Hypothermia in multiple sclerosis

K D White, D J Scoones, P K Newman

Abstract

Five patients with clinically definite multiple sclerosis are reported who presented with acute relapses associated with hypothermia. Repeated episodes of hypothermia were seen in four. Thrombocytopenia was associated with the hypothermia in four patients. Further investigation disclosed a tendency to chronic hypothermia and suggested an altered thermoregulatory set point in one patient, when MRI, endocrine, and autonomic studies failed to localise a lesion in the hypothalamus, but subsequent necropsy showed hypothalamic lesions. In such patients a predisposition to altered thermoregulation may occur due to direct involvement of the hypothalamus or from combined lesions affecting hypothalamic outflow to the brainstem and spinal cord.

(*J Neurol Neurosurg Psychiatry* 1996;61:369-375)

Keywords: hypothermia; multiple sclerosis; thrombocytopenia; hypothalamus

The ability of humans to precisely thermoregulate body temperature around 37°C is a complex process.^{1,2} Simplified, the system consists of peripheral thermoreceptors that relay afferent signals to central integrating mechanisms. Central and peripheral thermal information are thought to be integrated at various CNS sites, each of which can facilitate or inhibit other sites, which are hierarchically arranged. Integrators compare the information with that from internal thermosensitive cells and if necessary activate behavioural and autonomic mechanisms via efferent channels.^{3,4} Animal studies have shown that lower centres including the brainstem and cervical cord have the capability to mount independent responses to thermal stimuli.⁵⁻⁸ The hypothalamus acts as the chief integrator which coordinates the activity of the other centres. Discrete lesions of the anterior hypothalamus can lead to either hyperthermia or hypothermia, whereas lesions in the posterior hypothalamic nucleus tend to produce hypothermia. Hypothermia may also occur when there is damage to the reflex thermoregulatory pathways traversing the brainstem or spinal cord.^{7,9-14} Reports of disorders of control of temperature in patients with multiple sclerosis are few.¹⁵⁻²¹ Although plaques of demyelination affecting the hypothalamus have been described at necropsy, this occurs

only rarely²² and there has only been indirect evidence implicating disturbance of this structure in patients with hypothermia.¹⁶ In this report we present five cases of multiple sclerosis in which hypothermia was associated with relapses in the condition and additionally necropsy evidence of involvement of the hypothalamus in one patient with recurrent hypothermia.

Case reports

CASE 1

A 48 year old man with clinically definite multiple sclerosis for five years (Kurtzke disability scale 6)²³ was admitted in December 1991. Since diagnosis he had experienced several relapses with clinical involvement of the spinal cord and brainstem with some response to steroid treatment. During a two year period of azathioprine treatment, there had been a reduction in the number of relapses and no haematological abnormality had been detected. After this two year period the azathioprine was discontinued. Three months later he required admission because of three weeks of deteriorating mobility, with slurred speech, confusion, and disorientation. For 10 days before admission, he had become increasingly withdrawn and drowsy. In retrospect his wife had noticed that he had started to snore at night and that his feet were unusually cold.

On admission he was in stupor; there was increased tone in the upper limbs and a flaccid paraparesis. The axillary temperature was 36°C. An initial diagnosis of acute relapse of multiple sclerosis was made and he was treated with intravenous methylprednisolone. Haemoglobin was 12.7 g/dl, white blood cells $8.7 \times 10^9/l$, platelets $27 \times 10^9/l$, serum sodium 140 mmol/l, and urea 8.9 mmol/l. Treatment was started with cefuroxime on the assumption that there may have been a precipitating infection from the urinary tract. Over 48 hours he steadily deteriorated, becoming mute, with neck stiffness, agitation, repetitive facial twitching, left lower motor facial weakness, and decerebrate posturing. Haemoglobin was 9.9 g/dl, white blood cells $5.8 \times 10^9/l$, and platelets $19 \times 10^9/l$. Brain CT showed a moderate degree of cerebral atrophy; CSF was normal. A fall in respiratory rate was followed by periods of apnoea, whereupon ventilatory support was commenced and continued for 11 days. At the start of assisted ventilation rectal temperature was 31°C. Rewarming returned the core temperature to normal within 48

Department of
Neurology,
Middlesbrough
General Hospital,
Cleveland, UK
K D White

Department of
Neuropathology,
Newcastle General
Hospital, Newcastle
upon Tyne, UK
D J Scoones

Middlesbrough
General Hospital,
Middlesbrough,
Cleveland, UK
P K Newman

Correspondence to:
Dr K D White, Department
of Neurology,
Middlesbrough General
Hospital, Middlesbrough,
Cleveland, UK.

