HYPOCALCAEMIA IN INFANCY, WITH SPECIAL REFERENCE TO CARDIAC FAILURE*

W. E. B. EDGE, M.B., B.CH., M.R.C.P., D.C.H., D.(OBST.)R.C.O.G., *Durban*

Calcium has been known to have a profound effect on myocardial activity since 1883, when Ringer[1] published his classical observations. He showed that perfusion of the isolated heart with sodium-chloride solution led to arrest in diastole. The addition of calcium led to resumption of activity, followed by arrest in systole. Further addition of potassium caused a reversion to normal cardiac activity. The effects of hypocalcaemia on the electrocardiogram (ECG), viz. shortening of the P-Q interval, flattening or inversion of the T waves, and, most characteristically, prolongation of the Q-T interval, are well known.

It would be surprising if such marked changes were not accompanied by disturbance in cardiac function. Yet hypocalcaemia does not feature as a cause of cardiac failure. In fact, only one reference to this could be found in standard cardiological text-books. Keith *et al.*,[2] quoting the case of Schulman and Ratner[3] — a 12-year-old girl

* Paper presented at the 5th Congress of the South African Paediatric Association (M.A.S.A.), Durban, 26 - 28 July 1962.

with hypoparathyroidism in whom cardiac failure with cardiomegaly was ascribed to the marked hypocalcaemia (3·6 mg. per 100 ml.), and which reverted to normal as the serum calcium rose — admitted the possibility of hypocalcaemia causing failure. Other cardiology text-books make no mention of this, and in a recent review of heart failure in children,[4] which lists some 48 causes, hypocalcaemia does not appear. It seems, therefore, worth recording the following three personally encountered cases.

CASE REPORTS

Case 1

H. le S., a full-term White male baby, was born on 26 June 1960, following a normal pregnancy and spontaneous vertex delivery. Birth weight was 8 lb. 4 oz. He was slow to cry, and remained limp and cyanosed. When first seen at the age of 24 hours the striking features were generalized hypotonia, marked central cyanosis, and extensive oedema of the limbs and neck. Pulse rate was 130 per minute, respiration 88 per minute, and blood pressure 80/? mm.Hg. The fontanelle was not elevated, and the cry was feeble but not shrill. Air entry was good throughout the lung fields. The heart sounds were poor, but no murmurs were present. The liver was enlarged 3 cm. below the costal margin. A provisional diagnosis of severe congenital heart disease, possibly transposition of the great vessels, was made, and the baby was treated with digitalis, diuretics, and oxygen.

The following day the baby was slightly less cyanosed. The tone had increased, and a positive Chvostek's sign was noted. Shortly afterwards the baby had a generalized convulsion. Hypocalcaemia was now strongly suspected and the serum-calcium level was found to be 4·9 mg. per 100 ml. Under ECG control 10% calcium gluconate was given intravenously, to a total of 9 ml. This produced no very dramatic change, but did ease the respirations slightly and abolished the Chvostek's sign. Five ml. 6-hourly of 5% calcium chloride were then given by mouth. The following day the serum-calcium level was 6·6 mg. per 100 ml. The baby was considerably improved with only slight cyanosis, slower respirations (64 per minute), and normal tone, but the oedema and hepatomegaly remained. Thereafter improvement was steady and by 1 July he seemed normal in every respect and the serum-calcium level was 9·6 mg. per 100 ml. His subsequent progress was uneventful and his development when seen later was entirely normal.

Case 2

G.S., a Coloured male infant, was born on 24 May 1959, 10 weeks prematurely, with a birth weight of 2 lb. 10 oz. He thrived satisfactorily on breast milk and from about the fourth week was given a daily supplement of a multivitamin preparation containing 600 units of vitamin D. 'Imferon' was given after 2 months when the haemoglobin level had fallen to 7·7 G. per 100 ml.

At the age of 4 months he was transferred to the children's ward because of evidence of cardiac failure, with no apparent response to digitalis. His weight at this time was 7 lb. There was marked clinical rickets, subsequently confirmed radiologically, and in addition the baby was noted to be extremely stiff, maintaining an almost constant position of opisthotonos, with considerable respiratory embarrassment. The cardiac rate was 130 per minute. The neck veins were engorged, the liver was considerably enlarged, and there was pitting oedema of the extremities and back. Blood examination revealed a serum-calcium level of 6·2 mg. per 100 ml., a serum-phosphorus level of 2·8 mg. per 100 ml., alkaline phosphatase 70 King-Armstrong units, albumin 4·4 G. per 100 ml., and globulin 2·0 G. per 100 ml. The ECG showed a Q-Tc interval of 0·43 seconds.

