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Association of Oedema and Hypomagnesaemia with Hypocalcaemic Tetany of the Newborn

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Summary

The cases of 18 babies with hypocalcaemic tetany of the newborn are described. Studies were made before and 24 and 48 hours after therapy with calcium supplements. Twelve of the babies were non-oedematous and showed a positive correlation between serum calcium and magnesium levels. They showed a rise in serum magnesium levels during therapy with calcium. The other six had bilateral pitting oedema of the feet and greater weight gains in the first two weeks of life. They had abnormally low serum magnesium levels which did not correlate with the calcium levels. Furthermore, the serum magnesium levels, unlike those in the non-oedematous group, did not increase when calcium supplements were given. It is suggested that oedema in babies with hypocalcaemic tetany may be more common than is generally recognized, and that a contributory factor in the production of the hypomagnesaemia may be secondary aldosteronism.

Introduction

Hypocalcaemic tetany of the newborn may occur in a variety of clinical situations, and several factors are involved in the pathogenesis (Anast, 1969). Clinically, the manifestations of hypomagnesaemia are indistinguishable from hypocalcaemia, and the two conditions may coexist in hypocalcaemic tetany of the newborn. Primary hypomagnesaemia with secondary hypocalcaemia has been described, the evidence suggesting isolated malabsorption of magnesium from the gastrointestinal tract (Friedman *et al.*, 1967). Whether tetany ever occurs in magnesium-deficient babies with normal serum calcium levels is a controversial point (Gellis, 1970). The incidence of hypomagnesaemia in association with hypocalcaemic tetany of the newborn is difficult to assess. Most babies with hypocalcaemic tetany respond to calcium therapy without the need to resort to

magnesium supplements, and not all laboratories perform the estimation routinely. Various methods are used for the determination of serum magnesium levels, and these do not all give comparable results. Keen (1969) made serum magnesium estimations on 13 babies with hypocalcaemic tetany, and four of them had levels below 1.2 mEq/l. This was low by his standards, but it is not known if magnesium supplements were required to control the tetany. It is not known what factors govern the production of the abnormally low serum magnesium levels sometimes seen in this condition. This paper describes an association between oedema and hypomagnesaemia in newborn babies with hypocalcaemic tetany.

Method

Babies who presented with twitching in the first two weeks of life associated with a serum calcium level of 7 mg/100 ml or below were studied. A history, with particular attention to the pregnancy, mode of delivery, condition immediately after birth, and behaviour before the development of symptoms, was obtained in retrospect. During the initial examination, in addition to a careful neurological evaluation, attention was given to the presence of pitting oedema of the feet. This physical sign was elicited by moderate pressure of the examiner's thumb on the dorsum of the babies' feet for not longer than five seconds.

After an initial feed of 5% dextrose all the babies were fed on full cream National dried milk in full strength, in amounts varying from 90-160 ml/kg/24 hours on the second day to 140-160 ml/kg/24 hours on the sixth day and throughout therapy. The milk feeds began 10 to 18 hours after birth in all cases. Most of the babies were weighed at intervals of 48 hours, but some, including all those who were oedematous, were weighed at intervals of 24 hours.

Venous blood was taken at the onset of twitching and at 24 and 48 hours after the beginning of therapy. A further specimen of venous blood was taken from the babies with oedema after it had subsided. The chemical analyses were performed by automated procedures, serum calcium by flame photometry (Auto-Analyzer N21a), serum magnesium by atomic absorption spectroscopy, serum total protein by Technicon method file N14b, serum total globulins by turbimetry (Glenn, 1965), and serum albumin was calculated by difference from the last two methods. A Dextrostix determination was performed on all babies initially, capillary blood being used. A blood urea

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estimation was performed on the oedematous babies at the beginning of symptoms, and it was repeated only if the initial level was considered abnormal.

Initial therapy was a slow intravenous injection of 2-3 ml of 10% calcium gluconate, followed by oral supplements of about 110 mg of calcium every four to six hours (5 ml of Calcium—Sandoz syrup equivalent to 0.7 g of calcium gluconate). Oral therapy was continued for 7 to 10 days. Further intravenous calcium gluconate was given only if twitching recurred.

