# Hypomagnesaemic hypocalcaemia in renal failure

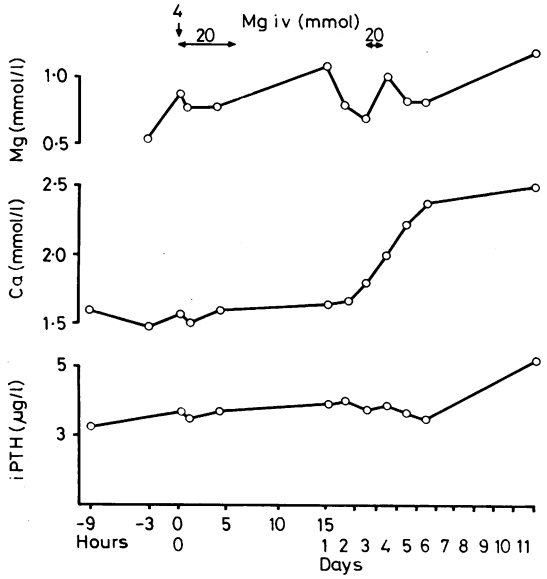
Hypocalcaemia as a result of hypomagnesaemia is said to be due to a combination of impaired parathyroid hormone release and resistance to its action in the periphery.[1] It is rare in patients with renal failure but it is also associated with inappropriately low concentrations of parathyroid hormone (iPTH), which increase with the return of normocalcaemia.[2] We report a case of hypomagnesaemic hypocalcaemia in a patient with renal failure where there was no change in the serum iPTH concentration either in the early phase after magnesium supplementation or in the subsequent days during which the serum calcium concentration returned completely to normal.

## Case report

A 38-year-old Caucasian woman had moderate renal failure as a result of analgesic nephropathy. The latter was diagnosed from a history of heavy analgesic intake over many years, typical radiological changes of papillary necrosis, and a history of a previous passage of one or more papillae. She also admitted to taking cathartics excessively. She was admitted to hospital with a history over several days of cramps and acroparaesthesia in the hands and feet. She also complained of circumoral paraesthesia and of generally feeling unwell. On examination she had a negative Chvostek's sign but a strongly positive Trousseau's sign. She weighed 48 kg and there was evidence of mild congestive heart failure as judged by ankle oedema and raised jugular venous pressure. Blood pressure was 130/80 mm Hg. Relevant investigations on admission were: Hb 7·6 g/dl, WBC $5·3 \times 10^9$/l (5300/mm$^3$), MCHC 30·2 g/dl, MCV 70 fl, serum Na 144 mmol (mEq)/l, K 3·3 mmol (mEq)/l, Cl 105 mmol (mEq)/l, $HCO_3$ 33 mmol (mEq)/l, Ca 1·5 mmol/l (6 mg/100 ml), Mg 0·5 mmol/l (1·2 mg/100 ml), $PO_4$ 0·7 mmol/l (2·4 mg/100 ml), alkaline phosphatase 59 IU/l, creatinine 145 μmol/l (1·6 mg/100 ml), 24-hour creatinine clearance 29 ml/min/1·73 m$^2$. Radiological skeletal survey showed no evidence of osteomalacia or osteosclerosis. There were early changes of secondary hyperparathyroidism in the fine grain films of the hands. Biopsy of iliac crest bone showed a normal total bone volume (12·9%), no evidence of increased osteoclastic resorption, a normal osteoid volume (0·5% of total bone), but a mildly diminished calcification front. Magnesium supplements were started with an intravenous bolus of 4 mmol ($MgSO_4$). Serial measurements (see figure) of serum calcium, magnesium, and iPTH (by a carboxyl terminal directed assay, normal range 0·3-1 μg/l) were performed at 5 minutes, 1 hour, 4 hours, 15 hours, and for several days after the return of the serum magnesium to normal. No further supplements were necessary. The patient became symptom free within 72 hours and was discharged after five days.