Received 29 January 1996
and in revised form
23 May 1996
Accepted 4 June 1996

hours and a return to normal conscious level occurred after four days. Thrombocytopenia persisted for 10 days. Excessive bleeding from around central and peripheral lines (prothrombin time (PT) ranging from 13–16 seconds and kaolin cephalin clotting time (KCCT) 49–56 seconds, platelet antibodies absent) necessitated transfusion of packed cells, platelets, and plasma protein fraction. Vitamin B12 was normal (690 nmol/l) but blood folate (1.4 µg/l) and red cell folate (66 µg/l) were low. The bone marrow showed increased megakaryocytes and features which were consistent with folate deficiency. Autoantibody titres (including antinuclear factor, rheumatoid factor, antimitochondrial, gastric parietal cell, smooth muscle, reticulins, thyroid microsomal, thyroglobulin antibodies) were negative.

Recovery rapidly ensued but the patient was left with a residual spastic paraparesis and sensory level to T 12, mild upper limb weakness, and incoordination. He returned home 30 days after admission and within two weeks had returned to work and was able to walk short distances with a stick. On discharge haemoglobin was 13.2 g/dl, white blood cells $7.6 \times 10^9/l$, platelets $208 \times 10^9/l$.

Six weeks after discharge the patient was readmitted after a recurrence of the original symptoms, with slurred speech, forgetfulness, and lethargy. Rectal temperature was 32.3°C. Neurologically there was facial asymmetry, left upper limb incoordination, and a worsening of the spastic paraparesis. Thrombocytopenia and clotting abnormalities were again documented (platelets $84 \times 10^9/l$, prothrombin time 13 s, KCCT 60 s) which corrected with rewarming. Close observation of rectal temperature over six days disclosed an inversion of the normal circadian rhythm, with a peak of 37°C between 6 00 and 10 00 am and lowest temperatures between 6 00 and 10 00 pm. More detailed thermoregulatory studies were declined by the patient. At discharge 14 days later platelets had risen to $294 \times 10^9/l$ and white blood cells to $9.9 \times 10^9/l$, but a slight fall in haemoglobin to 10.3 g/dl was noted. Over subsequent months rectal temperature measured at home ranged from 35 to 36.5°C. At temperatures above this there was a pronounced decline in functional lower limb power, from weight bearing to non-weight bearing.

Brain MRI in 1987 had been normal. Repeat imaging after both episodes of hypothermia, including administration of gadolinium on the second occasion, showed multiple high signal lesions in the periventricular white matter, but no plaques were detected in the region of the hypothalamus. No evidence of hypopituitarism was detected on formal dynamic endocrinological assessment. Blood pressure and heart rate response to Valsalva's manoeuvre and blood pressure response to standing were normal. There were borderline abnormalities of the 30:15 heart rate response to standing and beat to beat variation on deep breathing was reduced to a heart rate change of 8.5 beats per minute.

For the first year after these episodes the patient's condition remained stable. However, hypothermia became a recurrent problem in the winter months followed by further deterioration with dysmnnesia, periods of confusion, hypersomnolence leading to dementia, aphagia, and subsequent death. At necropsy the brain weighed 1350 g and showed no external abnormality. Plaques of demyelination were found in the typical periventricular distribution as well as in the midbrain, pons, and medulla. In addition there were plaques throughout the hypothalamus including the area of the posterior hypothalamic nucleus (figure).

CASE 2

A 59 year old man with a 30 year history of multiple sclerosis (clinically definite and laboratory supported, Kurtzke disability score 7), who was previously noted to have a spastic paraparesis, cerebellar signs, and mild dysarthria, presented in November 1993 with an insidious onset over four weeks of increasing fatigue, lethargy, and slowness of thought, which progressed to increasing drowsiness, dysphagia, and dysarthria. On admission he was in stupor with a rectal temperature of 33°C. Investigations showed a platelet count of $94 \times 10^9/l$, haemoglobin 11.5 g/dl, white cell count $7.0 \times 10^9/l$, and serum sodium 142 mmol/l. He was treated with passive rewarming and intravenous fluids and normothermia was achieved within 36 hours. Despite a further fall in platelets to $79 \times 10^9/l$ after 24 hours, the platelet count returned to normal within four days. His clinical recovery was complicated by a paranoid psychosis and confusion for 17 days, severe left ventricular

Section through half of the hypothalamus at the level of the mammillary bodies. (Luxol fast blue and cresyl fast violet originally $\times 5$.) Section shows two areas of demyelination. p = Plaques; pn = posterior nucleus of hypothalamus; v = third ventricle; mb = mammillary body.

failure, and myocardial infarction. Core temperature remained normal throughout this time. The disability status at discharge had increased to Kurtzke scale 8 and mentally he remained rather vague and intermittently confused. One further episode of hypothermia has since been treated.