Results

Eighteen babies presented with twitching associated with serum calcium levels of 7 mg/100 ml or below. None of them was hypoglycaemic. There were no associated features, either in the history or clinical examination, to account for the twitching, and all these babies were diagnosed as having hypocalcaemic tetany of the newborn.

Six of them had bilateral pitting oedema of the feet. No obvious cause for the oedema could be found. There was no significant difference between the birth weights of the oedematous babies and the others, nor did the oedematous babies have any features of congestive heart failure, haemolytic disease of the newborn, or other stigmata compatible with Turner's phenotype. In all cases the oedema was a transient feature, and disappeared completely in five to seven days after it was first detected. The blood urea levels of the oedematous babies were all less than 40 mg/100 ml, except for one with a level of 65 mg/100 ml. This fell to 35 mg/100 ml 24 hours later, and at this time the oedema was still present.

Details of birth weight, daily weight gain, and time of onset of tetany are shown in Tables I and II. The oedematous babies had a significantly greater daily weight gain before the onset of tetany ($P < 0.001$) and also took less time to regain their birth weights ($0.02 < P > 0.01$). There was no significant difference in the time of onset of tetany in the two groups. The average weight gain of the babies is shown in Fig. 1. There was no difference in the initial weight loss after birth in the two groups.

The serum calcium and magnesium levels are shown in Fig. 2. There was no significant difference in the serum calcium levels in the two groups. In all cases the twitching was rapidly controlled by the initial injection of calcium gluconate. Three of the babies who were not oedematous developed a further episode of twitching several hours after the initial episode, and this was

FIG. 1—Comparison of weight gain in the two groups of babies.

FIG. 2—Serum calcium and magnesium.

TABLE I—Details of Weight and Day of Onset of Tetany in 18 Babies. Babies 1-12 = Non-oedematous. Babies of 13-18 = Oedematous.

Case No.	Birth Weight (kg)	Daily Weight Gain Onset of Tetany (g)	Day of Regaining Birth Weight	Day of Onset of Tetany
1	3.68	23	10	8
2	3.68	25	8	9
3	2.92	22	9	8
4	3.20	30	9	10
5	3.95	30	8	5
6	3.42	27	11	5
7	2.59	17	6	5
8	4.01	27	8	6
9	2.87	28	11	11
10	3.62	15	7	5
11	3.92	35	8	5
12	2.90	30	7	6
13	3.98	48	6	7
14	2.92	53	5	5
15	2.90	58	5	6
16	3.88	47	6	8
17	3.65	55	5	6
18	3.46	36	7	7

TABLE II—Comparison of Oedematous and Non-oedematous Babies in Terms of Weight and Day of Onset of Tetany

	Mean Birthweight $\pm$ S.D. (kg)	Mean Daily Weight Gain before Onset of Tetany $\pm$ S.D. (g)	Mean Day of Regaining Birth Weight	Mean Day of Onset of Tetany
Non-oedematous	3.40 $\pm$ 0.47	25.8 $\pm$ 5.5	8.4	7.0
Oedematous	3.47 $\pm$ 0.42	49.5 $\pm$ 7.1	5.3	6.5
Significance	Not significant	$P < 0.001$	$0.02 > P > 0.01$	Not significant

again rapidly brought under control by intravenous calcium gluconate. Following this, no further twitching occurred in any of the babies. In spite of oral calcium supplements, five babies had serum calcium levels of 5.9-7.0 mg/100 ml at 48 hours. By 72 hours, however, all the babies had levels above 7 mg/100 ml (not shown in Fig. 2).

The serum magnesium levels of the oedematous babies were significantly lower than those of the other babies, both initially and during therapy ($P < 0.001$). In addition, the levels were abnormally low by our standards. The babies who were not oedematous showed a significant rise of serum magnesium levels during therapy with calcium supplements ($P < 0.001$). The oedematous babies did not show this rise, but serum magnesium levels performed on the six babies after they had lost the oedema, five to seven days after the onset of symptoms, increased significantly.