## Comment

Most patients with hypomagnesaemic hypocalcaemia have low or normal concentrations of circulating iPTH.[1 4] Although the biosynthesis of iPTH may be normal, the release from the gland has been found to be defective.[1 3] Intravenous replacement therapy with magnesium is reported to cause a rapid rise in levels of iPTH within minutes. The delay in restoration of normocalcaemia is suggested to be due to the peripheral resistance to the action of parathyroid hormone or to other mechanisms of impaired calcium mobilisation from the skeleton, or both. Previous reports have shown the rise in iPTH to be concomitant with the restoration of normocalcaemia.[1 4] We have shown that in our patient there was no rise in iPTH levels for several days despite the restoration of normomagnesaemia. Furthermore, although normocalcaemia was restored after five days the serum iPTH level remained unchanged. The late rise in circulating iPTH at 11 days suggests that in our patient the mechanism of hypocalcaemia seems not to be dependent on parathyroid hormone biosynthesis or release, since the reversal of magnesaemia was followed by normocalcaemia without any increase in circulating iPTH levels. The mildly raised baseline serum iPTH was compatible with the raised levels found in renal failure attributable to decreased degradation of the carboxyl fragment of the hormone,[5] and the subsequent increase at day 11 supports the contention that even in renal failure hypomagnesaemia results in an inappropriately low level of circulating iPTH.[2]




Serial measurements of serum calcium, magnesium, and iPTH before and after intravenous magnesium supplements.

I thank Dr T H Mathew for permission to study this patient.

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# Secondary copper accumulation with neurological damage in child with chronic liver disease

Copper retention in some patients with chronic liver disease has been known for many years.[1] We report a case in a child associated with unusual neurological features.

## Case report

A full-term baby girl was oedematous at birth and developed jaundice and white stools by 48 hours of age. She presented at 5 weeks with the unusual combination in an otherwise lusty baby of jaundice, hepatosplenomegaly, oedema, and ascites. The jaundice and oedema remained life-long problems and the lymphoedematous nature of the fluid collection became obvious after a few months. She died of liver failure and infection at the age of 5½ years. Unusual neurological features developed in the last 12 months of her life.

Specific known causes of neonatal liver disease were excluded. Both parents were English. Three siblings were healthy, but one baby had been stillborn. Leucocyte karyotype was 46XX. Needle liver biopsy specimens obtained at 6 weeks, 3 years 10 months, and 4 years 4 months showed changes of neonatal hepatitis progressing relentlessly to cirrhosis despite treatment with medium-chain triglyceride milk, cholestyramine and prednisolone, and a short course of penicillamine. Muscle co-ordination deteriorated progressively in the last six months causing difficulty in writing and drawing and finally preventing her walking. Involuntary movements and postural disturbance developed despite a normal conscious state. No Kayser-Fleischer rings were apparent on ophthalmoscopy, but slit-lamp examination was not performed.

The copper content of the liver on biopsy at 4 years and 4 months was much raised (629 6 μg/g dry weight). Histochemical stains showed diffuse granular copper deposition in liver cells and Küpfer cells. At necropsy the liver copper content was 1195 μg/g dry weight and the basal ganglia contained 286 μg/g dry weight. There was evidence of astrocytic and neuronal degeneration in the basal ganglia, in the basal layers of the cortical grey matter, in the dorsal nuclei of the medulla, and in the subthalamic nuclei.

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## Comment

The clinical features in this case were those of the recessively inherited syndrome of chronic cholestasis and lymphoedema described by Åagenaes.[2] The illness was unique among over 100 cases of neonatal hepatitis studied during the last 15 years[3] and incompatible with the simple diagnosis of Wilson's disease. The neurological features in the terminal stage of the disease, however, were those of lenticular degeneration, and the microscopic and chemical changes at necropsy seemed compatible with the proposal that they were caused by copper. We suggest that the patient's initial liver disease interfered with copper excretion, causing copper retention within the liver followed by overflow to the brain, and that the copper caused lenticular damage and contributed to the rapid progression of the liver disease. This sequence of events resembles that in Wilson's disease, except that the primary defect in Wilson's disease presumably affects biliary excretion of copper in a more specific way.

Several important points follow. Firstly, this complication should be sought in other patients with Åagenaes's syndrome with a view to using penicillamine more energetically. Secondly, the observations support the widely held view that the lenticular degeneration of Wilson's disease is a non-specific consequence of overflow of copper from the liver. Finally, this case has caused us to look for copper retention in other children with chronic liver disease. We have observed very high liver copper concentrations in several other children with childhood cirrhosis and have seen a gratifying response to penicillamine therapy in two of them. No particular relationship between the degree of copper retention and the form of the initial liver disease has emerged. Copper retention is particularly prominent in primary biliary cirrhosis. Controlled studies of penicillamine treatment in this disease have been reported and show encouraging results.[4] Other complications of secondary copper retention have been reported.[5]

We advocate measuring the liver copper content in patients with chronic liver disease at all ages to accumulate information which may allow meaningful trials of treatment with penicillamine in selected cases to test the hypothesis that copper retention can be a factor contributing to progression to cirrhosis.

We thank Mr Michael McKay, Biochemistry Department, Royal Children's Hospital, Melbourne, for measuring tissue copper concentrations.

