

Despite the operative intervention the child remained hypertensive and the function in the right kidney continued to deteriorate. HMMA output remains high but has shown a steady decline during the last year to near normal levels. A positive Saralasin infusion test (Streeton *et al.*, 1976) combined with increased plasma renin levels (>300 pmol/l per min) has shown her hypertension to be renal in origin. In view of the operative findings it was decided to treat the hypertension medically and she is now well controlled on a combination of propranolol and phenoxybenzamine. Appetite and weight gain have returned to normal.

It is now 2 years 10 months since the first skin nodule was noted. Another baby girl has been born to these parents and at 7 months shows no evidence of developing neuroblastoma. HMMA levels in this sibling and in both parents are normal.

Discussion

Despite the known favourable outlook in stage IV-S neuroblastoma, most reported cases have received some treatment. The purpose of this report has been to add information on the natural history of the condition. Three previous cases have been reported in which no treatment was given and the disease regressed spontaneously (Griffin and Bolande, 1969; Schwartz *et al.*, 1974). As chemotherapy and radiotherapy have had little effect on the survival of children with stage IV neuroblastoma (Koop and Johnson, 1971) their use in stage IV-S cannot be justified as several deaths in this group can be directly attributed to their use (Griffin and Bolande, 1969; Hassenbusch *et al.*, 1976). Surgical removal of the primary tumour may be justified as late reactivation of disease can occur (Konrad *et al.*, 1973) and, as in our case, adjacent structures may be damaged. It is also desirable to establish the cause of hypertension if this should develop: the obvious explanation is the raised catecholamine levels but, as our case demonstrates, renal hypertension may occur. The Saralasin infusion test, combined with peripheral venous plasma renin estimations, appears to be a reliable and relatively noninvasive method of making the distinction (Streeton *et al.*, 1976). Major surgery involving risk to life would not seem justified.

Summary

A case of stage IV-S neuroblastoma is presented in which treatment has deliberately been kept to a minimum. Gradual maturation to ganglioneuroma has been documented and the patient's generally good progress has justified this approach.

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Hypomagnesaemic hypocalcaemia with hypokalaemia caused by treatment with high dose gentamicin

We report a case of hypomagnesaemic hypocalcaemia with hypokalaemia in a 12-year-old boy after prolonged treatment with gentamicin.

Case report

After a severe road traffic accident in April 1976 the boy's injuries included a depressed skull fracture, a comminuted fracture of the left femur, a transverse fracture of the right femur, a fractured pelvis, and multiple lacerations. The frontal bone was raised and the crushed brain evacuated. The right femur was fixed internally after reduction of the fracture and a double hip spica was applied; he was then transferred from Libya to London.

At operation the left femur was found to be soundly united; the right femur was ununited and inadequately fixed, with gross surrounding sepsis.

Swabs grew *Proteus* species sensitive only to gentamicin. He was immobilised on skin traction and given gentamicin 60 mg IM twice daily. The right femoral fracture united and he was mobilised in a weight-relieving caliper. After 4 months swabs became sterile and gentamicin was stopped; a total of 14.4 g had by that time been administered. A few weeks later he felt unwell, began vomiting, and was transferred to the Central Middlesex Hospital on 21 December 1976.

On admission plasma Na was 119 mmol/l, K 1.1 mmol/l, bicarbonate 27 mmol/l, Cl 61 mmol/l, urea 15.1 mmol/l (91 mg/100 ml), creatinine 190 μ mol/l (2.1 mg/100 ml), osmolality 232 mmol/kg. The urine contained 60 WBC, 8 RBC, and casts ++.

Urine concentration and electrophoresis showed a pattern consistent with tubular proteinuria. Treatment with potassium supplements was begun.

On 5 January 1977 the patient complained of pains in his fingers and feet. Chvostek's and Trousseau's signs were positive. Serum Ca was 1.6 mmol/l (6.4 mg/100 ml) and Mg 0.2 mmol/l (0.5 mg/100 ml). Magnesium, calcium, and potassium balances during the next 2 months are shown in Figs 1 and 2. Blood pressure was normal; plasma renin activity and aldosterone concentrations were in the high normal range. Immunoreactive parathyroid hormone (iPTH) levels were inappropriately low.

