Neonatal hypocalcaemia associated with maternal hyperparathyroidism

New pathogenetic observations

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SUMMARY A 32-day-old male infant had hypocalcaemic convulsions associated with asymptomatic maternal hyperparathyroidism. Very low total and ionised serum calcium, increased serum phosphate, and normal serum parathyroid hormone (PTH) and 25-hydroxycholecalciferol (25-OHD₃) concentrations were found at admission. After treatment with calcium and vitamin D, serum PTH and 25-OHD₃ concentrations increased markedly before serum calcium levels returned to normal, perhaps indicating an inability to convert 25-OHD₃ to the metabolically active 1,25-dihydroxyvitamin D₃ during the hyperphosphataemic state. Treatment with 1,25-dihydroxyvitamin D₃ or its analogues is recommended.

Much interest has recently been focused on neonatal calcium, parathyroid, and vitamin D metabolism (Root and Harrison, 1976). Neonatal hypocalcaemic convulsions secondary to maternal hyperparathyroidism is a rare, but well-known, entity first described by Friedrichsen (1938). The mechanism underlying this relationship is not completely understood. Intrauterine suppression of the fetal parathyroids, caused by the hyperfunction of maternal parathyroid glands, has been suggested (Friedrichsen, 1938; Wagner *et al.*, 1964; Hartenstein and Gardner, 1966; Bocquentin *et al.*, 1973), but direct measurement of the hormones involved has not been reported. We studied these problems in a newborn infant with hypocalcaemic convulsions in an attempt to elucidate the pathogenesis.

Methods

Serum concentrations of 25-hydroxycholecalciferol (25-OHD₃) were determined by a competitive-protein-binding assay (Haddad and Chyu, 1971). Serum parathyroid hormone (PTH) concentrations were measured by a commercial double antibody radioimmunoassay using an antibody against the carboxy-terminal. PTH no. 71/324 from the Medical Research Council (England) was used as standard.

The coefficient of variation of the assay was 8-9% for values found in our study. All other estimations were carried out by routine laboratory methods. The range of normal serum values shown in the Fig. is unfortunately from infants one week old, because only an insignificant number of sera from normal infants aged 4-10 weeks were available for determination of normal ranges.

Case report

A male infant was born at term (birthweight 2500 g) to a 26-year-old mother who had had one abortion and one preterm delivery 2 and 3 years before, respectively. Pregnancy and delivery were uneventful and the mother took no drugs. Both parents were Pakistani workers. When the mother's milk disappeared in the second week of life, the infant was given Allomin 14%, containing 360 mg calcium, 380 mg phosphate, and 335 IU vitamin D per 1000 calories. A vitamin D supplement of 600 IU per day was given from the third week of life.

At 32 days of age he was admitted because of numerous convulsions during the previous 2 days. He weighed 3200 g, was hypertonic with hyperreflexia and a positive Chvostek's sign, and no laryngeal spasm. The total serum Ca was very low, 1.44 mmol/l (5.76 mg/100 ml) (Fig.). Ionised serum Ca was low, serum concentrations of PTH and

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25-OHD₃ were normal, serum phosphate concentration was increased, whereas creatinine, glucose, magnesium, alkaline phosphatase, sodium, potassium, and acid-base status were normal. Distribution of amino acids in the urine was normal. Electroencephalography, ophthalmological examinations,

and x-rays of the heart and skeleton were all normal; electrocardiogram showed prolonged Q-T interval.

Initially intravenous calcium laevulate was given. Oral treatment with vitamin D and increasing doses of Ca were started (Fig.). Human milk was used during the first week. Later Allomin 14% was given. After the initial increase in total serum Ca concentration it again fell. Doubling the vitamin D dosage induced a rise again and after 5 weeks normal levels of total and ionised serum Ca were reached (Fig.). Serum P decreased gradually. A Ca balance performed after 3 weeks of treatment showed a calcium retention of 338 mg/day (8.45 mmol).

Serum PTH increased during the first week of the study and remained slightly raised until total and ionised serum Ca became normal. Serum 25-OHD₃ increased during treatment to very high levels and decreased as serum Ca rose and serum P fell. Ca supplement was stopped when Ca reached normal levels, but vitamin D supplement was continued. The infant was followed for 12 months. Serum Ca, P, alkaline phosphatase, PTH, and 25-OHD₃ remained normal.

Examinations of the parents

Both parents were well on clinical examination. The laboratory values are given in the Table. Both parents had low serum values of 25-OHD₃. The mother had increased total and ionised serum Ca, low serum P, and increased serum PTH concentrations, indicating primary hyperparathyroidism. At operation a left parathyroid adenoma (5.6 g) was removed. Since then serum Ca and PTH concentrations have been normal.

