

Significance of Hypocalcaemia in Neonatal Convulsions

J. H. KEEN*

From the Department of Child Health, St. Mary's Hospital, Manchester

'I have observed that occasionally children born with difficulty are liable to convulsions for a short time; if these survive they commonly do well.'

Dr. Robert Barnes, Obstetrical Society, London, 1862.

For many years birth trauma has been stated to be the commonest cause of neonatal convulsions; there have, however, been few prospective studies to support this view.

In 1954 Burke studied 46 infants who had had convulsions in the first 2 weeks of life; in 70% of the series she found birth trauma or anoxia during birth to have been the likely cause of the fit, and over a third of the infants concerned died in the neonatal period.

In the past decade attention has increasingly been focused on those convulsions in the newborn due to metabolic disturbances, particularly the two relatively common temporary abnormalities of neonatal metabolism—hypoglycaemia and hypocalcaemia. Baum and his colleagues from Hammer-smith Hospital have recently suggested (Baum, Cooper, and Davies, 1968) that symptomatic hypocalcaemia is becoming more frequent, and Paine (1968), in an excellent review of fits in the newborn, found that tetany was the cause of fits in 17 of 35 neonates in the Children's Hospital, Washington D.C., in 1966, who survived for over a year.

Material and Methods

This prospective study of infants who had a convulsion in the first 4 weeks of life included all such infants delivered in two obstetric units in Manchester, one the main teaching unit (Hospital 1) and the other (Hospital 2) a large unit for abnormal obstetrics. Infants were included when they were observed to have either generalized clonic movements of limbs and face, whether preceded by generalized rigidity or not; or clonic movements of a single limb or of facial muscles or eyes.

In a period of 23 months 100 infants delivered in these two hospitals have been seen to have such convulsions, an incidence of 8·6 per 1000 live births. In 39

infants I witnessed the fit myself; of the remainder, 24 were seen by a special care unit sister but not by medical staff, and in 11 the convulsion was seen only by the nursing staff on the maternity wards, or by the mother.

In all infants who convulsed details were obtained in retrospect of the pregnancy and mode of delivery, as well as of the child's condition at birth, and behaviour and feeding regimen before the convulsion.

In convulsing infants the following investigations were carried out as soon as possible after the first recorded fit; in almost all cases this was within 4 hours: blood glucose, serum calcium and phosphorus, plasma protein, blood pH, and blood and urine amino acid chromatography.

Serum magnesium was measured in the later cases only. In 45 infants born in Hospital 2 serial EEGs were done.

Neither subdural tap nor CSF examination was performed routinely, but they were done when clinically indicated, as was blood culture.

Of the 100 infants, 65 have so far been followed up to 6 months of age, and 47 to 12 months.

Serum calcium and magnesium were estimated by EDTA chelation with murexide indicator, using EEL photoelectric titrator with a filter peak of 5750–5800 Å (Wilkinson, 1957). Duplicate 0·1 ml. samples of serum were used.

Amino acid chromatography: blood samples were collected into heparinized capillary tube, and analysed by one-dimensional paper chromatography with butanol acetic acid/water (Scriver, Davies, and Cullen, 1964).

Normal range of serum calcium in newborn.

There has been little agreement in the literature on the normal range of serum calcium in the newborn; Craig and Buchanan (1958) took a level below 8 mg./100 ml. as abnormal, as did Gittleman *et al.* (1956) using the calcium carbonate-boric acid micromethod described by Sobel and Sobel (1939). We carried out control calcium estimations on 15 infants matched with hypocalcaemic infants for birthweight, age in hours, type of delivery, and feeding (but not for season of delivery or amount of feed taken). A mean of 8·98 mg./100 ml. was obtained with a standard deviation of 0·71 and a variance of 0·50. In this study a calcium level below

Received November 26, 1968.

* Present address: Booth Hall Children's Hospital, Manchester 9; and Crumpsall Hospital, Manchester 8.

TABLE I
Presumed Cause of Convulsion in 100 Infants Under 28 days old

Cause of Convulsion	No. of Infants
Intracranial haemorrhage	5
Intrapartum anoxia	7
Cerebral cyst	1
Meningitis	2
Pneumonia with septicaemia	1
Hypoglycaemia alone—blood glucose under 20 mg./100 ml.	6
Hypocalcaemia alone—serum Ca ⁺⁺ under 7.5 mg./100 ml.	34
Hypoglycaemia with hypocalcaemia	4
Hypernatraemia—serum Na ⁺ over 150 mEq/l.	1
Adrenal hyperplasia	1
Cyanotic congenital heart disease	1
No cause found	37
	100

7.5 mg./100 ml. was accepted as hypocalcaemia (mean -2 SD). The mean of the calcium levels in the hypocalcaemic infants thus defined was 6.4 mg./100 ml., standard deviation 0.69, variance 0.48.

