Lesson of the Week

Hypothermia in hypoglycaemia

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The cardinal signs and symptoms of hypoglycaemia are well known. They include an initial sense of ill health, anxiety, and panic with feelings of detachment and hunger. On examination there is often tachycardia, sweating, and an unsteady gait. Other manifestations of hypoglycaemia are seen less often: hypothermia may be the first and, occasionally, the only sign of hypoglycaemia in both the conscious and the comatose patient. We believe that this important association is often overlooked and report a case of recurrent hypoglycaemia with hypothermia in a patient with a tumour producing insulin.

Case report

A 57 year old man was admitted for investigation of a grossly enlarged firm liver and facial flushing. A 10-fold rise in his urinary concentration of 5-hydroxyindoleacetic acid confirmed a diagnosis of metastatic carcinoid tumour, and argyrophilic cells were identified in a biopsy specimen of liver tissue. Despite a barium meal and enema, abdominal computed tomography, and ultrasound investigation the site of the primary tumour could not be found.

One month after his discharge from hospital he was readmitted at the urgent request of his general practitioner. On waking that morning his wife had found him irritable and drowsy. During the next eight hours he had lapsed into stupor. On arrival in casualty he was semi-conscious, totally disorientated, and growling. His plasma glucose concentration was only 1.3 mmol/l (23 mg/100 ml) and he responded dramatically to 50 ml 50% dextrose intravenously. Concentrations of insulin and C peptide at the time of admission proved to be inappropriately high; immunochemical staining of his original liver biopsy specimen showed the presence of insulin granules within the liver cells.

During his admission it proved difficult to control his plasma sugar concentration and he suffered frequent episodes of pronounced hypoglycaemia characterised by irritability and a decrease in his conscious level. During these episodes he felt warm but his skin was sweaty and cold to the touch. Temperatures taken with a low reading rectal thermometer were distinctly subnormal, falling to as low as 34°C. The association of hypothermia with hypoglycaemia in this patient was confirmed on each occasion by a plasma glucose concentration of less than 2.00 mmol/l (36 mg/100 ml). Within an hour of correcting his plasma glucose concentration his body temperature had returned to normal.

Despite the administration of diazoxide, bendrofluzide, and later cytotoxic drugs, it became difficult to sustain his plasma glucose concentration. He required continuous infusion of initially 10%, then 20%, and finally 50% glucose. He died suddenly one month after admission. Necropsy showed a massive pulmonary embolus and a carcinoid islet cell tumour of 2 cm diameter in the tail of the pancreas.

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There was no evidence of pancreatitis. The liver was almost totally replaced by tumour.

Discussion

The occurrence of hypothermia in hypoglycaemia during treatment for insulin shock has been recognised for more than two decades. Kedes and Fields, in a series of five case reports, drew attention to its usefulness in the diagnosis of hypoglycaemia both in asymptomatic and in profoundly affected patients.¹ Two case reports of hypothermia occurring in carcinoid syndrome were described by Vaidya and Levine, but in only one of these patients was hypoglycaemia associated with the hypothermia.² Both patients were receiving the drug parachlorophenylalanine and the authors suggested that the drug might have produced hypothermia.

Strauch *et al* were the first to investigate prospectively the association between hypothermia and hypoglycaemia.³ They measured body temperature in 15 consecutive patients with hypoglycaemia and in 20 patients with coma or stupor of diverse aetiology. Hypothermia was observed in eight of the group with hypoglycaemia (55%) and in only one of the control subjects. This high incidence surprised the authors, who suggested that inadequate shaking down of the thermometer in previous cases had resulted in failure to detect hypothermia in patients with hypoglycaemia. The accompanying leading article suggested that where hypothermia occurred it was the result of either disturbance of the thermoregulatory centres in the brain or the profuse sweating typical of insulin reactions.⁴

Experimental evidence for both these hypotheses has been forthcoming. Freinkel *et al* studied the synthetic glucose analogue 2 Deoxy-D-glucose.⁵ After phosphorylation, metabolism of 2 Deoxy-D-glucose is complete and it acts as a competitive inhibitor of glucose-6-phosphate for the isomerase reaction. Oral or intravenous administration of 2 Deoxy-D-glucose in man produces manifestations of hypoglycaemia in the presence of normal or supranormal plasma glucose concentrations. After infusions of 2-Deoxy-D-glucose in healthy male medical students, rectal temperatures fell to nadir levels averaging 1.1°C below baseline for six hours, indicating that hypothermia was conditioned by intracellular glucopenia rather than by the availability of circulating glucose. Furthermore, when they injected 2-Deoxy-D-glucose into mice by either the tail veins or the cerebral ventricles they found the latter route to be five times more potent in the production of hypothermia. They concluded that the exclusion of glucose from central rather than peripheral sites is the major determinant in hypothermia. Gale *et al*, however, showed that despite increased heat production in insulin induced hypo-