During the next 2 months these abnormalities returned to normal, as did renal function. After

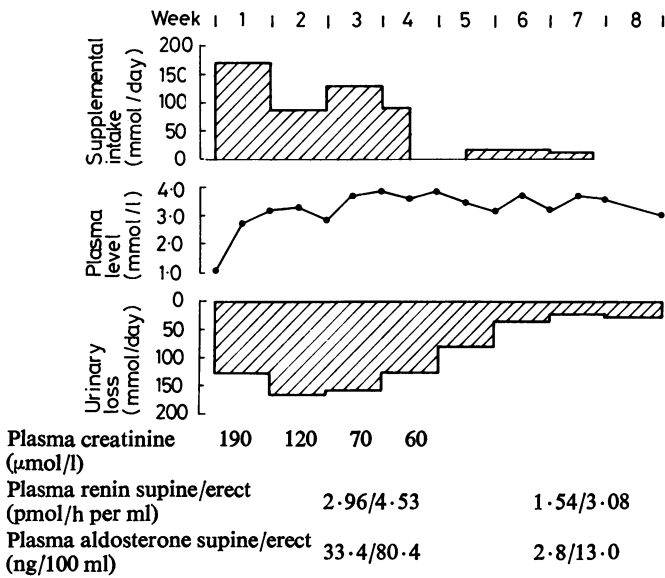


Fig. 1 Potassium balance over 2 months after admission to hospital.

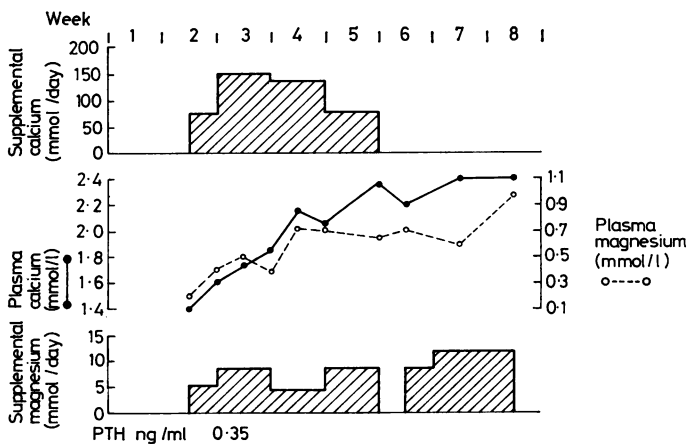


Fig. 2 Calcium and magnesium supplements and plasma levels over 2 months after admission to hospital.

further operations on the right femur and closure of the skull defect, the boy was discharged in good health.

Discussion

Magnesium is essential for maintaining potassium balance and for normal calcium metabolism. The occurrence of otherwise unexplained hypokalaemia and hypocalcaemia suggests the possibility of significant magnesium depletion, due either to dietary deficiency (Shils, 1969) or to abnormal losses. In this patient dietary history of the previous 4 months showed intakes within the recommended ranges for magnesium, calcium, and potassium.

Gentamicin is mainly excreted by glomerular filtration, with the tubules playing a minor role. Like other aminoglycosides it is bound to renal tissue (Luft *et al.*, 1975). The incidence of nephrotoxicity is 2–10%, manifested by proteinuria and cylindruria, with rising blood urea and creatinine. Most patients have a rise in serum creatinine, usually reversible on stopping treatment and dose-related. In rare cases acute renal failure develops and seems unrelated to dosage or serum levels. Although gentamicin is usually stated to be rapidly excreted by the kidneys, it has been recovered from the urine of patients with normal renal function 20 days after stopping treatment (Kahlmeter and Kamme, 1975). A study by Schentag and Jusko (1977) of 47 patients receiving gentamicin in which the serum peak, midpoint, and trough concentrations were measured as well as those in urine, other body fluids, and post-mortem tissue, showed that serum concentrations rose gradually in most patients throughout treatment. After the final dose these concentrations declined in 2 phases, the first similar to the apparent decline during each dosing interval and largely determined by renal function (half-life 12 hours), the second declining more slowly with an average half-life of 112 hours (range 27–693 hours (4 weeks)). Post mortem, renal cortical levels were 100 times those of serum, with the kidneys accounting for 40% of the total body gentamicin. Ability to detect gentamicin over long periods in serum and urine is the result of slow release from tissue-binding sites. Thus accumulation continues throughout treatment; the high concentration in the kidneys show how nephrotoxicity can occur.

Holmes *et al.* (1970) treated 4 patients with more than 10 g gentamicin over 6 months. These patients developed hypokalaemia and hypomagnesaemia with hypochloroemic alkalosis. There was an interval of several months before the onset of biochemical disturbances. These were attributed to secondary

hyperaldosteronism and hyperreninaemia. Recovery was delayed many months after stopping treatment. Bar *et al.* (1975) treated 2 patients with 10 990 and 1320 mg of gentamicin. The second patient had ototoxicity; both patients developed hypomagnesaemia, hypokalaemia, hypocalcaemia, and renal magnesium wasting. Plasma renin and aldosterone levels at the time of greatest urinary magnesium loss were normal. iPTH levels remained inappropriately low.