Results

Incidence. Convulsions were commoner in Hospital 2, 11.2 per 1000 live births (in 4288 deliveries) than in Hospital 1, 7.1 per 1000 live births (in 7370 deliveries). Both these figures are significantly higher than the 2 per 1000 in Burke's (1954) figures from Sheffield.

Aetiology. (Table I). Of the 100 infants with convulsions, 3 died of intracranial haemorrhage confirmed at necropsy, and in 2 others intracranial haemorrhage was diagnosed by the finding of a blood-stained, xanthochromic CSF. In 7 infants the fits were attributed to the effects of anoxia during delivery; this was in each case prolonged, and associated in 2 cases with cardiac arrest shortly after birth.

Meningitis was present in 2 infants, the organism being a *Proteus* in one and *Haemophilus influenzae* in the other; both infants died.

A metabolic abnormality was present in 45 infants, hypoglycaemia (blood glucose under 20 mg./100 ml.) alone in 6, and hypocalcaemia (under 7.5 mg./100 ml.) alone in 34—one-third of the whole group. In 4 infants hypocalcaemia was present with hypoglycaemia, and one hypocalcaemic child had a cyanotic congenital heart disease and has since died. One infant who convulsed at 72 hours was hypernatraemic; he was at the time 16% under his birthweight, with a serum sodium of

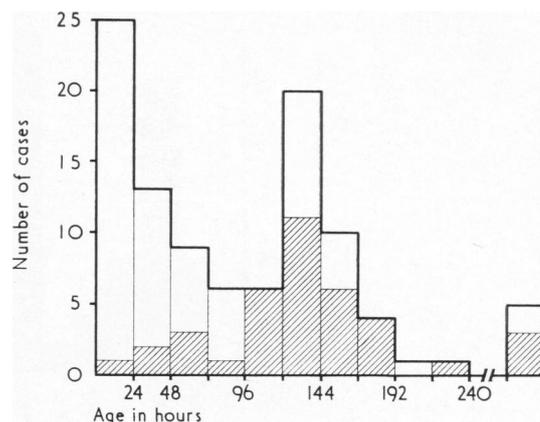


FIG. 1.—Age at first convulsion in 100 cases of neonatal convulsions. Hatching indicates cases with hypocalcaemia.

160 mEq/l., and a blood urea of 150 mg./ml.; no infection was detected and the biochemical findings returned to normal after rehydration. No significant aminoaciduria or aminoacidaemia was found in the series.

In 37 infants no cause for the convulsion was found.

Thus hypocalcaemia was a common association with neonatal convulsions in this series. Further details of the 38 infants with low calcium levels are presented below.

Convulsions with Hypocalcaemia

Sex incidence. There was no significant sex difference—21 males and 17 females. Fits without hypocalcaemia were also commoner in boys—37 boys to 25 girls.

Age at first fit (Fig. 1). 71% of the hypocalcaemic infants had their first fit between the 5th and 8th days of life. In contrast, only 21% of the normocalcaemic had their first fit in this period, 69% beginning their convulsions within 72 hours of birth. Of the 5 hypocalcaemic infants who convulsed under 72 hours old, 4 also had hypoglycaemia and were below the 10th centile of birthweight for gestational age.

Seasonal incidence (Fig. 2). The seasonal incidence of hypocalcaemia with convulsions is striking and in agreement with some other reported findings. Of the 17 hypocalcaemic infants born in 1967, the only complete year studied, 10 were born in the first quarter. This pattern is being repeated in 1968, as indicated in Fig. 2, and in 1966 a similar

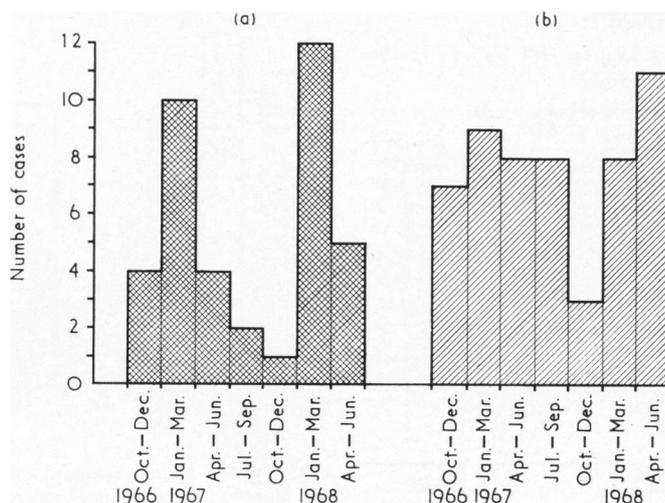


FIG. 2.—Seasonal incidence of neonatal convulsions, occurring within the same 21-month period: (a) 38 hypocalcaemic infants, (b) 54 non-hypocalcaemic infants. The illustration does not include 8 infants convulsing in August to September 1966, and July 1968, none of whom were hypocalcaemic.

seasonal peak stimulated me to start the investigation.