CASE 3

A 57 year old woman with a 20 year history of clinically definite multiple sclerosis (Kurtzke disability scale 7) was admitted in March 1992 with deteriorating mobility, lethargy, and intermittent dysphagia. On admission she was oriented but over two weeks her conscious level deteriorated. Skin temperature was normal. On transfer to the neurology unit she would open her eyes spontaneously and localise pain, but the only verbal response was grunting. There was bilateral optic atrophy and absence of oculocephalic responses but no other specific cranial nerve abnormalities. She had pronounced neck stiffness, general rigidity, and a spastic tetraparesis. Her core temperature was 35°C. She was rewarmed, given intravenous fluids, methylprednisolone, and antibiotics for respiratory and urinary infections. The temperature returned to normal within 24 hours. On admission haemoglobin was 12.1 g/dl, white cells $11.5 \times 10^9/l$, and platelets $141 \times 10^9/l$. Mild hyponatraemia was noted (serum sodium concentration 130 mmol/l). Plasma viscosity was increased at 2.17 cp. Clotting was abnormal with a slight prolongation of KCCT of 52 seconds and a minor increase in fibrin degradation products at 1.0 µg/ml (normal ≤ 0.5 µg/ml). A transient thrombocytopenia of $99 \times 10^9/l$ became apparent 24 hours after admission and returned to normal within 48 hours. An EEG was abnormal at the time of reduced conscious level, with diffuse delta and theta slow wave activity. Brain CT disclosed bilateral periventricular low density lesions in keeping with her longstanding multiple sclerosis. Protein in CSF was normal. Platelet associated antibody was raised at a level of 2.2 (normal < 1.6), antinuclear factor was positive with a speckled pattern at a titre of 1:160, with DNA antibodies negative and rheumatoid factor positive at a titre of $> 1:320$. IgM anticardiolipin antibody binding was borderline positive but IgG was negative. After improvement in conscious level she remained confused for nine days before regaining her premorbid mental state. A return to her previous physical level of function was achieved after one month. A second episode of hypothermia occurred nine months later and was detected after one week of progressive lethargy and dysarthria. Her rectal temperature was 34°C and she was conscious and oriented, although slightly slow in responses and confused. Neck stiffness was absent. There was evidence of a right internuclear ophthalmoplegia, cerebellar dysarthria, spastic tetraparesis, and upper limb cerebellar signs, all of which were longstanding. With rewarming there was an improvement in mental function and she was discharged after only six days. This patient's disease was of long

duration and clinically typical of multiple sclerosis with early relapses and remissions. Whether the presence of the autoantibodies is relevant is uncertain given the patient's age, but the pattern of early relapses and remissions was considered to be more in keeping with a diagnosis of multiple sclerosis than cerebral lupus erythematosus. Cerebral lupus erythematosus seemed less likely in view of the negative double stranded DNA antibodies, negative IgG anticardiolipin antibody, normal complement levels, and the distribution of the lesions on CT. Extraneurological features, particularly polyarthropathy, had never been present.

CASE 4

A 64 year old woman with clinically definite multiple sclerosis for 30 years (Kurtzke disability scale 9) was admitted in November 1993. Since diagnosis she had had many relapses and remissions with involvement of optic nerves, spinal cord, and brainstem. Over the previous eight years there had been a progressive physical decline. On this occasion she presented with a three month history of deteriorating upper and lower limb function, episodes of speech disturbance, and peripheral oedema. Three days before admission she was found unconscious and at her local hospital her conscious level remained depressed for 12 hours before there was a spontaneous, fluctuating, improvement. On transfer the rectal temperature was 34.7°C, she was alert although disoriented, with peripheral and periorbital oedema, optic atrophy, and nystagmus. Impaired palatal movement was a new feature and there had been a significant deterioration in the tetraparesis. Mild hyponatraemia (sodium concentration 130 mmol/l) was noted with normal urinary and plasma osmolalities, which corrected with fluid restriction. Cortisol and thyroid function were normal. Full blood count was normal. An EEG showed diffuse delta and theta activity which improved on rewarming. Temperature returned to normal without active treatment within 24 hours, although her mental state did not return to normal for seven days. Her functional capacity had returned to its previous level by the time of discharge. No further episodes of hypothermia have occurred.