Discussion

Early neonatal hypocalcaemia appears within the first 3 days of life and is usually seen in preterm

Fig. Serum values of total and ionised calcium, phosphate, 25-hydroxycholecalciferol (25-OHD₃), and parathyroid hormone from the time of admission of the hypocalcaemic infant and during treatment.

Table. Serum concentrations of total and ionised calcium, phosphate, parathyroid hormone (PTH), and 25-hydroxycholecalciferol (25-OHD₃) in the parents

Serum concentrations	Mother	Father	Normal range
Total Ca (mmol/l)	2.78	2.33	2.20-2.70
Ionised Ca (mmol/l)	1.52	—	1.10-1.20
Phosphate (mmol/l)	0.45	0.99	0.80-1.50
PTH (µg/l)	6.90	0.35	0.22-0.50
25-OHD ₃ (ng/ml)	6.80	7.20	12.1-33.3

Conversion: SI to traditional units—

Ca: 1 mmol/l $\approx$ 4 mg/100 ml. P: 1 mmol/l $\approx$ 3.09 mg/100 ml.

infants or after complications in pregnancy and delivery (Rösli and Fanconi, 1973; David and Anast, 1974; Root and Harrison, 1976). Neonatal hypocalcaemia is explained by a transient suppression of parathyroid function (Tsang *et al.*, 1973; David and Anast, 1974) as well as a decreased 25-hydroxylation of vitamin D (Hillman and Haddad, 1975). Delayed neonatal hypocalcaemia usually occurs towards the end of the first or during the second week of life (Rösli and Fanconi, 1973; Root and Harrison, 1976) and is associated with ingestion of cows' milk or formula with a high content of phosphate.

In infants in whom hypocalcaemia occurs more than 3 weeks after birth, alternative causes must be sought (Root and Harrison, 1976). In hypocalcaemia due to maternal hyperparathyroidism the convulsions stop within the first 3 weeks of life, indicating that the suppressed parathyroid function is gradually restored in the infant. In a survey of the literature Wagner *et al.* (1964) found 11 reported cases of tetany among 25 infants of hyperparathyroid mothers. 9 infants had developed tetany within the first 3 weeks of life and they were all on a formula diet. However, in the first reported case of tetany in a child of a hyperparathyroid mother (Friderichsen, 1938) symptoms occurred in the fifth month of life during weaning. In our case hypocalcaemic convulsions occurred 30 days after birth while on a formula diet.

The case is very unusual because several variables in the calcium homeostasis were measured. Asymptomatic hyperparathyroidism was diagnosed in the mother. The high serum phosphate might have indicated parathyroid gland insufficiency, but the serum PTH concentration was *normal* at the time of admission, increasing to hyperparathyroid levels during the following 2–3 weeks. A decreased serum PTH concentration during the initially hypocalcaemic state, followed by a gradual rise, was to be expected. Our findings therefore agree, to some extent, with the previous hypothesis of fetal and neonatal suppression of the parathyroid gland caused by the hyperparathyroid state of the mother (Friderichsen, 1938; Wagner *et al.*, 1964; Hartenstein and Gardner, 1966; Bocquentin *et al.*, 1973). We suggest that the convulsions first appeared when the hyperphosphataemia and hypocalcaemia were further aggravated by administration of formula (with a high P content).

The low serum concentrations of 25-OHD₃ in the parents agree with findings in Asians (Dent and Gupta, 1975; Pietrek *et al.*, 1976) and suggest a small maternal vitamin D store and an insufficient placental transfer of 25-OHD₃ during the gestational period (Hillman and Haddad, 1974). The normal serum concentration of 25-OHD₃ in the mother on

admission was probably due to vitamin D supplementation at home. During the following weeks, however, serum 25-OHD₃ concentrations increased to unusually high levels considering the moderate doses of vitamin D given (Hillman and Haddad, 1975), but the hypocalcaemic state of the infant remained. This might indicate a decreased turnover of 25-OHD₃ to the physiologically active metabolite 1,25-dihydroxyvitamin D₃ possibly due to the high serum and renal cortical phosphate concentration (Tanaka and DeLuca, 1973), although the serum PTH (Fraser and Kodieck, 1973) and the low serum calcium (Larkins *et al.*, 1973) should stimulate hydroxylation. The subsequent fall in serum phosphate and the raised serum PTH abolished this blockade and for this reason the marked fall in serum 25-OHD₃ was accompanied by a rise in serum calcium. These results seem to be in agreement with findings in infantile rickets (Arnaud *et al.*, 1976).