Gestational age and mode of delivery. The mean weight of 38 hypocalcaemic infants was 3.66 kg.; 33 were both over 37 weeks of gestational age and above the 10th centile of birthweight for gestational age. The 4 hypocalcaemic infants who were below the 10th centile of birthweight for gestational age had associated hypoglycaemia and convulsed in the first 72 hours of life.

Feeding (Table II). Only 4 hypocalcaemic infants were fully breast-fed at the onset of convulsions. The excess of hypocalcaemic convulsions in infants fed on evaporated milks when compared with those fed on dried milks does not seem to be attributable to the difference in mineral content of the milk, as prepared in the two hospitals studied

TABLE II
Feeding Before Convulsion in 38 Hypocalcaemic Infants

	Evaporated Milks	Dried Milks	Breast-fed
Hypocalcaemic infants with convulsions	66% (25)	24% (9)	10% (4)
Infants without convulsion —at 5 days, in the same hospitals	35%	45%	20%

(Table III). It will be seen, however, from Table III that both evaporated and powdered cow's milk preparations were fed in a more concentrated form at Hospital 2 than at Hospital 1, and this may account for the higher incidence of hypocalcaemia with convulsions in Hospital 2 —5.4 per 1000 live births compared with 2.2 per 1000.

Maternal factors. Serum calcium levels were measured in 18 mothers of hypocalcaemic infants: none had evidence of hyperparathyroidism in the immediate postnatal period. None of the mothers of hypocalcaemic infants was diabetic.

Prognosis. Nine infants, none hypocalcaemic, died in the neonatal period and one has died since; of the remaining 90, 34 had hypocalcaemia as the only discovered cause for their convulsions. Of

TABLE III
Average Mineral Content of Milk Feeds at the 2 Hospitals

	Breast Milk	Hospital 1		Hospital 2	
		Evaporated (Regal) 1:3	Dried (National)	Evaporated (Regal) 1:2	Dried (Os er-milk no. 1)
Calcium (mg./100ml.)	34	80	83	106	108
Phosphate—P (mg./100 ml.)	14	66	57	88	86

these, 20 are now aged 1 year or over, and 15 have been seen at this age. Among these 15, 12 are neurologically normal and have made normal developmental progress; however, 3 infants fared less well, 1 developed myoclonus at 5 months, and 2 others are developmentally retarded with hypotonia. There seems to be nothing in the neonatal course of these 3 infants to distinguish them from the remainder.

Clinical features. The convulsion occurring with hypocalcaemia is commonly first seen by the mother and described as 'jumping'; it consists of rhythmic jerking of one or more limbs at a rate of 1 to 2 per second. The episode may begin with intermittent spasm of the facial muscles and spread to a limb or limbs; attacks are frequently unilateral, but subsequently may occur on the opposite side. The attack usually begins when the infant is picked up for feeding and lasts for 1 to 10 minutes, after which the infant seems uncomfortable, and further attacks may be provoked by minor stimuli. Cyanosis and apnoea are unusual; carpopedal spasm was noted in only one of the cases described here; stridor was not noted on any occasion and Chvostek's sign was consistently negative, a finding confirmed by several authors including Paine (1968). Rapid relief followed the giving of intravenous calcium, and if feeding on a low phosphate milk, preferably breast milk, is started, the fits do not return.

Discussion

Of 100 infants convulsing in the first 28 days of life, 38 had serum calcium levels below 7.5 mg./100 ml., an incidence of 3.1 such infants per 1000 live births. This high incidence of hypocalcaemia in newborn infants with fits is in keeping with the findings of Paine (1968) and the comments of Baum *et al.* (1968), but contrasts with reports by British authors before about 1962. Harris and Tizard (1960), Craig (1960), and Eureka (1954) all described birth injury and anoxia as the common cause of neonatal convulsions, and they apparently did not encounter any large group of infants who had fits at the end of the first week of life. It is interesting that Saville and Kretchmer (1960) from New York found the incidence of neonatal tetany in the period 1940-1958 to be 1.7 per 1000 deliveries. They do not specify the type of feed that their patients received, but it seems probable that in the period of the study breast-feeding was less common in the United States than in Britain, and it may be that only in recent years has the

breast-feeding rate in this country fallen to the same low level.