CASE 5

A 47 year old woman was admitted to a medical unit with a few days history of withdrawal, lethargy, and then lapsing into coma. She had led a reclusive existence, and 12 years earlier had been admitted to a psychiatric unit with blurred vision, sensory symptoms, and difficulty in walking, labelled as hysterical in view of associated psychological disability. On the current admission she was unrousable, had neck stiffness, generalised hypertonia, and a rectal temperature of 29°C. There was no evidence of drug overdose and her biochemistry, including thyroid function and cortisol, was normal. Haemoglobin concentration was 10.2 g/dl, white cell count $8.5 \times 10^9/l$, platelets $33 \times 10^9/l$, and serum sodium con-

centration 143 mmol/l. Gentle rewarming led to a gradual return to normothermia over three days, at which time she was conscious but confused and neurological evaluation showed bilateral optic disc pallor, mild limb incoordination, mild paraparesis, and bilateral extensor plantar responses. The platelet count returned to normal. Subsequent investigation showed bilateral delay of P₁₀₀ latency of visual evoked potentials and a high CSF IgG index with oligoclonal bands in the CSF but not in the serum. Brain MRI showed diffuse cortical atrophy with multiple hyperintense periventricular lesions on T2 weighted sequences but without abnormality in the region of the hypothalamus. Initially EEG showed a generalised encephalopathic picture with widespread theta and delta activity, but this subsequently improved to a mixture of alpha and theta components. Chest radiography was normal and autoantibodies were negative.

On discharge from hospital after one month the patient was normothermic, disinhibited, and garrulous with mild cognitive blunting. She had slight gait ataxia, pale optic discs, and a right extensor plantar response.

Thus this patient had presented with hypothermia and a new diagnosis of multiple sclerosis was made after a review of the history, the current neurological findings, and results of investigations. A second episode of hypothermia occurred 11 months later after one week of increasing drowsiness, anorexia, and unsteadiness. Her rectal temperature was 34°C and she was drowsy and confused. There was nystagmus on horizontal gaze, decorticate posturing of the upper limbs, and a spastic tetraparesis with bilateral extensor plantar responses. Core temperature returned to normal after 48 hours and she was discharged eight days later with return to her previous neurological status.

Discussion

Impairment of consciousness in multiple sclerosis is well recognised, if uncommon, but previously only seven patients have been reported with relapses of their multiple sclerosis with obtundation which has been associated with hypothermia.^{15-18 20} We present four patients seen in a three year period from one neurology unit and a fifth case from a nearby unit, which led us to believe that it is probably more common than previously recognised. The patients share common features which might suggest which are more at risk of this complication. All of our patients presented with an insidious neurological decline, associated with depressed conscious level and considerable hypothermia. Each had multiple sclerosis of at least five years duration and all but one were very disabled (Kurtzke EDSS $\geq$ 6). All displayed signs during the acute relapse suggesting an active lesion in the brain stem and in four patients signs consistent with brainstem involvement had previously been noted. From the available histories it is likely that the periods of hypothermia exceeded one week. All responded to rewarming within 48 hours.

Improvement in cognitive function lagged behind establishment of normothermia, with confusion persisting for up to 17 days. Four patients had repeated episodes of hypothermia and in two chronic hypothermia developed.

Normal thermoregulation relies on peripheral thermoreceptors in skin and the upper gastrointestinal tract, which send afferent signals via the cervical cord, brainstem, and thalamocortical system to the cortex for conscious appreciation of ambient temperature.¹ Thermoregulation occurs at several levels or centres, the hypothalamus, including the preoptic area, the anterior and posterior hypothalamus, brainstem, and cervical cord.²⁻⁶ Afferent cold impulses synapse in the posterior hypothalamic heat maintenance centre, not only with efferent pathways initiating heat production but also with cells which receive inhibitory impulses from the anterior hypothalamus in response to local warming. The anterior hypothalamic heat loss centre is situated near the preoptic nuclei and destruction of this area in animals results in normal temperature in cold but overheating in hot environments.^{7 8} The anterior hypothalamic efferent impulses for heat dissipation are mediated by the sympathetic nervous system, which induces sweating and vasodilatation. The site of the thermostat in humans has been variously considered to be in either the anterior or posterior hypothalamus and even the whole brainstem.¹ Reflex thermoregulatory pathways that function independently of this central control have been shown to pass through the brainstem and cervical cord.²⁴ The raphe nuclei are key sites for the integration of peripheral and central thermal stimuli, and in processing information ascending to the preoptic/anterior hypothalamic area (POAH). Many of these neurons seem to be warm sensitive.⁹ Animal studies provide evidence for predominantly cold responsive neurons in the pontine dorsomedial reticular formation of the guinea pig¹⁰ and in the rat the medulla itself has cold receptors, which when damaged result in chronic hypothermia.⁷ Thermoregulation studies on lesions in rat brains concluded that communication between the preoptic(PO) and anterior hypothalamic(AH) nuclei is necessary for normal thermoregulation at extremes of temperatures and similar effects to those seen with destruction of the PO/AH could be produced by cutting the neural connections between the PO/AH and other brain structures. However, a secondary central temperature control system was indicated by the ability of the rats to maintain regulation of temperature in a neutral environment despite large lesions destroying the medial preoptic region and the anterior hypothalamic tissue. Isolated lesions of the medulla resulted in a profound fall in body temperature in some animals, inability to regulate against cold rather than heat in others, and a reduction of resting body temperature in some animals.⁷ Other studies in rats suggested that lesions which prevented cold induced vasoconstriction but did not impair heat induced vasodilatation must be separately controlled at

