such situations IPPV has been used for combating severe oedema (Robin et al., 1973). In other reports surgical ligation of the patent ductus has been advocated (Gay et al., 1973). However, treatment with CPAP for prolonged periods can be a most efficient therapy as shown in our case. In our experience, as in Robert’s (1974), surgical treatment can be avoided and IPPV is only necessary in the most severe cases for a short time, followed by CPAP.

Transpulmonary distending pressure with CPAP has become an established method for treatment of RDS. CPAP via face chamber (Fi 100, Siemens-Elema) has been used for prolonged periods without hazards (Ahlström et al., 1976). The cardiopulmonary effects of an increased transpulmonary pressure include counteraction of alveolar collapse with opening of atelectases, reducing intrapulmonary shunting, and increasing oxygenation. The resulting increase in arterial oxygenation presumably initiates ductal constriction. In addition the applied pressure may have some effect on concomitant pulmonary oedema.

Our observations show that changes in left atrial size, indicating changes in shunt flow even within a short period of time, can be followed closely by repeated echocardiographic examination. In this way the duration of CPAP treatment for infants with RDS plus PDA can be decided.

Summary

In a preterm infant with the respiratory distress syndrome complicated by patent ductus arteriosus, continuous positive airways pressure (CPAP) treatment relieved the signs of cardiac decompensation associated with left-to-right shunt. Echocardiography enabled the change in left atrial size, an indirect measure of the shunt, to be followed. In this way the rapid effect of CPAP in reducing left-to-right shunting could be monitored. This noninvasive technique could have many applications in neonatology.

References


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Cystinotic rickets treated with vitamin D metabolites

Nephropathic cystinosis is a lethal inborn error of metabolism characterized by the autosomal recessive inheritance of an unknown biochemical defect which produces massive intracellular cystine accumulation. The disorder presents in childhood with failure to thrive, thirst, dehydration, stunting of growth, photophobia, and rickets. Most of these features appear to be secondary to a widespread failure of renal tubular reabsorptive function, which produces glycosuria, phosphaturia, generalized aminoaciduria, renal tubular acidosis, and hypokalaemia (Schneider and Seegmiller, 1972). The rickets may have several possible causes which include acidosis, hypophosphataemia, and renal glomerular failure. Treatment of the bone disease usually involves correction of the acidosis, together with administration of vitamin D in large doses and of phosphate, separately or in combination.

The rickets of cystinosis does not respond to physiological doses of vitamin D and part of this resistance may be due to reduced formation of the active metabolite 1,25 dihydroxycholecalciferol (1,25-DHCC) (Kodicek, 1974) in the diseased kidney.

In short-term studies, Balsan et al. (1975) were unable to detect any biochemical change in 2 cystinotic children given 2 μg 1,25-DHCC in daily doses, but Gertner et al. (1976) demonstrated healing of rickets in 3 boys with cystinosis given 1α-hydroxy-
cholecalciferol (1α-HCC) in daily microgram doses for up to 11 months, in addition to their usual therapy.

We here report an additional child with cystinotic rickets in whom improvement was associated with treatment with 1,25-DHCC and with the metabolically active analogue 1α-HCC.

**Case report**

A 22-month-old girl was admitted in September 1974 with a one-week history of cough, cold, and respiratory difficulty. Motor development had been retarded from about 6 months of age. She had not grown significantly in height since the age of one year and had never walked independently. She had 2 normal sibs, aged 13 and 15; her parents were normal and not consanguineous.

On examination she was a pale, dehydrated blonde child who was acidicotic, with signs of pneumonia and a perianal abscess. Height and weight were below the 3rd centile. On admission serum bicarbonate was 2·0 mmol/l (2 mEq/l), potassium 2·6 mmol/l (2·6 mEq/l), and Hb 5·4 g/dl. There was proteinuria, glycosuria, and a generalized aminoaciduria. A blood culture grew *E. coli*. Cystine-like crystals were found in the bone marrow and cornea. There were x-ray changes of rickets (Fig. 2a).

The biochemical course after initial resuscitation is shown in Fig. 1, and the radiological changes in Fig. 2. Initially sodium bicarbonate (45 mEq/day) and potassium bicarbonate (15 mEq/day) corrected the acidosis, but she remained hypophosphataemic with an increasing alkaline phosphatase. Repeat x-rays in January 1975 (not illustrated) showed persistent rickets. In February 1975 neutral sodium phosph ate solution giving approximately 0·33 g P per day in divided doses was added to her treatment. This increased the plasma phosphate and temporarily the alkaline phosphatase and was probably associated with some healing of the rickets. In early July 1975 wrist x-ray (Fig. 2b) showed patchy calcification in the region of the growth plate but there was still marked abnormality. Treatment was therefore started with oral 1,25-DHCC 1 μg daily. In the ensuing months the alkaline phosphatase fell to low normal levels, and the rickets healed rapidly (Fig. 2c, October 1975). There was also some increase in linear growth rate. Since supplies of 1,25-DHCC were limited, 1α-HCC was later substituted in the same dose. This dose was halved in November 1975 because of a rising plasma Ca, and was stopped in December 1975. Subsequently the plasma phosphate has fallen and the alkaline phosphatase has slowly increased though the wrists remain radiologically normal. The parathormone level in the blood...
Fig. 2 Radiological appearances of the left wrist. (a) Sept 1974, on admission. (b) July 1975, after treatment with bicarbonate (10 months) and phosphate (5 months). (c) October 1975, after additional treatment with 1,25-DHCC for 3 months.