The correlation between the calcium and magnesium levels in all the babies, before and during therapy, is shown in Fig. 3. In the babies who were not oedematous there was a significant

correlation between the levels before therapy ($0.05 > P > 0.02$) and 24 hours after therapy ($0.05 > P > 0.02$). The correlation 48 hours after therapy was less significant ($0.1 > P > 0.05$). At no time was there any correlation between the calcium and magnesium levels in the oedematous babies.

FIG. 3—Correlation between serum calcium and magnesium levels in the non-oedematous babies to whom the regression line refers.

FIG. 4—Serum protein and albumin.

The serum total protein and albumin levels are shown in Fig. 4. The levels are slightly lower in the oedematous babies, but this difference is not significant. The plasma sodium and

FIG. 5—Plasma sodium and potassium levels.

potassium levels are shown in Fig. 5. The sodium levels were lower in the oedematous babies before therapy ($0.05 > P > 0.02$) and at 24 hours ($0.05 > P > 0.02$) and 48 hours ($0.02 > P > 0.01$) after therapy was begun. After the oedema had subsided in the six babies there was a significant rise in the plasma sodium levels. There was no difference in the plasma potassium levels in the two groups of babies.

All the biochemical analyses are summarized in Table III.

Discussion

Tetany in the newborn period was described by Kehrer (1913). In addition to convulsions, he described oedema in a group of newborn babies who responded to treatment with calcium chloride. Other early descriptions of neonatal hypocalcaemic tetany also noted the frequent finding of oedema in these babies (Shannon, 1929; Dodd and Rapoport, 1949). Shannon (1929) discussed the aetiology of the oedema and attributed it to an increase in capillary permeability. The six oedematous babies in this paper had evidence of excess weight gain, suggesting that the oedema was related to an increase in total body water, rather than merely a redistribution in the extravascular compartment. The low serum sodium levels are in keeping with dilution in the intravascular compartment. It is more likely that the oedema is caused by salt and water retention when the

TABLE III—Comparison of Results in the Two Groups of Babies

Time in hours:	Serum Calcium (mg/100ml)			Serum Magnesium (mg/100 ml)			Plasma Sodium (mEq/l.)		
	0	24	48	0	24	48	0	24	48
Non-oedematous {	3.7-7.0	4.2-7.6	5.9-8.5	1.0-1.9	1.2-2.0	1.4-2.1	135-144	134-145	135-146
Mean (S.E.)	5.4 (± 0.4)	6.1 (± 0.3)	7.5 (± 0.2)	1.5 (± 0.09)	1.6 (± 0.07)	1.7 (± 0.07)	140.8 (± 2.8)	140.9 (± 2.4)	140.9 (± 3.1)
Oedematous {	4.0-6.3	5.4-7.0	6.6-8.0	0.8-1.2	0.7-1.2	0.8-1.1	129-139	130-139	132-137
Mean (S.E.)	5.0 (± 0.3)	6.2 (± 0.1)	7.2 (± 0.2)	1.0 (± 0.06)	0.9 (± 0.08)	1.0 (± 0.06)	134.1 (± 2.8)	134 (± 3.3)	134.3 (± 1.6)
P	Not significant			<0.001	<0.001	<0.001	0.05 > P > 0.02	0.05 > P > 0.02	0.02 > P > 0.01
Time in hours:	Plasma Potassium (mEq/l.)			Serum Protein (g/100 ml)			Serum Albumin (g/100 ml)		
	0	24	48	0	24	48	0	24	48
Non-oedematous {	3.4-5.9	3.4-5.8	3.6-5.9	4.5-7.2	4.5-7.2	4.7-7.1	2.5-4.9	2.5-4.8	2.6-4.8
Mean (S.E.)	4.4 (± 0.2)	4.5 (± 0.22)	4.8 (± 0.22)	6.2 (± 0.25)	6.2 (± 0.25)	6.2 (± 0.22)	3.7 (± 0.22)	3.7 (± 0.18)	3.7 (± 0.18)
Oedematous {	3.4-5.5	3.5-5.8	3.7-5.5	4.9-7.0	5.1-6.7	5.2-6.7	2.8-4.2	2.9-4.3	2.9-4.2
Mean (S.E.)	4.4 (± 0.3)	4.6 (± 0.35)	4.6 (± 0.27)	5.9 (± 0.26)	5.8 (± 0.22)	5.9 (± 0.21)	3.8 (± 0.22)	3.7 (± 0.2)	3.7 (± 0.26)
P	Not significant			Not significant			Not significant		

heavy solute load in cow's milk is presented to kidneys with a relative functional immaturity.