Clinical features of patients with hypothermia and multiple sclerosis

Patient No	Reference No	Age/sex	Kurtzke score	Rectal temp (°C)	Neck stiffness	Myoclonus	Conscious level	Brain stem signs	Platelet count $\times 10^9/l$	Recurrent hypothermia
1	15	61/F	10	29.4	NK	NK	+++	Yes	19	No
2	16	41/F	7	32.9	No	No	+	NK	61	Yes
3	16	52/F	8	31.0	No	No	+++	NK	50	Yes
4	17	55/F	6	33.0	Yes	Yes	+++	No	80	Yes
5	17	52/M	7	32.5	No	No	+	Yes	100	Yes
6	17	49/F	6	32.0	Yes	Yes	+	No	Normal	Yes
7	18	38/F	6	32.0	No	No	++	Yes	Normal	Yes
8	20	63/F	4	32.4	NK	No	++	NK	Normal	No
9	20	68/F	6	31.6	NK	No	++	Yes	Normal	No
10	*	48/M	6	31.0	Yes	Yes	++	Yes	27	Yes
11	*	59/M	7	33.0	No	No	++	Yes	95	Yes
12	*	57/F	7	35.0	Yes	No	++	Yes	99	Yes
13	*	64/F	9	34.7	No	No	+	Yes	172	No
14	*	47/F	3	29.0	Yes	No	+++	Yes	33	Yes

*Patients in current series. Conscious level: + = confused, ++ = stupor, +++ = coma; NK = not known.

a site more caudal than the POAH, possibly in the medulla.⁸ Based on electrical stimulation of the CNS and lesion studies it has been proposed that thermoregulation involves the connection of multiple integrators and multiple thermostats at many levels of the neuraxis which have evolved to enable very fine control of temperature regulation.² That this is likely in humans is suggested by the array of different neuroanatomical sites associated with hypothermia. It is well documented that patients with high cervical cord injury can develop hypothermia due to impaired peripheral sensitivity to ambient temperature, lack of shivering response, and lack of vasoconstriction when lesions above T1 are present.²⁵ Hypothermia is recognised in various neurological disorders other than multiple sclerosis.²⁶⁻⁴⁰

O'Brien *et al*¹⁵ reported a patient with terminal multiple sclerosis and hypothermia, stressing the haematological effects of hypothermia, but not the possible causative link with multiple sclerosis. Sullivan *et al*¹⁶ first reported hypothermia associated with multiple sclerosis in two patients. Lammens *et al*¹⁷ reported three patients with whom hypothermia was associated with both exacerbation of pre-existing and the development of new neurological signs. Geny *et al*²⁰ reported hypothermia in two patients with multiple sclerosis. Both had cerebellar and pyramidal signs, confusion, and psychomotor slowing and one also developed a partial lateral rectus palsy. Neither had any history of alcoholism or severe dietary restriction, although one had refused meat for a month. Despite the fact that these signs could be accounted for by a combination of multiple sclerosis and hypothermia, Geny *et al* concluded that both patients had Wernicke's encephalopathy.²⁰ Further evidence for this was proposed by the poor initial response to passive rewarming and subsequent normalisation of temperature on day two after treatment with thiamine. It could be argued that this was a coincidence as normalisation of core temperature after pronounced hypothermia does not occur in 24 hours and may have occurred despite the thiamine. However, in one patient when thiamine was withdrawn there was a pronounced drop in core temperature which returned to normal with the reintroduction of thiamine. This has been noted previously.³⁷