measured in February 1975 was 4·06 ng/ml, which is high for a normal plasma Ca (upper limit of normal, 0·9 ng/ml), and in October 1975 (during treatment with vitamin D metabolites) it had fallen to 0·4 ng/ml. The respective plasma Ca values on these two occasions were 2·68 mmol/l and 2·8 mmol/l (10·7 and 11·2 mg/100 ml). Plasma 25-hydroxycholecalciferol concentration was measured in July 1975 when it was 39 ng/ml, and in October 1975 when it was 30 ng/ml. These values are around the upper limit of normal for the time of the year (Preece et al., 1975).

Discussion

Cystinotic rickets does not respond to physiological doses of vitamin D, or to small doses of 25-hydroxycholecalciferol (25-HCC) (Balsan and Garabedian, 1972), and it is reasonable to suppose that in this disease there is defective renal conversion of 25-HCC to its subsequent metabolites. In our patient the healing of the rickets during 1,25-DHCC therapy tends to support this idea. However, interpretation is confused by the concurrent phosphate treatment, which produced a considerable increase in the alkaline phosphatase associated with partial radiological healing. The fall in parathormone level may be due to the slight rise in plasma Ca, or it may be a direct effect of 1,25-DHCC (Rasmussen et al., 1974). If we accept that physiological amounts of 1,25-DHCC or its metabolically active analogue 1α-HCC (Gertner et al., 1976) can cure cystinotic rickets, their further clinical evaluation is important. One possible advantage of such metabolites over much larger doses of native vitamin D required to cure rickets in this disorder is their shorter biological half life (Kanis et al., 1977) which permits easier reversal of iatrogenic hypercalcaemia.
Summary

A 22-month-old girl with cystinotic rickets was given 1 μg 1,25-dihydroxycholecalciferol (1,25-DHCC) daily in addition to standard treatment. Her rickets healed and linear growth rate appeared to increase. It is suggested that the effect of 1,25-DHCC and its metabolically active analogues on cystinotic rickets should be further studied.

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References


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Short stature with pigmentation

The course of 4 children who grew slowly has been followed for from 2½ to 23 years; they were all below average in intelligence but not severely subnormal; the skin showed excessive brown pigmentation which was not racial—2 were of southern English descent and 2 Jewish. Pigmentation increased on exposure to light. One was an only child, each of the others had one healthy sib of normal size and colouring; the parents were healthy and not consanguineous. In each case pregnancy, birth, and neonatal state were normal; the babies were not small at birth, their weight being in the range 2950–3450 g. Other features are indicated in the Table.

Table Features of 4 patients with short stature and pigmentation

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1</td>
</tr>
<tr>
<td>Adult height (cm)</td>
<td>143*</td>
</tr>
<tr>
<td>Relatively short limbs</td>
<td>+</td>
</tr>
<tr>
<td>Small hands and feet</td>
<td>+</td>
</tr>
<tr>
<td>Reduced bone age</td>
<td>+</td>
</tr>
<tr>
<td>Sparse scalp hair</td>
<td>+</td>
</tr>
<tr>
<td>Refractive error</td>
<td>+</td>
</tr>
<tr>
<td>Weak lateral rectus</td>
<td>+</td>
</tr>
<tr>
<td>Systolic murmur</td>
<td>+</td>
</tr>
<tr>
<td>Mental dullness</td>
<td>+</td>
</tr>
<tr>
<td>School</td>
<td>ESN Normal Normal ESN</td>
</tr>
<tr>
<td>Menarche (years)</td>
<td>22</td>
</tr>
<tr>
<td>Cerebral atrophy on AEG</td>
<td>+</td>
</tr>
<tr>
<td>ACTH level normal in blood</td>
<td>+</td>
</tr>
<tr>
<td>MSH</td>
<td>+</td>
</tr>
<tr>
<td>Growth hormone level after stimulation</td>
<td>+</td>
</tr>
<tr>
<td>Chromosome analysis normal</td>
<td>+</td>
</tr>
</tbody>
</table>

*Under 3rd centile at the age of 8 years.
†AEG not done but x-rays showed a tubular bony spur arising from the anterior wall of the pituitary fossa.
ESN = school for educationally subnormal; ACTH = adrenocorticotropic hormone; MSH = melanocyte-stimulating hormone; AEG = lumbar pneumoencephalogram.

In 3 cases vomiting was severe in the early months and also in the fourth case at 3 years; fever was associated with vomiting in 3. Tonsillitis occurred often in 3, leading to tonsillectomy. In each head size was increased or was concordant with age rather than bodily size at some stage. Dentition was normal.

Available information suggests that when grown up these patients are rather hypomelic little people with brownish skins, cheerful, with useful social accomplishments and somewhat low intelligence. As an example, at the age of 26 in Case 1 the weight was of an average 16-year-old, the height of a 10-year-old, with chest circumference suitable for 12 years, and span and upper:lower segment ratio for 6 years.
Cystinotic rickets treated with vitamin D metabolites.

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