Progressive periodic hypothermia and bradycardia

Introduction

Hypothermia, defined as a core body temperature <35°C, is generally associated with environmental exposure, where centrally mediated thermoregulatory mechanisms are overwhelmed, so-called primary hypothermia. Secondary hypothermia refers to a low body temperature resulting from medical illness, lowering the thermoneutral set-point.

This article presents a patient experiencing recurrent episodes of hypothermia and bradycardia.

Discussion

In this case, established causes of secondary hypothermia (*Table 1*) were excluded, with the exception of performing an electroencephalogram. Although diencephalic epilepsy has previously been described in association with diaphoresis and structural brain lesions, neither were present in this patient. This patient is diabetic, although features are not typical of diabetic autonomic dysfunction, both in terms of paroxysmal presentation and the absence of postural hypotension.

However, hyperinsulinaemia or hyperinsulinaemic hypoglycaemia are postulated as triggers of spontaneous hypothermia by interaction with central serotoninergic pathways (Capanna et al, 2009). Descriptions of spontaneous episodic hypothermia include Shapiro's syndrome, a rare condition characterized by episodic hypothermia, generally associated with hyperhydrosis and agenesis of the corpus callosum (Shapiro et al, 1969). Damage to critical thermoregulatory centres, including the thalamus, by demyelinating plaques has also been described in paroxysmal hypothermia (Linker et al, 2006).

The effects of mild–moderate hypothermia on mental state and cardiovascular parameters are well described, some of which (fatigue, reduced mental alertness, sinus bradycardia, PR interval prolongation) correlated temporally with the degree of hypothermia and its recovery in this case. Pancytopaenia is also described in association with hypothermia (Alty and Ford, 2008).

A pacemaker was implanted to eliminate the bradycardic contribution to these episodes. As spontaneous periodic hypothermia is likely to be centrally mediated, therapies remain speculative. Among candidates, anticonvulsant agents, cyproheptadine (anti-serotonergic), flunarizine (calcium-channel blocker used in the prophylaxis of migraine) and clomipramine (tricyclic antidepressant) have shown some success in individual cases (Ruiz et al, 2003; Hemelsoet and De Bleeker, 2007; Capanna et al, 2009).

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Case Report

A 65-year-old woman presented 6.5 years ago with general malaise. Examination revealed mild peripheral sensory neuropathy. Her temperature on admission was 36°C. Type 2 diabetes was diagnosed. Blood tests revealed iron deficiency anaemia and vitamin D deficiency. Vitamin B_{12}, folate, clotting studies, renal, liver, including gamma glutaryl transferase, thyroid function, autoimmune screen, calcium, creatinine kinase, inflammatory and tumour markers (α–fetoprotein, chorionic embryonic antigen, CA125, CA153) were normal. Oesophago-gastroscopy, colonoscopy and computed tomography of the abdomen and pelvis were unremarkable. Commenced on insulin, metformin, simvastatin and omeprazole, her body temperature returned to normal and she was discharged.

Since mid-2006, there have been seven further admissions, characterized by spontaneous hypothermia and bradycardia (*Figure 1*). Serial electrocardiograms document a fall in heart rate, with progressively longer first degree heart block. On each occasion she was severely obtunded, without shivering. There was no history of drug, alcohol or adverse environmental exposure. Improvement in cognition and heart rate appeared to correlate with normalization of body temperature. Between episodes the patient remained well, living independently in a centrally heated house.

Serial echocardiograms showed good biventricular function, dilated atria and left ventricular hypertrophy (15 mm). Pituitary function (synacthen test, gonadotrophins, prolactin, random growth hormone) and repeated thyroid function tests (thyroid stimulating hormone, thyroxine and tri-iodothyronine) were normal. Septic screens (blood and urine cultures), cytomegalovirus, Epstein–Barr virus and parvovirus antibody titres were normal. Lumbar puncture revealed a non-specific increase in total CSF protein (1.1 g/litre), with no evidence of pleocytosis. Cerebral computed tomography and magnetic resonance scans indicated a normal pituitary fossa and mild supratentorial signal change, representing small vessel ischaemia. There was no evidence of hypothalamic–pituitary abnormality, infarct, tumour, demyelination or corpus callosum dysgenesis.

