Short report

Chronic hypothermia following tuberculous meningitis

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SUMMARY A patient who developed chronic hypothermia following tuberculous meningitis is described. A central defect of thermoregulation was discovered, probably due to a discrete vascular lesion in the anterior hypothalamus.

The long-term sequelae of tuberculous meningitis may be due to the development of hydrocephalus, the formation of tuberculomata, or cerebral infarction due to arteritis. We report a patient with tuberculous meningitis who, after resolution of the acute illness, developed a profound defect of memory and chronic hypothermia. Investigation revealed a central defect of temperature control, with preservation of the hypothalamic-pituitary axis. This suggested a lesion in the hypothalamus and pre-optic area, and to our knowledge has not previously been reported in association with tuberculous meningitis.

Case report

A 20 year old white student nurse presented to Middlesbrough General Hospital, in November 1977 with a five week history of malaise, headache and photophobia. She had also noticed double vision for a few days. On examination she was drowsy, but would respond appropriately to verbal comments. Her temperature was 38.5°C and she had marked neck stiffness, and bilateral sixth nerve palsies. She had no other neurological signs. Routine haematology revealed an ESR of 40 mm/hr. (Westergren), WBC of $13.5 \times 10^9/l$ with a neutrophil leucocytosis. The chest radiograph was normal, the serum sodium was 124 mmol/l, the other electrolytes being within the normal range. Lumbar puncture yielded clear cerebrospinal

fluid (CSF) at a pressure of 260 mm H₂O, with a glucose concentration of 1 mmol/l (blood glucose 4.5 mmol/l). The CSF contained 40×10^6 cells per litre, of which 65% were lymphocytes, but no organisms were seen on Gram and Ziehl-Nielsen stains. An electroencephalogram (EEG) revealed a bilateral excess of slow wave activity. A diagnosis of tuberculous meningitis was made, and the patients commenced on streptomycin 1 g daily, isoniazid 350 mg daily and rifampicin 450 mg daily. Subsequently, culture of the CSF confirmed the presence of mycobacterium tuberculosis sensitive to all three antibiotics.

The patient's progress was initially satisfactory; she became afebrile and the CSF protein and cell count returned to normal. However, she remained apathetic and her mentation was slow. Computed tomography (CT) was normal. During the next six weeks her mental state improved, but profound loss of short-term memory persisted. She was eventually discharged on rifampicin and isoniazid treatment. Both drugs were continued for 15 months.

In August 1979, the patient was readmitted after several grand mal seizures. On examination she was found to be drowsy, hypotensive (blood pressure 75/55 mmHg) and her rectal temperature was 33.5°C. Treatment with phenytoin was started. Blood pressure and temperature returned to normal within 24 hours, and her mental state returned to its previous level. Full blood count, plasma electrolytes and liver function tests, were normal and blood sugar, thyroxine, cortisol, follicular stimulating hormone, prolactin and growth hormone levels were also within the normal range. Urine osmolality was 760 mosmol/l kg. Throughout this admission the patient displayed intermittent disturbances of appetite and sleep. She would sleep by day, be active at night and at times had

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a voracious appetite. This behavioural disturbance gradually improved and she was discharged taking 250 mg phenytoin per day.

She remained well for the following two months, but was again admitted in November 1979, after having several major seizures. Once more she was drowsy, hypotensive and her rectal temperature was 32°C. On this occasion although her conscious level and blood pressure returned to normal, she remained hypothermic. The rectal temperature varied between 32°C and 34.5°C and was not improved by stopping her anticonvulsant drugs. The EEG was still diffusely disturbed but a repeat CAT scan was normal. Psychometry showed a verbal IQ of 74 (borderline subnormal range) and a performance IQ of 61 (mildly subnormal range) with a severe defect of short-term memory which was producing disorientation of time, place, person and current events. Old rote learning processes were well preserved but she had problems with comprehension, logical thinking and motor co-ordination. Further investigations of the hypothalamic and pituitary function, cardiovascular reflexes and thermoregulatory status were carried out.