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# Breakfast and dietary aspects of Crohn's disease

There has been considerable speculation about the cause of Crohn's disease. Diet may play a part. A recent study[1] showed that patients with the disease consumed large quantities of refined carbohydrate. James[2] examined breakfast habits in 34 patients and found that most of them ate cornflakes regularly at the onset of their illness. We have re-examined some aspects of diet, particularly breakfast habits, in 100 patients and 100 matched controls.

## Patients, methods, and results

We interviewed 48 men and 52 women with Crohn's disease. Their ages ranged from 15 to 81 years (mean±SD 41·7±15·8). The mean interval since the initial diagnosis was 8·9±7·2 years. We chose 100 controls, matched for age and sex, from either patients or their relatives attending a fracture clinic. Patients and controls were interviewed by the same person using a questionnaire in an open study. The frequency at which certain breakfast foods were currently eaten was recorded as regular (at least twice weekly) or irregular (less than twice weekly). The results (table) showed no statistical difference except for fruit or fruit juice, which were taken more often by controls ($P<0·02$). Those who regularly had cereals at another time of day or changed their cereals between winter and summer were also noted. All subjects were asked whether any of a given list of foods precipitated abdominal symptoms. A significant difference was noted for a large range of products which included cheese, chocolate, eggs, nuts, vegetables (especially cabbage), meat (mainly pork), and cereals.

*Number of patients and controls regularly consuming certain foods at breakfast at least twice weekly and of those with other habits unrelated to breakfast. Analysis is by $\chi^2$ on one degree of freedom except for subjects who swallowed toothpaste, when a two-tailed Fisher test was used*

| Dietary and other habits | Crohn's patients (n = 100) | Controls (n = 100) | Significance (P) |
|---|---|---|---|
| Foods at breakfast | | | |
| Bread | 91 | 86 | |
| Toast | 59 | 64 | |
| Egg | 31 | 37 | |
| Fruit or fruit juice | 14 | 30 | <0·02 |
| Porridge | 20 | 18 | |
| Weetabix, Shreddies, or Shredded Wheat | 21 | 19 | |
| Cornflakes | 29 | 22 | |
| Special K | 4 | 7 | |
| Rice Krispies | 6 | 6 | |
| Sugar Puffs | 3 | 1 | |
| Bran or All Bran | 13 | 12 | |
| Muesli | 3 | 10 | |
| Any cereal | 55 | 55 | |
| Cereals at other times of day | 12 | 12 | |
| Seasonal variation | 18 | 13 | |
| Other habits | | | |
| Coca Cola consumption (twice weekly) | 38 | 34 | |
| Alcohol consumption | 42 | 55 | |
| Smokers | 46 | 44 | |
| Toothpaste users | 73 | 74 | |
| Toothpaste swallowers | 6 | 1 | |
| Addition of sugar to: | | | |
| Tea or coffee | 78 | 52 | <0·001 |
| Mean number of teaspoons to each cup | 1·79±1·3 | 1·14±1·3 | <0·001 |
| Cereals | 57 | 42 | <0·05 |
| Mean number of teaspoons to each bowl | 1·38±1·5 | 0·84±1·21 | <0·006 |

In view of previous reports about cornflakes and Crohn's disease patients were asked whether they knew of an association between food (unspecified) and the disease. Twenty-nine knew of the possible association with cornflakes and 12 of these had stopped eating them, having previously taken them regularly. The corresponding figure for their 29 matched controls was only three ($P<0·02$). Twenty-one of the 71 patients who were unaware of the association had also discontinued cornflakes. The figure for their 71 controls was 10 ($P<0·05$). Seemingly patients with Crohn's disease had significantly reduced their consumption of cornflakes compared with controls, irrespective of whether they were aware of the possible association. The amount of sugar added to beverages and cereals was recorded. There were more sugar takers among patients than controls. This was true for addition of sugar to tea and coffee ($\chi^2=13·74$; $P<0·001$) and cereals ($\chi^2=3·92$; $P<0·05$). The amount of sugar consumed was also significantly greater for addition to drinks ($t=3·52$; $P<0·001$) and to cereals ($t=2·80$; $P<0·006$). Other questions related to toothpaste, smoking, and consumption of alcohol and Coca Cola.

## Comment

We looked at current breakfast habits because people's recollection of previous detailed habits may be inaccurate. The difference in sugar consumption between patients and controls is difficult to interpret. Patients may increase their consumption in an attempt to compensate for loss of energy or weight. They may exclude other foods which cause symptoms, or include those which are better tolerated. A direct causal relationship between Crohn's disease and food could be difficult to establish.

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