Short reports

Neonatal hypocalcaemia after intrauterine exposure to anticonvulsant drugs

The interference of anticonvulsant drugs with the metabolism of vitamin D, resulting in osteomalacia and rickets in children and adults with epilepsy, has been the subject of many investigations (Mirkin, 1971; Christiansen et al., 1974; Stamp, 1974; Hahn, et al., 1975). We report 2 cases of prolonged hypocalcaemia with tetany in newborn infants, whose mothers had been treated for several years with anticonvulsant drugs.

Case reports

Case 1. The first child, male, of a 23-year-old woman, who had had epilepsy with grand-mal seizures since the age of 13. During pregnancy the frequency and severity of her convulsions increased considerably. She was treated with phenytoin, supplemented by phenobarbitone during the last 3 months of pregnancy. Serum values of phenytoin and phenobarbitone are given in Fig. 1. A few hours before delivery 150 mg phenytoin and 30 mg diazepam were given intravenously. The serum calcium measured one month before delivery was 2.09 mmol/l (8.4 mg/100 ml). Her daily intake of milk and vitamin D was unremarkable.

The birth was uncomplicated. Birthweight 3490 g. Although the Apgar score was normal, he was pale and hypotonic, and was transferred to the neonatal department. From the third day of life he was hypertonic and jittery, vomited often, and failed to thrive; these symptoms persisted for about 2 weeks. On day 11 generalized tonic-clonic seizures, lasting about 30 seconds, were observed. After about 2 weeks all symptoms disappeared, and he began to thrive.

From day 2 low serum calcium values were noted and treatment with calcium levulinate (max. 2 g/24 h) was started. This treatment was continued until the 26th day of life, but did not improve the condition and had no effect on the serum Ca values (Fig. 2). Serum phosphorus was high (max 3.05 mmol/l; 9.4 mg/100 ml). Serum magnesium was normal. Phenytoin and phenobarbitone in the cord blood corresponded to the serum values of the mother just before delivery (Fig. 1). He was fed with breast milk for the first 3 days of life only. Vitamin D (800 IU/24 h) was given from day 15. Electroencephalograms at the age of 6 and 13 days were normal. He was followed until the age of 13 years, when development was normal. Serum Ca and P remained normal. EEG was normal at the age of 3 and 7 months. After 16 months he had a single febrile seizure.
Case 2. The first child of a 34-year-old mother who had had epilepsy since the age of 14, grand-mal seizures occurring in recent years once or twice a year. During pregnancy she was given phenytoin 300–600 mg daily and phenobarbitone 100 mg daily because of now frequent grand-mal seizures. Serum levels of these drugs are seen in Fig. 1. Serum Ca was not measured during pregnancy, but 2 weeks after delivery this was normal (2.29 mmol/l; 9.2 mg/100 ml), as was serum P and alkaline phosphatase. Her daily intake of milk and vitamin D was unremarkable.

The girl was born 3 weeks before term by caesarean section because of falling oestriol values. 4 hours before delivery the mother was given 400 mg intravenous phenytoin because of convulsions. No signs of intrauterine asphyxia. Birthweight 3250 g. Normal Apgar score. During the first hours of life there were no respiratory problems, but at 6 hours she was admitted to the neonatal department with respiratory distress. She required intubation and treatment with continuous positive airways pressure for 3½ days, and received two blood transfusions. Arterial Po2 never fell below 54 mmHg.

After extubation on day 4 she was hypotonic and jittery. From the 10th day she was agitated with jerking movements and a positive Chvostek sign. On day 15 she had facial twitching, and on the 16th and 17th days she had attacks of generalized tonic-clonic seizures, lasting 1–2 minutes.

From day 8 the serum Ca was low despite treatment with calcium levulinate intravenously and orally (max 1·2 g/24 h) (Fig. 2). Serum magnesium was low on days 11 and 13 (min 0·55 mmol/l; 1·3 mg/100 ml). From day 15 she received MgSO4 500 mg intramuscularly and later orally for 4 days. Serum P was raised from the 14th to the 22nd day (max 3·08 mmol/l; 9·5 mg/100 ml). She was fed with breast milk for the first 12 days. Vitamin D (400 IU/d) was given from the 5th day, increased from day 10 to 800 IU/d.

EEG at 2 weeks showed repeated generalized paroxysmal bursts, some of them limited to the right hemisphere. At 7 weeks the EEG was normal. At one month she was developing normally.

In both patients the following were normal: CSF; serum bilirubin, alkaline phosphatase, bicarbonate, sodium, potassium, glucose, urea; x-ray of long bones and skull. No abnormal aminoaciduria.

Discussion

The sustained course of tetany, resistant to therapy in the two term babies, is unusual and cannot be explained by the factors which usually cause neonatal hypocalcaemia (Röśli and Fanconi, 1973). The convulsions were related to the low serum calcium values. The short period of asphyxia in one child and the symptoms of respiratory distress in the other might have contributed to the initial hypocalcaemia, but do not explain the prolonged course.

Phenytoin, phenobarbitone, and other anti-convulsant drugs are known to induce hepatic microsomal enzyme activity, which results in an increased hydroxylation of vitamin D to biologically inactive metabolites (Stamp, 1974; Hahn et al., 1975). The extent of enzyme induction is individual. Large doses and combination therapy involve a greater risk of enzyme induction (Hahn et al., 1975).