It was postulated that the cardiac failure might be due to the hypocalcaemia, and 10% calcium gluconate was therefore given intravenously under ECG control. After 3 ml. there was remarkable clinical improvement, with disappearance of the muscle spasm, and the Q-Tc interval diminished to 0·35 seconds. Thereafter the baby was given larger doses of vitamin D — 5,000 units daily — and rapidly improved in all respects, the signs of cardiac failure disappearing within a few days.

Case 3

J.P., a Coloured female infant, was born normally at home 3 weeks before admission on 26 July 1961, with a history of diarrhoea and coughing for 1 day. Examination revealed a malnourished baby weighing 4 lb. 12oz., hypothermic and cyanosed, with rapid, shallow respirations. There were ulcers on the legs and perineum suggestive of syphilis, and serology subsequently proved positive. The neck veins were distended, and the liver was palpable 1 inch below the costal margin. There was some hypertonicity of the limbs and a doubtfully positive Chvostek's sign. The baby was diagnosed as probably having septicaemia, and was treated with tetracycline and novobiocin. A lumbar puncture produced clear cerebrospinal fluid containing 37 polymorphs per c.mm., protein 160 mg. per 100 ml., with globulin much increased, and sugar 106 mg. per 100 ml.

Because of the clinical evidence of tetany and cardiac failure, the serum-calcium level was estimated and found to be 3·0 mg. per 100 ml. Fifteen ml. of 10% calcium gluconate were given slowly intravenously under ECG control, and although the hypertonicity and respiratory embarrassment improved considerably, the baby remained cyanosed and ill. The ECG showed a diminution in the Q-Tc interval from 0·375 seconds before administration of calcium, to 0·28 seconds afterwards. The following day the serum-calcium level was 10 mg. per 100 ml., and the baby seemed better. That afternoon, however, she died suddenly, possibly as the result of inhalation of vomitus.

This case was complicated by other factors, chiefly infection, but it is felt worth recording in view of the very low serum-calcium level in a breast-fed baby 3 weeks old.

DISCUSSION

Hypocalcaemia in infants is of 3 main types — neonatal, rachitogenic, and enterogenic. Neonatal tetany was first described in 1913 by Kehrer,[5] who noted, in spite of his inability to perform biochemical estimations, that a good response occurred to oral administration of calcium chloride. In 1917 Howland and Marriott[6] demonstrated the relationship between tetany and hypocalcaemia, at the same time confirming Kehrer's observations on the value of oral calcium chloride.

Shannon,[7] in 1929, described 3 neonates with tetany associated with oedema, cyanotic attacks and convulsions. Ten years later Willi[8] reported 13 cases of 'spasmophilia' and pointed out that typical carpopedal spasm was not always present and that vomiting and convulsions were common presenting symptoms. Dodd and Rapoport,[9] in their review of 33 cases of neonatal tetany in 1949, found that the most common presenting features were convulsions, vomiting, oedema, cyanosis and alimentary-tract haemorrhage. Craig and Buchanan[10] found in 26 tetanic infants (mostly prematures or babies of diabetic mothers) that the commonest signs were hyperexcitability alternating with extreme quietness, cyanosis, apnoeic attacks, a squeaky cry, convulsions, tachypnoea and tachycardia. Saville and Kretchmer[11] recently reported 125 cases of neonatal tetany and found the following signs:

Twitching and/or jitteriness	in 75%
Convulsions	in 61%
Cyanosis	in 42%
Vomiting	in 30%
Positive Chvostek or Trousseau sign	in 18%
Gastro-intestinal bleeding	in 10%
Oedema	in 9%

It is clear, therefore, that the manifestations of neonatal tetany are very variable. Cyanosis and oedema are common, and when they are accompanied by hepatomegaly it is impossible to say that cardiac failure is not present. Craig[13] reported that 6 of his 7 severely affected infants had enlarged livers. It could be argued that hypocalcaemia does not necessarily produce heart failure, but merely simulates the signs thereof. This would appear to be unreasonable hair-splitting, particularly in view of the difficulty of defining heart failure. It is the purpose of this paper simply to point out that when confronted with the clinical picture of heart failure in an infant, hypocalcaemia must be considered.

Aetiology of Neonatal Tetany

The aetiology of neonatal tetany is of some interest. The calcium content of the cord blood is normally 1 - 2 mg. per 100 ml. higher than that of the maternal blood. During the first few days of life the calcium falls and the phosphorus rises, but the calcium subsequently rises, returning to normal values by the tenth day. It was postulated by Bakwin[12] that these changes indicate a transient hypoparathyroidism. Craig,[13] on the other hand, from his experience of diabetic mothers, suggested that an adrenopituitary disturbance might be the operative factor. Whatever the mechanism, it is certain that early tetany, i.e. tetany occurring within the first 2 days of life, is associated with traumatic delivery, premature birth, caesarean section and maternal diabetes in a high proportion of cases.[10,13-15] This was so in 66% of Saville and Kretchmer's series.