Though the changes which occur in serum calcium and magnesium levels in the neonatal period have been studied by others (Gittleman *et al.*, 1964; Harvey *et al.*, 1970), there is little agreement on the precise values which should be accepted as abnormal. A serum calcium level of 7 mg/100 ml or below was chosen in this paper, and this is lower than has generally been accepted in the past (Keen, 1969). No attempt has been made to define accurately normal serum magnesium levels. Harvey *et al.* (1970), using atomic absorption spectrophotometry, showed a mean serum magnesium concentration of 1.4 mg/100 ml in 25 bottle-fed babies on the sixth day of life. However, the range of results was very wide, 0.85-1.9 mg/100 ml. Suffice to note that the oedematous babies had abnormally low levels for this laboratory, as did several of the non-oedematous babies with the lower serum calcium levels.

The positive correlation between calcium and magnesium levels was apparent only in the babies who were not oedematous. There is conflicting evidence concerning the role of parathyroid hormone in magnesium metabolism (Jones and Fourman, 1966). However, the case of a newborn baby with congenital absence of the parathyroid glands, described by Taitz *et al.* (1966), supports the view that serum calcium and magnesium levels are influenced in the same way by parathyroid hormone, as this baby had tetany associated with hypocalcaemia and hypomagnesaemia.

The rise in the serum magnesium levels which was seen in the non-oedematous babies when calcium supplements were given has been noted previously in hypocalcaemic babies (Gittleman *et al.*, 1964). It may be that the correction of the hypocalcaemia in these babies allows magnesium to be released from bone and muscle, in keeping with the view that there is a common transport mechanism for calcium and magnesium (Alcock and MacIntyre, 1962).

With regard to the six oedematous babies, the fact that the serum magnesium levels were abnormally low, that there was no correlation between magnesium and calcium levels, and that magnesium levels did not rise on giving calcium supplements, suggests that there was some other factor influencing the magnesium levels. The low magnesium levels cannot be explained by a lowered protein-bound magnesium fraction, as the total protein and albumin levels were similar in the oedematous and non-oedematous babies.

Aldosterone favours renal excretion of magnesium, and

increased renal excretion rates of magnesium have been found in primary aldosteronism (Mader and Iseri, 1955), and may also occur in secondary aldosteronism (Kobayashi and Shiraki, 1967). It may be that secondary aldosteronism, induced by the transient fluid retention, influenced the serum magnesium levels in the oedematous babies under study. The low plasma sodium and normal plasma potassium levels are consistent with secondary aldosteronism in association with fluid retention (Johnston, 1969).

Though none of the babies with hypomagnesaemia reported in this paper required magnesium supplements to control the twitching, it is suggested that oedema should be carefully sought in babies with hypocalcaemic tetany, together with a careful appraisal of the weight chart. The presence of oedema and excess weight gain in a baby with tetany not responding to calcium supplements should alert one to the possibility of hypomagnesaemia. Further work may show whether the use of an aldosterone antagonist is more basic to the needs of the oedematous baby with hypocalcaemic tetany.

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Post-Halothane Jaundice in Relation to Previous Administration of Halothane

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Summary

The time interval since previous anaesthesia was compared in a surgical population in South Wales and in patients who developed jaundice after halothane. There was a significant difference in the pattern of time interval since previous general anaesthetics in the surgical population and in those patients who developed jaundice

after halothane. In the group who developed jaundice there was an "excess" of patients who had had a previous halothane anaesthetic within four weeks. Halothane should if possible be avoided in patients who have had it before, particularly if this was within the previous four weeks. In the case of repeat halothane anaesthetics within four weeks, the risk seems to lie between 1 in 6,000 and 1 in 22,000.

Introduction

The rare occurrence of jaundice after halothane anaesthesia is of much concern to anaesthetists. This complication could be avoided if the use of halothane were stopped altogether.

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