Our patient was given 14 400 mg over 4 months for osteomyelitis due to a resistant organism. The interval between stopping treatment and symptoms was 5 weeks, similar to that in the patients described above. Renin and aldosterone levels were normal and iPTH levels were inappropriately low for the serum Ca. Renal Mg excretion was inappropriately high for the concurrent hypomagnesaemia: in hypomagnesaemia due to inadequate intake renal excretion normally decreases to less than 1 mEq (0.5 mmol) daily within one week (Shils, 1969).

Hypomagnesaemia presumably caused the hypocalcaemia and hypokalaemia (Shils, 1969). The mechanisms are uncertain. Magnesium deficiency may prevent parathyroid hormone release, produce end-organ unresponsiveness to the hormone, or both, possibly by causing defective cyclic-AMP generation in the parathyroid glands and target organs (Rude *et al.*, 1976). Gentamicin may cause secondary hyperaldosteronism, with resulting hypermagnesaemia and hyperkaluria (Holmes *et al.*, 1970). However, in our case, as in those of Bar *et al.* (1975), renin and aldosterone levels were normal despite hypokalaemia with renal potassium wasting.

All reported cases with this gentamicin-induced syndrome were treated with large doses over extended periods. All but one received over 10 000 mg and the remaining patient had other features of gentamicin toxicity despite a lower total dose.

In gentamicin therapy the importance of monitoring serum levels during even short courses to reduce risks of nephrotoxicity and ototoxicity is well known. Accumulation may result in nephrotoxicity, and particular care is therefore needed when it is used for long periods. In patients receiving prolonged courses plasma Mg, Ca, and K levels should be monitored frequently during and after treatment.

Summary

A 12-year-old boy developed renal wasting of magnesium, calcium, and potassium, with secondary hypomagnesaemia, hypocalcaemia, and hypokalaemia (without hyperaldosteronism) after treatment with 14 400 mg gentamicin over 4 months. Gentamicin should not be given for prolonged courses

if less toxic antibiotics are suitable. If it is used, plasma magnesium, calcium, and potassium levels should be monitored during and after treatment.

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Infrared irradiance from phototherapy units and the effect on osmolality of serum and urine in term infants

The technical simplicity of phototherapy has resulted in many neonatal departments having phototherapy units built for them by local craftsmen, usually to a similar specification as those available commercially. Infrared radiation of >650 nm is emitted by these light sources and causes an increase in skin blood flow (Oh *et al.*, 1973; Wu *et al.*, 1974), and a 2- to 3-fold increase in insensible water loss in infants (Oh *et al.*, 1972; Oh and Karecki, 1972). We decided to measure the osmolality of urine and blood in term infants receiving phototherapy for hyper-

bilirubinaemia of unknown cause. We also measured the infrared emission from commercial and locally constructed phototherapy units.

Methods

The group studied comprised 10 normal baby boys born spontaneously at term after normal pregnancies, of appropriate weight-for-gestational-age, and Apgar scores of 8 or more at 1 and 5 minutes. Indirect bilirubin concentration at start of therapy was >250 $\mu\text{mol/l}$ (>14.6 mg/100 ml) and none of the babies had evidence of haemolytic disease, infection, or galactosaemia. The babies were placed in an Air Shields Isolette C86, with proportional control of heating. A urine bag was applied and urine was collected as it was passed immediately before, during, and for 24 hours after discontinuing phototherapy. 1 ml venous blood was obtained 12-hourly for serum bilirubin and osmolality estimations, the latter being determined by freezing point depression using an Advanced Instruments osmometer. Infants were weighed before and after breast feeds, and the volumes of milk given by bottle were carefully measured.

The Air Shields phototherapy unit PT 531 comprises a bank of 8 Philips 40 W daylight 33 fluorescent lamps, encased in a protective metal box with a plexiglass G acrylic plastic cover 6 mm thick (sold in UK as Oroglass G, its irradiation transmission characteristic is illustrated in Rohm and Hass technical leaflet OR-53). The light source is adapted to be 45 cm above the infant. The locally made units are of similar design. Infrared radiation was measured using a Heimann bolometer KT14, calibrated in degrees centigrade (Micron Marketing, Gordon House, Station Road, Mill Hill, London). The range chosen was 0 to 50°C and accuracy was $\pm 0.5^\circ\text{C}$ when standardised with an AGA black body source for the range 27-39°C. The initial incubator reading was 30-32°C, with humidity of 60%. Infrared radiation measurements of the light source emission were made at the level of the infant, within the incubator and outside it. Air temperature was recorded by an Ellab universal digital thermometer DU3 with probe N TRA 1 at the level of the infant. Measurements were made at 0, 30, 60, 90, and 180 minutes after beginning phototherapy and the results expressed as the average of 3 separate studies. The unpaired Student's *t* test was used to evaluate the significance of the results.

Results

The infants were studied between days 5 and 8 of life, and phototherapy was given for 24 to 46 hours.