Dietary factors appear to be of considerable importance in tetany appearing later, usually on about the fifth day of life.[11] This type is almost entirely confined to artificially fed babies. Although the calcium content of cow's milk is 3½ times higher than that of human milk (1,220 mg. per litre and 340 mg. per litre respectively), the phosphorus content is 6 times as high (900 mg. per litre and 150 mg. per litre respectively), giving a considerably lower Ca : P ratio. It has been shown by Gardner *et al.*[16] that whereas the serum-phosphorus level in breast-fed babies is about 6 - 7 mg. per 100 ml., babies fed on cows' milk have levels of 10 - 12 mg. per 100 ml. Gittleman and Pincus,[14] in a series of neonates, demonstrated an incidence of hypocalcaemia of 10·9% in those artificially fed, compared with 0% in breast-fed babies. The same authors[17] also showed that the addition of vitamin D lowered the serum calcium, 600 units per quart of milk per day increasing the incidence of hypocalcaemia to 30%. This effect is, of course, well known in rickets, in which initial treatment with vitamin D may precipitate tetany by increasing calcium deposition before there has been significant increase in absorption.

It appears, therefore, that dietary factors play the main role in the aetiology of neonatal tetany appearing after the first 2 days of life. This type may continue for a considerable time. One of my patients, an Indian baby, in spite of supplementary calcium chloride in doses of 2 G. per day, continued to have almost incessant convulsions for 2 months, until changed to a low-phosphorus milk.

Apart from neonatal tetany, hypocalcaemia may be associated with rickets (of which case 2 is an example), gastro-enteritis, intestinal malabsorption, hypoparathyroidism and pseudo-hypoparathyroidism. Of these, only the first 3 are of importance in infancy, and neonatal tetany is by far the most commonly encountered type. Rickets is only rarely accompanied by a low serum calcium, and although hypocalcaemia is not at all uncommon as part of the electrolyte disturbance of acute gastro-enteritis, particularly in African infants, its degree is often falsely accentuated by the coincident hypoalbuminaemia. Though tetany often occurs in this type, cardiac failure ascribable to this has not been seen.

Diagnosis

Regarding the diagnosis of neonatal tetany, it is clear from the preceding discussion that the symptomatology is not confined to the neuromuscular irritability commonly associated with this condition. When suggestive symptoms are present, the serum-calcium level should obviously be estimated. Although figures for the normal in neonates vary slightly,* 8·5 mg. per 100 ml. is generally acceptable as the lower limit. Bakwin[20] maintained that neonatal tetany is always associated with hypocalcaemia, but Dodd found that one-third of a group of 24 full-term neonates with clinical tetany had a serum-calcium level above 9 mg. per 100 ml., and Craig and Buchanan[10] described 7 patients with clinical tetany and a normal serum-calcium level. Personal experience supports the view that hypocalcaemia is not invariably present.

Treatment

Treatment of neonatal tetany depends on the severity of the case and the time of onset. When this is within the first 48 hours, symptoms almost always disappear spontaneously by the fifth day. Calcium chloride by mouth is advocated in doses of ½ - 2 G. a day. In severe cases, however, such as those described here, intravenous calcium gluconate, carefully given and preferably with ECG control, seems indicated, although the results are usually not striking. It must be pointed out that calcium gluconate contains only 9% calcium, whereas calcium chloride contains 30% calcium. In tetany associated with cows' milk feeding, a calcium chloride supplement is usually effective in raising the serum-calcium level and alleviating symptoms, but diminution of the phosphorus intake may also be desirable or indeed necessary.

SUMMARY

Three cases of infantile hypocalcaemia with signs of cardiac failure are reported. It is suggested that there is a causal relationship and that tetany should be considered as a possible aetiological factor in obscure cases of heart failure.

The symptomatology, aetiology, diagnosis and treatment of neonatal tetany are discussed in some detail and the pertinent literature is reviewed.

* The following figures show the rather wide range of values found at this age:

Investigators	*Mean serum-calcium level (mg. per 100 ml.)*	*Range (mg. per 100 ml.)*
Todd *et al.*[18]	10·15	8·63 – 11·67
Aburel and Ornstein[19]	10·6	8·3 – 13·2
Bakwin and Bakwin[12]	11	8·5 – 13·5

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