Mirkin (1971) has shown that the concentration of phenytoin in umbilical artery or vein blood is almost the same as that in maternal blood, as we observed in Case 1. In Case 2 the concentration of phenytoin in the infant’s blood at birth must have been high in view of the large doses given to the mother immediately before delivery.

Because of active transplacental transport we expect the fetal serum calcium during the last months of pregnancy to have been at the same level or higher than the maternal serum calcium (Watney and Rudd, 1974). The prolonged hypocalcaemia with symptoms of tetany indicates a disturbance of the calcium metabolism. The rise in serum calcium values, delayed for 2 weeks after birth, in spite of calcium supply, indicates a shortage of calcium deposits in bone of long duration.

In previous studies the 25-hydroxycholecalciferol level in mixed arterial-venous cord serum was correlated with maternal serum levels (Hillman and Haddad, 1974). We presume that lack of vitamin D during intrauterine life was responsible for defective fetal bone mineralization in these two infants, the resultant deficient fetal stores of calcium being unable to sustain neonatal calcium homeostasis. Neonatal hypoparathyroidism following high circulating levels of maternal parathyroid hormone during intrauterine life may have contributed to the neonatal hypocalcaemia (Watney and Rudd, 1974).

Maturation of the hepatic parahydroxylating capacity is low in the first days of life (Mirkin, 1971). Only after maturation of the hepatic function are phenytoin and phenobarbitone eliminated. Hereafter a normal 25-OH-cholecalciferol concentration can be established resulting in mineralization of bone and normalization of serum calcium values. Large doses of anticonvulsants, combination therapy, and individual enzyme induction can explain the pronounced hypocalcaemia in our patients. Seasonal influence on pregnancy and birth in winter and spring may have been a contributing factor (Hillman and Haddad, 1974).
Treatment with higher doses of vitamin D to epileptic patients has been proposed before (Christiansen et al., 1974; Hahn et al., 1975; Stamp, 1974). Vitamin D treatment to these epileptic mothers might have prevented the hypocalcaemia in their children. Further investigations are needed to elucidate these problems.

**Summary**

Two cases are reported of prolonged hypocalcaemia with tetany in infants born at term, whose mothers had been treated with phenytoin and phenobarbitone in high doses. Both infants presented with jitteriness and tetany in the first and second weeks of life, and in both the hypocalcaemia was resistant to therapy over a longer period. An effect on the fetal vitamin D metabolism by phenytoin and phenobarbitone, resulting in defective bone mineralization and neonatal hypocalcaemia is suggested.

**References**


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Pure oestrogen-secreting feminizing adrenocortical adenoma

Adrenocortical tumours associated with raised oestrogen secretion causing feminization are rare in childhood. We have traced only 7 reported cases (Wilkins, 1948; Fontaine et al., 1954; Snaith, 1958; Mosier and Goodwin, 1961; Bacon and Lowrey, 1965; Castelman et al., 1972; Leditschke and Arden, 1974). We report the clinical and laboratory findings in a boy before and after surgical removal of an adrenocortical adenoma.

**Case report**

A 6-year-old boy had a 4-month history of enlargement of the breasts. He had received no previous medication. His height was 122 cm (75th centile); he was not obese, had not acne or striae, his voice was not deep, and there was no facial, axillary, or pubic hair. Blood pressure was 90/60 mmHg. No abdominal masses were palpable. The breasts were 8 cm in diameter, firm and nontender. The areola were ballooned but not pigmented; no secretion could be expressed. The penis was 3.5 cm in length and the testes, of normal consistency, measured 1.0 x 1.5 cm.

Blood count, analysis of urine, serum electrolyte concentrations, liver function tests, and radiographs of the skull and chest were all normal. Serum thyroxine was 13.5 nmol/l (10.5 μg/100 ml) (normal range 6.4–16.7 nmol/l) and the karyotype was 46,XY. The bone age was 7 years. Breast biopsy showed prominent ducts with proliferation and dilatation. Urinary 17-oxosteroid excretion was 1.7 μmol/24 h (0.5 mg/24 h) (normal for age 1.7–10.2 μmol/24 h) and total 17-oxogenic steroids 4.2 μmol/24 h (1.2 mg/24 h) (normal 3.5–14 μmol/24 h). Plasma cortisol was 276 nmol/l (10 μg/100 ml) at 9 am and 33.1 nmol/l (1.2 μg/100 ml) at midnight. The urinary steroid profile by gas-liquid chromatography by Van de Calseyde's method showed a very low excretion of adrenal androgens (Table). Urinary total oestrogens measured by Brown's method were grossly raised to 528 μg/24 h (normal adult males 5.20 μg/24 h).

<table>
<thead>
<tr>
<th>Table</th>
<th>Urinary steroid profile (mg/24 h)</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Normal adult males (mean ± SD)</td>
</tr>
<tr>
<td>Androsterone</td>
<td>0.46</td>
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<tr>
<td>Etiolocholanolone</td>
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</tr>
<tr>
<td>Dehydroepiandrosterone</td>
<td>0.19</td>
</tr>
<tr>
<td>11-Ketoandrostosterone</td>
<td>—*</td>
</tr>
<tr>
<td>11-Ketoetiocholanolone</td>
<td>—*</td>
</tr>
<tr>
<td>11-OH Androsterone</td>
<td>0.16</td>
</tr>
<tr>
<td>11-OH Etiolocholanolone</td>
<td>—*</td>
</tr>
<tr>
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</table>

*Undetectable.*