Neonatal hypocalcaemia, like neonatal convulsions, has two peaks of incidence, one in the first 48 hours of life, the second between the 4th and 10th days of life; in the present study the second peak accounts for 34 of the 38 cases. The factors causing hypocalcaemia in these two groups are almost certainly different. Infants who develop hypocalcaemia in the first 48 hours of life are typically the product of an operative delivery, and are often of low birthweight for gestational age, with associated hypoglycaemia; the prognosis for life and neurological normality in this group is poor. Gittleman *et al.* (1956) have shown that after premature or traumatic delivery, calcium levels fall in the first 48 hours below the levels for infants delivered spontaneously at term. It has been suggested by Saville and Kretchmer that the increase of cortisol production by the mother during operative delivery may account for this finding.

The association of maternal hyperparathyroidism with neonatal hypocalcaemia was first described by Friderichsen (1939) and has been reported on many occasions since; I found no evidence of this association in the present series, but in the year after delivery, 2 of the 38 mothers whose infants became hypocalcaemic were found to have renal calculi, though still with normal serum calcium levels.

Those newborn infants who develop hypocalcaemia later are, by contrast, commonly full-term babies of average or above average weight who have been artificially fed and have often shown a voracious appetite. A dietary mechanism for hypocalcaemia developing at this age is widely accepted (Gittleman and Pincus, 1951; Oppé and Redstone, 1968; Dundon and O'Brien, 1967), the infant is faced with a high phosphate load as a result of early cow's milk feeding, and hyperphosphataemia results, probably as a result of the low glomerular filtration rate of the immature kidney. Confirmation of the inability of the newborn to excrete a phosphate load is provided by Widdowson *et al.* (1963) who added 120 mg. extra phosphorus daily to the diet of 11 baby boys aged between 6 and 8 days; they showed that phosphate retention followed. The hypocalcaemia which follows may be accounted for in a number of ways: either the newborn may fail to produce parathormone in response to the stimulus of hyperphosphataemia, or the parathyroid may be unable to produce the increased amounts required to maintain normal calcium levels in face of the avidity of rapidly

growing bone. Alternatively, bone at this age may be relatively insensitive to parathormone. That the hypocalcaemia is not due entirely to a failure of parathyroid response was suggested by the work of Gardner (1952) who found, in necropsy material, that parathyroid hypertrophy was associated with cow's milk feeding in the first 2 weeks of life; the advent of serum parathormone assay should resolve this point.

While the findings of the present study are consistent with a dietary explanation of the hypocalcaemia occurring toward the end of the first week, several factors suggest that this may not be the sole explanation. These include the seasonal variation in incidence, the inconstant association with hypomagnesaemia, and the low incidence in premature infants. The higher incidence of hypocalcaemia in the months January to March is not satisfactorily explained by the known seasonal variations in the composition of milk. Similar observations were recorded by Saville and Kretchmer from New York, who in 1960 described 125 cases with a peak incidence in March, and from Portland, Oregon, where Todd, Chuinard, and Wood (1939) reported the serum calcium levels of 571 infants aged between 4 and 7 days in whom the modal levels were lower in the months March to June than during the rest of the year. There is good evidence that the dried and evaporated milk preparations used during this study, and generally in the country, do vary in calcium phosphate and vitamin D content over the year; however, milk drawn from a cow at a particular time of year reaches the baby as dried or evaporated milk after a variable interval of from 2 to 12 months later.

Secondly, the association of hypomagnesaemia with hypocalcaemia in the newborn may be a further important factor in producing symptoms. Davis, Harvey, and Yu (1965) have drawn attention to the occurrence of convulsions in the newborn with this combination, showing that the administration of magnesium will sometimes terminate a fit when calcium alone is ineffective. In the present study a sufficient number of serum magnesium levels was not available for valid conclusions to be drawn; of 13 later cases, 4 had magnesium levels below 1.2 mEq/l., while 9 had levels above this (EDTA: murexide method, Wilkinson, 1957). Thirdly, the low incidence of late hypocalcaemia in premature infants suggests that renal immaturity may not play a major part in its production, especially now that early feeding of premature infants is becoming routine.

There seems little doubt that, as demonstrated by Oppé and Redstone (1968), the return of breast-

feeding or the use of low phosphate milks would reduce very substantially the incidence of neonatal hypocalcaemia.