Since 2011, the patient has demonstrated an intermittent moderate pancytopaenia. A myeloma screen (Bence–Jones protein, serum immunoglobulins and electrophoresis) was normal and a bone marrow biopsy showed a mild elevation (7%) in plasma cells; CD20 and CD138 immunostains were negative with no amyloid. Platelet and white cell parameters recovered in parallel with an improvement in temperature. During the most recent admission a pacemaker was inserted (*Figure 1*). Sequential trials of clonidine (α_2 adrenoceptor agonist) (Walker et al, 1992) and the synthetic amphetamine methylphenidate hydrochloride (Ritalin), with an unlicensed use in narcolepsy, also failed to provide symptomatic improvement.

The patient is currently being monitored with twice daily temperature recordings and adjustments to the ambulant heating. No further hospital admissions have occurred using this strategy.

Conclusions

The authors have succeeded in stabilizing this patient although an explanation for this clinical scenario remains elusive, despite extensive investigation. BJHM

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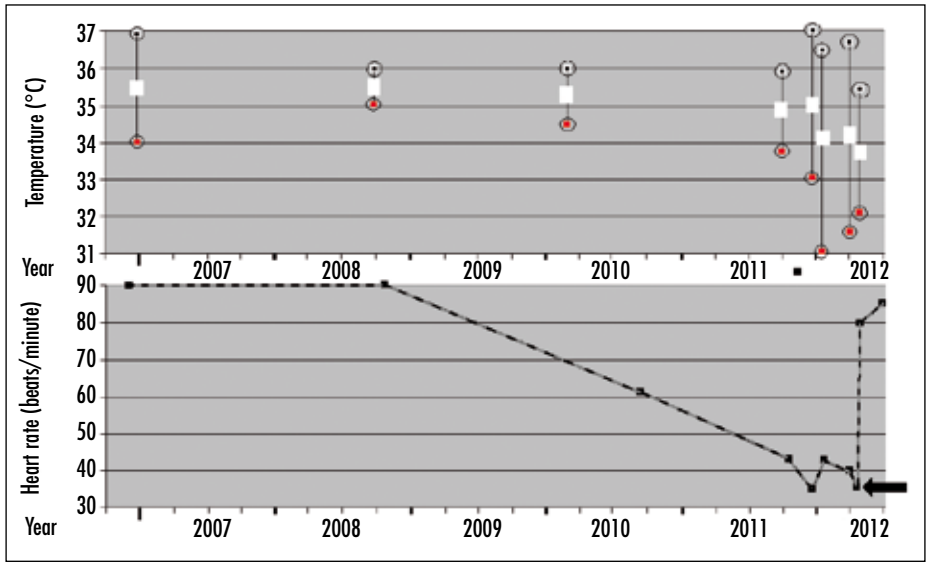
Figure 1. Temperature and heart rate over the last 6 years. a. The lowest temperature recorded during each of eight admissions between 2006 and 2012. On each vertical line, the lower red symbol represents the lowest temperature documented on that admission and the black symbol the value recorded on discharge home. b. The heart rate on admission. The black arrow represents the point of cardiac pacemaker implantation.



LEARNING POINTS

- Idiopathic spontaneous periodic hypothermia is an unusual clinical phenomenon.
- Shapiro's syndrome is a rare cause of periodic hypothermia with associated agenesis of the corpus callosum.
- Several medications have been proposed to treat spontaneous hypothermia; all remain speculative in their efficacy and are used 'off-licence'.

Table 1. Causes of secondary hypothermia

Sepsis	Notably Gram negative sepsis
Drug induced	Alcohol, benzodiazepines, neuroleptics, poisoning
Neurological	Migraine
	Epilepsy
	Demyelination (multiple sclerosis)
	Post-traumatic (contusional brain injury)
	Limbic encephalitis
	Central autonomic dysfunction (i.e. Parkinsons disease)
	Cerebrovascular accident
	Malnutrition (e.g. Wernicke's)
	Cerebral neurotransmitter disorder (i.e. serotonin, vasopressin)
Metabolic	Hypothyroidism
	Hypopituitarism
	Hypoadrenalism

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