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thermia core temperature fell because of peripheral vasodilatation and sweating. Furthermore, central inhibition of shivering occurred when plasma glucose concentrations were below 2.5 mmol/l (45 mg/100 ml), resulting in more profound hypothermia. Intravenous glucose rapidly restored the shivering response.⁶

Awareness of the association between hypoglycaemia and hypothermia is clinically important. In the patient described correction of hypoglycaemia led to rapid restoration to normal body temperature. In some patients presenting with hypothermia the primary event may be hypoglycaemia. Where hypothermia and hypoglycaemia coexist the most appropriate treatment could be the immediate administration of intravenous glucose. Plasma glucose concentration should, therefore, be measured in all patients with hypothermia.

References

- ¹ Kedes LH, Field JB. Hypothermia: a clue to hypoglycaemia. *N Engl J Med* 1946;**271**:785-7.
- ² Vaidya AB, Levine RJ. Hypothermia in a patient with carcinoid syndrome during treatment with para-chlorophenylalanine. *N Engl J Med* 1971;**284**:255-7.
- ³ Strauch BS, Felig P, Baxter JD, Schimpff SC. Hypothermia in hypoglycaemia. *JAMA* 1969;**210**:345-6.
- ⁴ Anonymous. (Editorial.) *JAMA* 1969;**210**:340.
- ⁵ Freinkel M, Metzger BE, Harris E, Robinson S, Mager M. The hypothermia in hypoglycaemia. Studies with 2 deoxy-D-glucose in normal human subjects and mice. *N Engl J Med* 1972;**287**:841-5.
- ⁶ Gale EAM, Bennett T, Hilary Green J, MacDonald IA. Hypoglycaemia, hypothermia and shivering in man. *Clin Sci* 1981;**61**:463-9.

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Medicine in the United States

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I have never practised in the United States; what knowledge I have of medicine there comes largely from some 25 visits. I have been singularly fortunate in knowing a great many American medical scientists; I have shared the experiences of relatives and close friends who have been gravely ill in American hospitals; and perhaps my main excuse for daring to broach this subject lies in my having undergone an emergency operation in New York, from which I recovered only after two more operations in London and months of critical illness. Hence this account of the vast subject of medical education, practice, and research in the United States cannot avoid being both largely subjective and superficial.

The true comparison is not, of course, between the United States and the United Kingdom but between the United States and western Europe, where sadly—in contrast to the United States—the wealth of talent in medical science and clinical practice is not cooperatively exploited, to the detriment both of Europeans and also of the multitude of suffering families in our fragmented, sick, and pitiless world who look in vain to Europe for understanding and relief.

America's population

The United States is big, with a population about five times bigger than that of England and Wales. The expectancy of life is around 70 years for white and 63 for black men and 78 years for white and 72 for black women. Women exceed men in the population by about six million. The birth rate is fairly stable, with white women giving birth to 14/1000 and non-white women to 22/1000 population. The proportion of elderly citizens, as in other industrialised countries is rising appreciably; those over 65 constituted 9% of the population in 1970 and 11.2% in 1979 and are expected to exceed 12% before the end of the century.

The crude death rate is higher than that reported for Japan, Canada, and Australia but lower than that for the Scandinavian countries, France, Germany, and the United Kingdom. Though deaths from heart disease and infectious diseases have decreased significantly, deaths from cancer, homicide, and suicide have continued to increase. Infant mortality has fallen considerably throughout this century, from 162/1000 live births in 1900 to 47 in 1920, 20 in 1970, and 11.02 in 1983; it would be even lower if non-white women enjoyed the same standard of care as white women.

American people are extraordinarily mobile: up to a quarter of them may change their homes every year, many by distances of thousands of miles. The average national earned income appears to be about \$17 000 a year, but perhaps as many as 40 million Americans live on or below the poverty line (\$10 000 a year for a family of four), and, whatever may be said by the politicians, these people have notably higher levels of maternal and infant morbidity and mortality, are more often addicted to drugs, and suffer disproportionately from serious crime. Also, many have malnutrition, especially iron and vitamin A deficiency.

The gross national product of this huge, industrious nation is about \$2650 billion (nearly 35% of the world's gross national product); 10% of this has been estimated as the amount spent annually on health—a sum, for a population five times the size of that of England and Wales, equivalent to about £175 billion. Britain's National Health Service now costs around £14 billion a year, and that does not include the amount of money spent privately; but expenditure is not, of course, a full and accurate reflection of the quality and availability of care. Nevertheless, Americans do spend an extraordinarily large amount of money on doctors and hospitals.

Health problems

The main health problems in the United States are those to be expected in an industrialised, comparatively prosperous society. Heart disease is the chief killer, but individual Americans' self care, by controlling diet, taking exercise, and abstaining