weeks for apnoeic attacks and pneumonia (2 infants), and neonatal diabetes mellitus (1 infant). In each of these, the illness exceeded 4 weeks in duration and was a major problem of management compromising the infant's survival.

There was no significant difference in the incidence of antepartum haemorrhage, jaundice, initial serum calcium, or initial respiratory illness (respiratory distress or apnoea). The vitamin D prophylaxis dose was the same in both groups (Abidec multivitamin preparation, Parke Davies).

Significant factors were severe pre-eclampsia in the pregnancy (5/6 index cases, 1/12 of the controls, $P<0.05$) and prolonged illness in the infant (4/6 of the index cases, 0/12 of the controls, $P<0.025$) using Pike's method for each factor. Therefore pre-eclampsia in the pregnancy and a prolonged debilitating illness in the infant seemed to be aetiological factors determining the predisposition to rickets. There may be other factors but none was significantly identified in this small series.

The results of this analysis show that very preterm infants with major problems in their management are at risk for developing rickets. The most common illness was heart failure from a patent ductus arteriosus.

Discussion

There have been many reports of rickets in preterm infants, and recently a report of respiratory distress apparently due to rachitic involvement of the chest wall. Rickets should be a preventable disease, and the fact that infants can develop respiratory distress as a result of this aroused our interest in the aetiology and why it seems to affect only a few infants.

Our 6 infants were all ill with respiratory distress. One had severe tetany and hypocalcaemia very resistant to treatment with calcium. This infant also had pronounced respiratory distress sufficient to compromise her feeding. Two others had a similar degree of respiratory distress and another 2 infants, although very breathless, were tube fed throughout. We found no evidence of infection—haematological, viral, or bacterial—to cause this syndrome.

Our analysis indicates that pre-eclamptic toxæmia is one aetiological factor. Pre-eclampsia would be expected to affect placental function, and Khattab and Forfar¹¹ showed that the transfer of calcium to the infant is impaired in pre-eclampsia. Also pre-eclampsia leads to a degree of hypoxia and starvation which may affect the liver and enzyme systems and perhaps affects the initial hydroxylation of vitamin D3 to 25-hydroxy-vitamin D (25-OHD) taking place in the liver. However, there may be other explanations. These infants had a low dose of vitamin D3 prophylaxis (800 IU or less daily) and it may be that the preterm infant is less able to absorb or hydroxylate vitamin D3 than the mature infant. The serial 25-OHD levels performed by Hillman and Haddad¹² showed that such levels fall in very preterm infants, and later rise when they are gestationally equivalent to 36 weeks' gestation. There are no recent studies to indicate a suitable form or dose of antirachitic prophylaxis; current recommendations of 400 IU/day¹³ were presumably based on early studies.¹⁴ It is possible that the preterm infant needs either much larger doses of vitamin D3 or perhaps 1,25 dihydroxy-vitamin D instead.

Another factor must be operative however, as not all preterm infants born after pregnancies with severe pre-eclamptic toxæmia go on to develop rickets in early infancy. We think the debilitating illness may be the other contributory influence.

Infants with heart failure from a patent ductus arteriosus may have a congested liver and gut, and therefore a degree of malabsorption and impaired liver function. It would not be surprising to see the metabolism compromised in the sick infant, various enzymes and cofactors could be depleted, and hydroxylation of vitamin D3 to 1,25-dihydroxy-vitamin D be thus limited.

As in the infants reported by Davies *et al.*¹⁵ and

Glasgow and Thomas³ the vitamin D level at the time of presentation with rickets was not unduly low. In one baby in our series a level was obtained at the time of presentation with late-onset respiratory distress, and was in the low normal range (15 ng/ml). Nevertheless we feel from our biochemical, radiological, and clinical observations that the infants we describe had rickets, and that their respiratory distress and rib fractures were a feature of this also, as no other explanation for the respiratory features seems to fit. Copper deficiency seems unlikely as no baby showed hypoalbuminaemia or neutropenia, which are features thereof. We hope the 2 aetiological factors we describe will allow babies at risk to be monitored for rickets and that they be given appropriate antirachitic prophylaxis (possibly as 1,25-dihydroxy-vitamin D) early in their postnatal life. The only other fact that we noted is that 5 out of our 6 index cases were boys, as were 3 out of the 4 cases reported by Glasgow and Thomas.³

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