Ghawache and Destee¹⁸ reported a patient who had three separate episodes of hypothermia 14 years after the onset of multiple sclerosis. Hypothermic episodes correlated closely with aggravation of spastic paraparesis and a consistent inappropriate antidiuretic hormone secretion. Brain MRI did not show any evidence of hypothalamic plaques and there was no other endocrine evidence of hypothalamic disturbance. Unlike our patients, there was no significant deterioration in clinical status after the hypothermic episodes. By contrast, thermoregulatory abnormality resulting in hyperthermia has been reported in multiple sclerosis and in one case pathological evidence was found of plaques involving the lateral and posterior hypothalamus.¹⁹ The table summarises clinical data from patients with multiple sclerosis and hypothermia.

In a condition in which there are known to be multiple lesions it is difficult to implicate a single anatomical site as being responsible for the thermoregulatory abnormality. Sullivan *et al*²⁰ presented evidence of a central thermoregulatory centre lesion with a fall in core temperature and a restricted skin vasoconstrictor response to cooling in their patients. The hyponatraemia seen in one patient suggested that the lesion was likely to lie in the hypothalamus. In our patients thermoregulatory studies were not possible. An inversion of the normal circadian rhythm of temperature was seen in the first case, suggesting a central disturbance but MRI on two occasions after episodes of hypothermia did not show any lesions in the region of the hypothalamus, a negative finding also noted by Geny *et al*²⁰ and Lammens *et al*.¹⁷ Furthermore, postmortem examination in one of the patients failed to show any hypothalamic plaques. Similarly in a postmortem report by Nagashi *et al*²¹ of a patient with coexistent pituitary hypothyroidism and Devic's disease no lesions were seen involving the hypothalamus. As far as we are aware patient 1 is the first reported patient in which hypothermia has occurred with multiple sclerosis and subsequent necropsy has shown direct involvement of the hypothalamus by plaques of demyelination. We think that it is possible that in some patients the thermoregulatory abnormalities are due to brain stem disease, for which clinical evidence was seen in all of our patients. In patient 1 there were also borderline abnormalities of auto-

onomic function. Previous studies of autonomic function in patients with multiple sclerosis have shown that abnormalities of cardiovascular regulation and thermoregulatory sweating are common, and abnormal sweating responses correlate with more severe disease or presence of impotence⁴¹⁻⁴³ and brainstem disease.⁴⁴ In syringomyelia and syringobulbia subclinical disturbances of autonomic function were commonly found when there was evidence of brainstem involvement.⁴⁵ Isolated lesions of the brainstem producing hypothermia have occurred with central pontine myelinolysis¹¹ and mesodiencephalic haematoma.¹² Brainstem involvement was a common feature of our patients, not in itself unusual, but suggesting that such patients with widespread disease may have a predisposition to hypothermia, related to brainstem disease, impaired peripheral response, lack of shivering with cervical cord involvement, and possibly involvement of the preoptic/anterior hypothalamic junction and are associated with a poor outcome.

Thrombocytopenia as seen in patients with hypothermia and multiple sclerosis has been reported in other cases of accidental and spontaneous hypothermia.⁴⁶⁻⁴⁷ Initially noted in early cardiac surgery patients who were cooled to 20°C, it is thought to occur due to sequestration of platelets in the spleen as was shown in studies of labelled platelets in dogs.⁴⁸⁻⁴⁹ However, in patients with recurrent hypothermia there may be a deleterious effect on haemopoiesis causing thrombocytopenia.¹⁵ Information on patients in intensive care units suggests that hypothermia may contribute to the multifactorial coagulopathy seen in the critically ill multiple transfused patient.⁵⁰ A temperature effect on the enzyme coagulation cascade is implied. In a patient with multiple sclerosis and thrombocytopenia occult hypothermia should be considered.

In conclusion we have reported five patients with multiple sclerosis who presented over a three year period and had relapses associated with subacute hypothermia followed by chronic hypothermia in two cases. This complication may be more widespread than previously recognised and relates to duration of disease and possibly presence of brainstem involvement. Complaints of drowsiness, confusion, and snoring should lead to recording of temperature with a low reading rectal thermometer. Thrombocytopenia may be an indicator of unsuspected hypothermia.

We thank Dr RA Shakir, Dr P Tilley, and Dr TJ Walls for allowing us to report on their patients and to Dr DJ Burn for his helpful comments on this manuscript.

