Internuclear ophthalmoplegia in pernicious anaemia

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We report a case of internuclear ophthalmoplegia in association with vitamin B₁₂ deficiency, which has not to our knowledge been described in Europe.

Case report

A 44 year old man presented in July 1987 with a one year history of progressive numbness of his feet, paraesthesia of his hands, a tendency to trip, and urgency of micturition. His mother suffered from pernicious anaemia. On examination he had ataxic nystagmus on right lateral gaze and bilateral pyramidal signs in the legs, consisting of increased tone, exaggerated knee jerks, and extensor plantar responses. Ankle jerks were unobtainable, and there was mild proprioceptive loss in the toes.

Recording of visual evoked responses, examination of cerebrospinal fluid (including oligoclonal bands), cervical myelography, and magnetic resonance imaging all yielded normal results. Haemoglobin concentration was 158 g/l with a mean corpuscular volume of 106 fl. A blood film showed a macrocytic, normochromic picture with hypersegmentation of neutrophils. Serum concentration of vitamin B₁₂ was 19 ng/l (normal 170-900), and serum folate concentration was normal. Antibodies to gastric intrinsic factor

were absent. Results of a Schilling test were consistent with a diagnosis of pernicious anaemia.

Subacute combined degeneration of the cord was diagnosed, and the patient was treated with intramuscular hydroxocobalamin, 1 mg daily for five days and three monthly thereafter. The ataxic nystagmus had completely resolved two months after treatment started, but the myelopathy persisted with little change in its severity.

Comment

Two patients with pernicious anaemia who had defects of upward gaze have been reported.^{1,2} Gamstorp and Kupfer found this to be due to denervation of the extraocular muscles as shown by electromyography.¹ Also, a Japanese patient with Addison's disease complicated by pernicious anaemia and medial longitudinal fasciculus syndrome has been reported.³ Our patient had an internuclear ophthalmoplegia and myelopathy in association with vitamin B₁₂ deficiency. The myelopathy of B₁₂ deficiency is known not to improve much with treatment, but this patient's internuclear ophthalmoplegia resolved entirely.

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- 2 Sandyk R. Paralysis of upward gaze as a presenting symptom of vitamin B₁₂ deficiency. *European Neurology* 1984;23:198-200.
- 3 Matsumoto T, Togawa K, Yamamoto M, Yamagami Y, Ogata E. A case of idiopathic Addison's disease complicated with alopecia universalis, vitiligo vulgaris, superficial mycosis, pernicious anaemia and bilateral medial longitudinal fasciculus syndrome. *Nippon Naika Gakkai Zasshi* 1977;66:1588-94.

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Are all infants of diabetic mothers "macrosomic"?

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Macrosomia has been defined as a birthweight exceeding an arbitrary limit—for example, 4000 g or the 90th centile for gestation. The condition is of interest because of the difficulties of delivering a large infant. Fetal size has been used as an indication of the degree of control of diabetes during pregnancy, and the infants are often referred to as either "macrosomic" or "non-macrosomic," implying a bimodal distribution of birthweights.

In this study we examined details of the deliveries of 280 infants to diabetic mothers to determine whether there are two populations according to birthweight.

Patients, methods, and results

We reviewed the case notes of 280 women who were diabetic when pregnant and who gave birth at this hospital in 1976-85. Those with pre-existing diabetes (247) were treated with insulin during pregnancy, whereas most (25) of the 33 women with gestational diabetes were managed by restricting their intake of carbohydrate. The mean (SD) maternal weight (67.5 kg (12.3)) and height (161 cm (7.3)) did not differ significantly from those of 3959 non-diabetic mothers (64.9 kg (13.2) and 160 cm (7.1)) who gave birth at the hospital during the same period.

The birth weights were expressed as the number of standard deviations by which they differed from the mean birth weights for gestational age of a reference range constructed from 3959 consecutive singletons born in the hospital during the study. In all cases gestational age had been confirmed by measuring the

biparietal diameter and the length of the femur by ultrasound early in the second trimester.²

The birthweights of the 280 infants of diabetic mothers formed a unimodal normal distribution (mean +1.23; SD 1.35; Anderson-Darling test of normality 0.65, $p=0.18$). This distribution was shifted significantly to the right of the reference range ($p<0.0001$) by 1.23 standard deviations (roughly 500 g) (figure 1).

The distribution of birthweights (standard deviations from the normal mean for gestational age) for 280 infants of diabetic mothers and 3959 infants of normal mothers

Comment

The findings of this study dispute the classification of infants of diabetic mothers as either "macrosomic" or "non-macrosomic." Such classification ignores the continuous distribution of birthweight and may conceal any correlations between the biochemistry of the infants and fetal size. The data suggest that every infant of a diabetic mother, irrespective of actual birth weight, is growth promoted and exceeds its genetic

potential for growth, presumably as a result of metabolic disturbances during the pregnancy, and may therefore be termed "macrosomic."