The appropriate treatment for this type of neonatal hypocalcaemia seems to be 'substitution' with 1,25-dihydroxyvitamin D₃. This treatment has recently been recommended in other types of neonatal hypocalcaemia (Kooh *et al.*, 1976) and in different states of hypoparathyroidism (Kind *et al.*, 1975).

References

- Arnaud, S. B., Stickler, G. B., and Haworth, J. C. (1976). Serum 25-hydroxyvitamin D in infantile rickets. *Pediatrics*, **57**, 221–225.
- Bocquentin, F., Safar, A., Aicardi, J., and Job, J.-C. (1973). Tetanie hypocalcémique néonatale chez deux enfants d'une mère hyperparathyroïdienne. *Archives Françaises de Pédiatrie*, **30**, 989–998.
- David, L., and Anast, C. S. (1974). Calcium metabolism in newborn infants. *Journal of Clinical Investigation*, **54**, 287–296.
- Dent, C. E., and Gupta, M. M. (1975). Plasma 25-hydroxyvitamin-D levels during pregnancy in Caucasians and in vegetarian and non-vegetarian Asians. *Lancet*, **2**, 1057–1060.
- Fraser, D. R., and Kodieck, E. (1973). Regulation of 25-hydroxycholecalciferol-1-hydroxylase activity in kidney and parathyroid hormone. *Nature, New Biology*, **241**, 163–166.
- Friderichsen, C. (1938). Hypocalcémie bei einem Brustkind und Hypercalcémie bei der Mutter. *Monatsschrift für Kinderheilkunde*, **75**, 146–151.
- Haddad, J. G., and Chyu, K. J. (1971). Competitive protein binding radioassay for 25-hydroxycholecalciferol. *Journal of Clinical Endocrinology and Metabolism*, **33**, 992–995.
- Hartenstein, H., and Gardner, L. I. (1966). Tetany of the newborn associated with maternal parathyroid adenoma. *New England Journal of Medicine*, **274**, 266–268.
- Hillman, L. S., and Haddad, J. G. (1974). Human perinatal vitamin D metabolism. I. 25-hydroxyvitamin D in maternal and cord blood. *Journal of Pediatrics*, **84**, 742–749.
- Hillman, L. S., and Haddad, J. G. (1975). Perinatal vitamin D metabolism. II. Serial 25-hydroxyvitamin D concentrations in sera of term and premature infants. *Journal of Pediatrics*, **86**, 928–935.

- Kind, H. P., Prader, A., DeLuca, H. F., and Gugler, E. (1975). 1,25-dihydroxycholecalciferol in hypoparathyroidism and pseudohypoparathyroidism. *Lancet*, **1**, 1145-1146.
- Kooh, S. W., Fraser, D., and Toon, R. (1976). Response of protracted neonatal hypocalcaemia to 1α , 25-dihydroxy-vitamin D_3 (1976). *Lancet*, **2**, 1105-1107.
- Larkins, R. G., MacAuley, S. J., Colston, K. W., Evans, I. M. A., Galante, L. S., and MacIntyre, I. (1973). Regulation of vitamin-D metabolism without parathyroid hormone. *Lancet*, **2**, 289-291.
- Pietrek, J., Preece, M. A., Windo, J., O'Riordan, J. L. H., Dunnigan, M. G., McIntosh, W. B., and Ford, J. A. (1976). Prevention of vitamin-D deficiency in Asians. *Lancet*, **1**, 1145-1148.
- Root, A. W., and Harrison, H. E. (1976). Recent advances in calcium metabolism. *Journal of Pediatrics*, **88**, 177-199.
- Rösli, A., and Fanconi, A. (1973). Neonatal hypocalcaemia. "Early type" in low birth weight newborns. *Helvetica Paediatrica Acta*, **28**, 443-457.
- Tanaka, Y., and DeLuca, H. F. (1973). The control of 25-hydroxyvitamin D metabolism by inorganic phosphorus. *Archives of Biochemistry and Biophysics*, **154**, 566-574.
- Tsang, R. C., Chen, I.-W., Friedman, A., and Chen, I. (1973). Neonatal parathyroid function: role of gestational age and postnatal age. *Journal of Pediatrics*, **83**, 728-738.
- Wagner, G., Transbøl, I., and Melchior, J. C. (1964). Hyperparathyroidism and pregnancy. *Acta Endocrinologica*, **47**, 549-564.

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