- 1 Maclean D, Emslie-Smith D. Regulation of body temperature. In: *Accidental hypothermia*. Oxford: Blackwell, 1977: 14-56.
- 2 Hensel H. Principles of temperature regulation. In: *Thermoreception and temperature regulation*. London: Academic Press, 1981:5-17. (Monographs of the Physiological Society No 38.)
- 3 Satinoff E. Neural organization and evolution of temperature regulation in mammals. *Science* 1978;201:16-22.
- 4 Hensel H. Central thermoregulatory connections. In: *Thermoreception and temperature regulation*. London: Academic Press, 1981:139-54. (Monographs of the Physiological Society No 38.)
- 5 Jessen C. Thermal afferents in the control of body temperature. In: E Schönbaum, P Lomax, eds. *Thermoregulation, physiology, and biochemistry*. London: Pergamon Press, 1990:153-84.
- 6 Crawshaw LJ, Wollmuth LP, O'Connor CS, Rausch RN, Simpson L. Body temperature regulation in vertebrates: comparative aspects and neuronal elements. In: E Schönbaum, P Lomax, eds. *Thermoregulation, physiology, and biochemistry*. Pergamon Press, 1990:153-84.
- 7 Lipton JM, Dwyer PE, Fossler DE. Effects of brainstem lesions on temperature regulation in hot and cold environments. *Am J Physiol* 1974;226:1356-7.
- 8 Gilbert T, Blatteis CM. Hypothalamic thermoregulatory pathways in the rat. *J Appl Physiol* 1977;43:770-7.
- 9 Gordon CJ, Heath JE. Integration and central processing in temperature regulation. *Ann Rev Physiol* 1986;48: 595-612.
- 10 Hinkel P, Schroder-Rosenstock K. Responses of pontine units to skin-temperature in the guinea pig. *J Physiol* 1981;314:189-94.
- 11 D'Anglejan Chatillon J, Broussier PM, Boukoba M, Pannier I. Hypothermie au cours d'un syndrome de Gayet-Wernicke et myélinolyse centropontine infraclinique. *La presse medicale*, 1988;17:1858.
- 12 Gaymard G, Cambon H, Dormont D, Richard A, Derouesne C. Hypothermia in a mesodiencephalic haematoma. *J Neurol Neurosurg Psychiatry* 1990;53: 1014-7.
- 13 Pledger HG. Disorders of temperature regulation in acute traumatic tetraplegia. *J Bone Joint Surg* 1962;44:110-3.
- 14 Menard MR, Hahn G. Acute and chronic hypothermia in a man with spinal cord injury: environmental and pharmacologic causes. *Arch Phys Med Rehabil* 1991;72:421-4.
- 15 O'Brien H, Amess JAL, Molin DL. Recurrent thrombocytopenia, erythroid hypoplasia and sideroblastic anaemia associated with hypothermia. *Br J Haematol* 1982;51: 451-6.
- 16 Sullivan F, Hutchinson M, Bahandeka S, Moore RE. Chronic hypothermia in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1987;50:813-5.
- 17 Lammens M, Lissioir F, Carton H. Hypothermia in three patients with multiple sclerosis. *Clin Neurol Neurosurg* 1989;91:117-21.
- 18 Ghawche F, Destee A. Hypothermie et sclérose en plaques, un cas avec trois épisodes d'hypothermie transitoire. *Rev Neurol (Paris)* 1990;146:767-9.
- 19 Castaigne P, Escourelle R, Laplane D, Augustin P. Comas transitoires avec hyperthermie au cours de la SEP. *Rev Neurol* 1966;114:147-50.
- 20 Geny C, Pradat PF, Yulis J, Walter S, Cesaro D, Degos JD. Hypothermia, Wernicke encephalopathy and multiple sclerosis. *Acta Neurol Scandinavica* 1992;86:632-4.
- 21 Nagashima T, Yamada K, Uono M, Nagashima K. Multiple sclerosis co-existent with myxoedema. An autopsy case report. *J Neurol Sci* 1984;66:217-21.
- 22 Brownell B, Hughes T. The distribution of plaques in the cerebrum in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1962;25:315-20.
- 23 Kurtzke JF. Further notes on disability evaluation in multiple sclerosis with scale modifications. *Neurology* 1961;15:654-61.
- 24 Johnson RH, Delahunt JW, Robinson BJ. Do thermoregulatory reflexes pass through the hypothalamus?—studies of chronic hypothermia due to hypothalamic lesion. *Aust NZ J Med* 1990;20:154-9.
- 25 Attia M, Engel P. Thermoregulatory set point in patients with spinal cord injuries (spinal man). *Paraplegia* 1983; 21:233-48.
- 26 Shapiro WR, Williams GH, Plum F. Spontaneous recurrent hypothermia accompanying agenesis of the corpus callosum. *Brain* 1969;92:423-36.
- 27 Editorial. Episodic hypothermia. *Lancet* 1973;ii:246-7.
- 28 Summers GD, Young AC, Little RA, Stoner HB, Forbes WSTC, Jones RAC. Spontaneous periodic hypothermia with lipoma of the corpus callosum. *J Neurol Neurosurg Psychiatry* 1981;44:1094-9.
- 29 Carr-Locke D, Millac P. Diencephalic epilepsy in a patient with agenesis of the corpus callosum confirmed by computerised axial tomography. *J Neurol Neurosurg Psychiatry* 1977;40:808-14.
- 30 Dick DJ, Sanders GL, Saunders M, Rawlins MD. Chronic hypothermia following tuberculous meningitis. *J Neurol Neurosurg Psychiatry* 1981;44:255-7.
- 31 Fox RH, Davies TW, Marsh FP, Ulrich H. Hypothermia in a young man with an anterior hypothalamic lesion. *Lancet* 1970;ii:185.
- 32 Gray HH, Smith LDR, Moore RH. Idiopathic periodic hypothermia and bizarre behaviour in the presence of occult syringomyelia. *Postgrad Med J* 1986;62:289-90.
- 33 Joshi VV, Chaudhuri A, Karnand DR, Tilve GH. Hypothermia due to transient hypothalamic dysfunction in tuberculous meningitis with hydrocephalus. *Br J Neurosurg* 1992;6:385-8.
- 34 Ratcliffe PJ, Bell JL, Collins KJ, Frackowiak RS, Rudge P. Late onset post-traumatic hypothalamic hypothermia. *J Neurol Neurosurg Psychiatry* 1983;46:72-4.
- 35 Griffiths AP, Henderson M, Penn NED, Tindall H. Haematological, neurological, and psychiatric complications of chronic hypothermia following surgery for craniopharyngioma. *Postgrad Med J* 1988;64:617-20.
- 36 Branch EF, Burger PC, Brewer DL. Hypothermia in a case of hypothalamic infarction and sarcoidosis. *Arch Neurol* 1971;25:245-55.
- 37 Mann MW, Degos JD. L'hypothermie dans l'encephalopathie Wernicke. *Rev Neurol (Paris)* 1987;143:684-6.
- 38 Bannister RG. *The classification and causes of heat illness* [DM thesis]. Oxford: University of Oxford,