Summary

The results are presented of a prospective study of 100 infants with generalized convulsions in the first 28 days of life.

The cases occurred in a period of 23 months in two obstetric units in Manchester, an incidence of 8.6 per 1000 live births. In 37 infants no cause could be found for the convulsion; the commonest discovered cause was hypocalcaemia (level of under 7.5 mg./100 ml.) which occurred alone in 34 infants, and was combined with hypoglycaemia in a further 4.

In the hypocalcaemic group, 71% had the first fit between the 5th and 8th days of life; only 21% of the remaining 62 convulsing infants started in this period. All but 4 of the hypocalcaemic infants were artificially fed; feeding with an evaporated milk was nearly twice as frequent, and with a dried milk preparation only half as frequent as in the hospital population as a whole. In those infants followed up to a year not all of the group of infants with hypocalcaemia alone were neurologically normal.

Hypocalcaemia in the first or second day of life presents a distinct clinical picture and has a different cause.

I should like to express my gratitude to Dr. G. M. Komrower, in whose Department the amino acid chromatography was carried out, to Dr. W. H. Patterson and Dr. A. Holzel for permission to study cases under their care, and to Professor J. A. Davis for encouragement and advice.

REFERENCES

- Barnes, R. (1862). In discussion to: Little, W. J. On the influence of abnormal parturition, etc., on the mental and physical condition of the child. *Trans. obstet. Soc. Lond.*, **3**, 342.
- Baum, D., Cooper, L., and Davies, P. A. (1968). Hypocalcaemic fits in neonates. *Lancet*, **1**, 598.
- Burke, J. B. (1954). The prognostic significance of neonatal convulsions. *Arch. Dis. Childh.*, **29**, 342.
- Craig, W. S. (1960). Convulsive movements occurring in the first 10 days of life. *ibid.*, **35**, 336.
- , and Buchanan, M. F. G. (1958). Hypocalcaemic tetany developing within 36 hours of birth. *ibid.*, **33**, 505.
- Davis, J. A., Harvey, D. R., and Yu, J. S. (1965). Neonatal fits associated with hypomagnesaemia. *ibid.*, **40**, 286.
- Dundon, S., and O'Brien, N. (1967). Classical neonatal tetany (neonatal tetany of renal origin). *J. Irish med. Ass.*, **60**, 96.
- Friderichsen, C. (1939). Tetany in a suckling with latent osteitis fibrosa in the mother. *Lancet*, **1**, 85.
- Gardner, L. I. (1952). Tetany and parathyroid hyperplasia in the newborn infant: influence of dietary phosphate load. *Pediatrics*, **9**, 534.
- Gittleman, I. F., and Pincus, J. B. (1951). Influence of diet on the occurrence of hyperphosphatemia and hypocalcemia in the newborn infant. *ibid.*, **8**, 778.
- , —, Schmerzler, E., and Saito, M. (1956). Hypocalcemia occurring on the first day of life in mature and premature infants. *ibid.*, **18**, 721.

- Harris, R., and Tizard, J. P. M. (1960). The electroencephalogram in neonatal convulsions. *J. Pediat.*, **57**, 501.
- Oppé, T. E., and Redstone, D. (1968). Calcium and phosphorus levels in healthy newborn infants given various types of milk. *Lancet*, **1**, 1045.
- Paine, R. (1968). Characteristics of fits in the newborn period. In *Studies in Infancy* (Clinics in Developmental Medicine, No. 27), p. 70. Ed. by R. MacKeith and M. Bax. Spastics International Medical Publications and Heinemann, London.
- Saville, P. D., and Kretchmer, N. (1960). Neonatal tetany: a report of 125 cases and review of the literature. *Biol. Neonat.* (Basel), **2**, 1.
- Scriver, C. R., Davies, E., and Cullen, A. M. (1964). Application of a simple micromethod to the screening of plasma for a variety of aminoacidopathies. *Lancet*, **2**, 230.
- Sobel, A. E., and Sobel, B. A. (1939). Microestimation of calcium in serum. *J. biol. Chem.*, **129**, 721.
- Todd, W. R., Chuinard, E. G., and Wood, M. T. (1939). Blood calcium and phosphorus in the newborn. *Amer. J. Dis. Child.*, **57**, 1278.
- Widdowson, E. M., McCance, R. A., Harrison, G. E., and Sutton, A. (1963). Effect of giving phosphate supplements to breast-fed babies on absorption and excretion of calcium, strontium, magnesium, and phosphorus. *Lancet*, **2**, 1250.
- Wilkinson, R. H. (1957). A micro-method for serum calcium and serum magnesium. *J. clin. Path.*, **10**, 126.