Hypothalamic and pituitary function

Plasma cortisol rose from 270 nmol/l to 810 nmol/l and plasma growth hormone rose from 2.6 mu/l to 4.4 mu/l after intravenous insulin (0.15 u/kg). Serum thyroxine was 98 nmol/l and T_3 uptake 28.1% (normal). After administering intravenous thyroid releasing hormone (200 µg),³ thyroid stimulating hormone concentration rose from 1.9 mu/l to 9.9 mu/l and plasma prolactin concentration from 489 nu/l to 3357 nu/l. Urinary 17 beta oestradiol was in the pre-ovulatory range (125 pmol/l), and after intravenous injection of 100 mcg luteinising hormone releasing hormone, luteinising hormone concentrations rose from 11.6 u/l to greater than 50 u/l with a rise in follicle stimulating hormone from 15.4 u/l to 34.0 u/l. Urinary circadian rhythms were examined by the method of Payne and De Wardener.¹ Excretion of the solutes, sodium and potassium showed normal diurnal variation.

Cardiovascular reflexes

Blood pressure was examined from recordings from the femoral artery and blood flows by forearm and hand plethysmography. Normal responses were obtained to Valsalva's manoeuvre and to ice on the neck, but there was no response to sudden loud noise. Mental arithmetic (serial subtraction with harassment) caused reflex peripheral vasoconstriction (hand blood flow 15 ml/100 ml/min to 3.6 ml/100 ml/min).

Thermoregulatory reflexes

Continuous recording of rectal temperature over 72 hours showed no circadian temperature rhythm, but a gradual increase in deep body temperature from 33.9°C to 35.4°C. Intravenous injection of bacterial pyrogen (as a sterile suspension of killed organisms; 10 million *Salmonella typhi*, 5 million *S. paratyphi A*

and 5 million *paratyphi B*) produced a rise in deep body temperature of 2.6°C. Maximum temperature (37°C) was recorded 3½ hours after the injection of pyrogen. Resting hand blood flow at a rectal temperature of 35°C, and a plethysmograph temperature of 34°C, was 18.8 ml/100 ml/min (normal range at this temperature 2–8 ml/100 ml/min). Oxygen consumption at rest was 54 ml/min¹m² (predicted 118/ml min¹m²). Thermoregulatory reflex sensitivity was investigated by measuring the ratio of oral temperature response (°C minutes) to measured heat loads (cal/kg body weight) using the technique described by Cooper, Cranston, and Snell.² Sensitivity was expressed as °C min cal⁻¹kg⁻¹, and three separate measurements yielded values of 0.12, 0.04, 0.11°C min cal⁻¹kg⁻¹. This is grossly abnormal when compared to the results of normal subjects (0.017±0.006°C min cal⁻¹kg⁻¹). Deep body temperature was raised by heating the patient with an electric blanket and sweat loss was measured continuously over the patient's right shoulder. Sweat onset point was 36.5°C.

Discussion

The reported cases of hypothermia due to neurological disease form two separate groups. Periodic hypothermia first described by Penfield³ has been called diencephalic epilepsy. In this, and other reports,^{4–6} the hypothermia is usually associated with sweating and cutaneous vasodilation. Recurrent episodic hypothermia has also been noted to accompany agenesis of the corpus callosum.^{7,8} These patients also exhibited profuse sweating, and a personality change associated with the fall in body temperature. Their disturbance of body temperature has also been described as diencephalic epilepsy.

A second group is composed of patients with chronic, persistent, hypothermia. Bauer⁹ reviewed 60 cases of hypothalamic disease, of which 17 had a defect of temperature regulation. Thirteen were due to neoplastic lesions, two followed undefined meningoencephalitis, and the remainder appeared to be due to degenerative changes in the hypothalamus. Subsequent reports^{10–12} have examined thermoregulatory function in more detail: three patients had defective temperature control resulting in poikilothermia, whilst in another two, the authors concluded that their temperature regulation mechanisms were "reset" at a lower level than normal.

Our patient had chronic, persistent hypothermia with no evidence of any episodic phenomena which are characteristic of diencephalic epilepsy. She had normal cardiovascular reflexes but an absent circadian temperature rhythm. Her

oxygen consumption at rest, and her cutaneous blood flow, were inappropriate to her "core" temperature. She showed marked thermoregulatory reflex insensitivity. These are all features of poikilothermia, rather than of a lowered temperature "set-point." She does, however, retain some thermoregulatory function as shown by her normal "sweat-onset" point, and her response to bacterial pyrogens. The patient's chronic hypothermia has probably resulted from tuberculous arteritis which has involved the anterior hypothalamus. Other hypothalamic functions which were investigated were normal, but her severe defect in short-term memory and intellectual impairment suggests that the disease process was diffuse. There was no improvement in her mental function when her body temperature was raised to 37.2°C so that attempts to maintain her body temperature within normal limits would have little therapeutic value. At the present time the only reasonable manoeuvres were considered to be the avoidance of cold and maintenance of a thermoneutral environmental temperature.

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