- 39 Kugler SL, Costakos DT, Aron AM, Spiera H. Hypothermia and systemic lupus erythematosus. *J Rheumatol* 1990;17:680-1.
- 40 Holm IA, McGlaughlin JF, Feldman K, Stone EF. Recurrent hypothermia and thrombocytopenia after severe neonatal brain infection. *Clin Pediatr* 1988;27:326-9.
- 41 Cartledge NEF. Autonomic function in multiple sclerosis. *Brain* 1972;95:661-4.
- 42 Sterman AB, Coyle PK, Panasci DJ, Grimson R. Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. *Neurology* 1985;35:1665-8.
- 43 Mutani R, Clemente S, Lamberti A, Monaco F. Assessment of autonomic disturbances in multiple sclerosis by measurement of heart rate responses to deep breathing and to standing. *Ital J Neurol Sci* 1982;2:111-4.
- 44 Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina, C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. *J Neurol Sci* 1993;120:82-6.
- 45 Nogues MA, Newman PK, Male VK, Foster JB. Cardiovascular reflexes in syringomyelia. *Brain* 1982;105:835-49.
- 46 Easterbrook PJ, Davis HP. Thrombocytopenia in hypothermia: a common but poorly recognized complication. *BMJ* 1985;291:23.
- 47 Vella MA, Jenner C, Betteridge DJ, Jowett NI. Hypothermia induced thrombocytopenia. *J R Soc Med* 1988;81:228-9.
- 48 Villalobos TJ, Adelson E, Riley PA, Crosby WH, Glauke HA. A cause of the thrombocytopenia and leukopenia that occur in dogs during deep hypothermia. *J Clin Invest* 1958;37:1-7.
- 49 Hessel EA, Schmer G, Dillard D. Platelet kinetics during deep hypothermia. *J Surg Res* 1980;28:23-34.
- 50 Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. *Crit Care Med* 1992;20:1402-5.