Acker *et al*³ reported that the incidence of shoulder dystocia in the deliveries of diabetic mothers was 50%, 23%, and 9% for infants weighing ≥ 4500 g, 4000-4499 g, and 3500-3999 g, respectively, compared with 23%, 10%, and 2% for deliveries of non-diabetic mothers. Thus many more infants of diabetic mothers are too large for their maternal pelvis, even when their birthweight is apparently normal.

Control of diabetes in pregnancy should not be described as "good" or "bad" as it forms a continuous range and thus would not be expected to have an all or nothing effect on promoting fetal growth. A substantial percentage of infants of diabetic mothers with birth weights within the normal range will be affected by the metabolic disturbances in the uterus caused by diabetes. In a review of 225 infants of diabetic mothers Lemons *et al* reported that neonatal hypoglycaemia occurred not only in 36 (47%) of the macrosomic infants, but also in 31 (21%) of the infants with

birth weights that were not large for gestational age.⁴ The extent to which an infant will be affected by maternal diabetes, as measured by birth weight or neonatal hypoglycaemia, will vary, explaining why "good" control in the conventional sense may result in a big baby who becomes hypoglycaemic whereas "bad" control may result in a small baby who does not.

Our results suggest that all infants of diabetic mothers, irrespective of birth weight, are growth promoted to some degree by their mothers' disease, and thus every infant should be considered to be at risk from the biochemical and mechanical consequences of macrosomia.

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Magnesium free dialysis for uraemic pruritus

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The treatment of uraemic pruritus is difficult, as reflected by the variety of treatment that has been tried.¹ Hypermagnesaemia is common in chronic renal failure² and has been shown to correlate with itch.³ We investigated the effect on itch of lowering the serum magnesium concentration in a group of patients suffering from uraemic pruritus.

Patients, methods, and results

From an initial study of renal itch in patients undergoing long term haemodialysis 20 patients were identified as being severely affected by uraemic pruritus (itch score more than 200 a week).³ Three patients were excluded as they were on non-standard dialysis fluid, and the others continued to fulfil the previous entry requirements³ and were not taking drugs containing magnesium. The 17 patients included in the trial (one woman) were aged 25-69; had been undergoing maintenance haemodialysis for 4-79 months; received 9-14 hours of dialysis a week on Dylade D2 or Gambro AK10 machines, with Travenol ST12/11 dialysis membrane, and remained on the same machines and dialyser throughout the trial.

The patients were randomly allocated into two groups by a double blind technique. Group 1 (seven patients) remained on the standard dialysis fluid (McCarthy's QE136) with a magnesium concentration of 0.85 mmol/l, while group 2 was changed to one free of magnesium (McCarthy's S597). In all other respects the composition of the dialysis fluid was identical. After two weeks the dialysis fluids of the two groups were swapped for a further fortnight. The serum magnesium concentration was measured before and after dialysis at entry and weekly throughout the trial. Serum parathyroid hormone concentration was measured at entry and at two and four weeks. The degree of itch was assessed by the patients completing visual analogue charts.³ All 17 patients completed the trial with no adverse symptoms noted.

On the standard dialysis fluid serum magnesium concentration was raised in most patients with mean concentrations before and after dialysis of 1.38 and 1.33 mmol/l (SEM 0.05 mmol/l; normal range 0.70-1.00 mmol/l). The magnesium free dialysis fluid reduced the serum magnesium concentration to normal after a week, and after a fortnight the concentrations before and after dialysis were 0.87 and 0.62 mmol/l (SEM 0.06 mmol/l). The reduction of the concentration was highly significant ($p < 0.001$, analysis of variance). Lowering the serum magnesium concentration was associated with a significant increase ($p < 0.01$, analysis of variance) in serum parathyroid hormone concentration (figure). Analysis of the itch score for weeks two and four (weeks one and three were omitted to diminish the carryover effect) showed no evidence of an effect from the treatment ($p > 0.1$, Wilcoxon signed rank test).

Change in serum parathyroid hormone concentration (SE) of group 1 (○ --- ○) on magnesium free dialysis fluid for weeks three and four and group 2 (● — ●) on magnesium free dialysis fluid for weeks one and two. Shaded area shows normal range of serum parathyroid hormone concentration

Comment

Graf *et al* reported a case of recalcitrant uraemic pruritus responding within a week to a low magnesium dialysate,⁴ a finding corroborated, but not quantified, by Nilsson *et al* using a similar dialysis fluid with a magnesium concentration of 0.2 mmol/l.⁵ More recently we have shown a correlation between renal itch and serum magnesium concentration in patients