

Spontaneous Periodic Hypothermia

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Introduction

The hypothalamus acts as the body's main "thermostat" (111), with a central thermoreceptor sensitivity of ± 0.2 °C (115). The hypothalamus defends the "set point" temperature, which can be altered by central nervous system (CNS) disease or pyrogens. Hypothermia is arbitrarily defined as a core temperature of less than 35 °C (95.0 °F) (101, 115). Poikilothermia is defined as variance of more than 2 °C secondary to ambient temperature changes (78). Normally, the mean body temperature varies diurnally, with an early morning nadir, late afternoon to early evening zenith, and mean amplitude of variability of 0.5 °C (0.9 °F) (79, 98). Over a 24-hour period, the normal oral temperature varies between a 5th percentile low of 35.7 °C (96.3 °F) and a 95th percentile high of 37.6 °C (99.6 °F) (79). The mean normal oral temperature is 36.8 °C (98.2 °F), with women maintaining temperatures slightly higher than men (79). Women manifest a small rise in basal body temperature (0.2–0.5 °C) in response to the thermogenic effect of progesterone during the luteal phase of the menstrual cycle (19). Two hypothalamic centers act reciprocally to maintain body temperature. The posterior center conserves heat by inducing vasoconstriction, shivering, and perhaps by raising the metabolic rate. The anterior center (preoptic anterior hypothalamic area) controls heat dissipation by stimulating a caudal hypothalamic region which induces vasodilatation and sweating (Figure 1) (54, 82, 91, 111).

Hypothermia may occur in multiple clinical settings including induced or accidental, metabolic, protein-calorie malnutrition, drug-induced, dermal dysfunction, sepsis, and hypothalamic and CNS dysfunction (101). Destruction of the anterior "heat loss" center may cause hyperthermia, while bilateral posterior hypothalamic lesions may result in hypo-

thermia or poikilothermia (54, 82). Persistent hypothermia or poikilothermia due to thermoregulatory dysfunction with associated hypothalamic damage is well recognized (8, 9, 23, 29, 39, 62, 66, 78, 80, 99, 101, 111). Acute CNS dysfunction with hypothalamic involvement is recognized to cause transient hypothermia (74).

Periodic hypothermia has been observed with agenesis of the corpus callosum (Shapiro syndrome) (111), with CNS abnormalities affecting structures related to thermoregulation (17, 21, 30, 37, 75, 89, 96, 129), and, very rarely, without an associated systemic disease or obvious brain lesion (24, 29, 40, 81, 114, 116, 121). These last cases are distinct from other recurrent cases such as from environmental exposure. Most of these unusual patients appear to defend a lowered temperature set point by active body heat dissipation through vasodilatation and sweating, and decreased generation of heat (5, 74, 75). These dramatic episodes have been variously referred to as "periodic," "recurrent," "intermittent," "remittent," and "episodic."

The author recently encountered a patient with recurrent episodes of marked hypothermia without an associated CNS structural abnormality (referred to here as "spontaneous periodic hypothermia"). A review of all similar cases identified through a search of the MEDLINE (National Library of Medicine, Bethesda, MD) data base or referenced by other authors during an extensive literature search is assembled here in an attempt to provide a comprehensive clinical picture of this rare disorder.

Illustrative Case

A 57-year-old white man was referred in October 1993 for recurrent episodes of hypothermia with profuse sweating, nausea, and vomiting. His past medical history included a concussive motor vehicle injury in the late 1950s, and again in 1965 (age 29 years). The latter was associated with an unknown duration of unconsciousness and multiple traumatic injuries including blood in the anterior chamber of the right eye and a compound and comminuted mandibular fracture with an otherwise normal skull X ray. His history also included 20 years of smoking 2–3 packs of cigarettes per day, essential hypertension, coronary artery disease with 2 myocardial infarctions, and 2 coronary angioplasties. The patient had been stationed in east Asia during the Korean War. Purified protein derivative skin testing for tuberculosis was nega-

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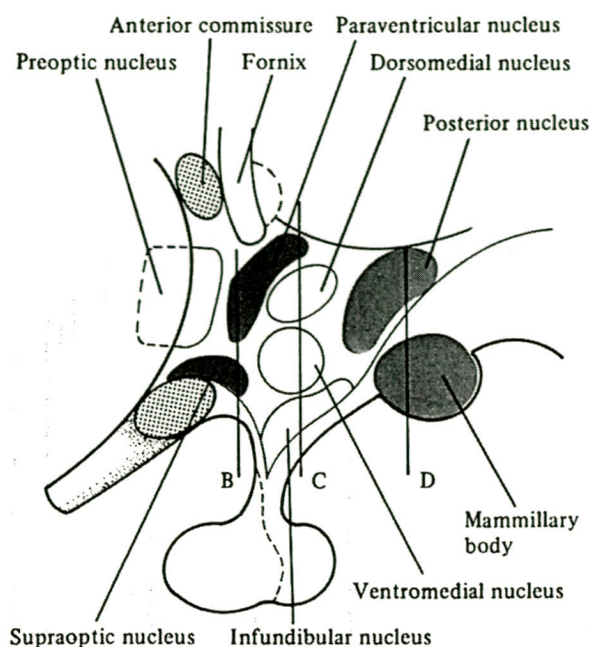


FIG. 1. Ventricular surface of the hypothalamus illustrating approximate locations of the most important hypothalamic nuclei (reproduced with permission from reference 54).

tive in 1987. The family history included seizures in 1 of 4 brothers (whose son also had seizures), a cerebrovascular accident, type II diabetes mellitus, and coronary artery disease. No family members had experienced episodes of hypothermia. The patient's social history included 1 cola per day and no coffee, tea, or alcohol. Medications included nifedipine (Procardia XL 60–90 mg po qd, Pfizer Pratt Pharmaceuticals, New York, NY), lisinopril (Prinivil 10–20 mg po qd, Merck, West Point, PA), sucralfate (Carafate 1 g po qid, Marion Merrell Dow, Kansas City, MO), and infrequent sublingual nitroglycerin.

The patient's first episode of hypothermia occurred in 1975, with a second in 1987. These episodes became more frequent, recurring 1–2 times per year, until 6–7 episodes occurred in 1993. No provocative stimulus was identified. At onset, the patient experienced a "funny feeling" in his head and nausea. The sensation was powerful, consuming, and combined with a sense of weakness, incoordination, and gait unsteadiness, which made him feel like "falling over and dying" and like he "didn't care what happened" to him. During this time he wanted to lie down. The incoordination and gait unsteadiness were described as similar to being drunk. He vomited multiple times and was flushed. Head movements did not worsen the symptoms. Associated with these events he felt very hot, perspired profusely, and his body temperature plummeted to as low as 33.3 °C (92.0 °F) orally and at the tympanic membrane. When he was hypothermic, he stated that he did not feel cold, but his wife noted that his skin felt cold to the touch, "as if he had just been brought out of a freezer," and that it was "clammy." The nausea and vomiting usually lasted 3–4 hours (occasionally longer), and were followed by complaints of feeling cool without associated chills. His face then turned "white." The feeling in his head, general weakness with a sense

of being "drained," and incoordination gradually disappeared over 1–2 days. He was unsure of how long it took his temperature to recover, although he recalled 1 episode of hypothermia lasting 2 days. There were no associated complaints of abdominal pain, headache, diarrhea, confusion, wheezing, rash, seizure activity, or shakiness. Episodes were not related to meals, time of day, or season. He had normal erections and sexual function. Between episodes of hypothermia, the patient was without complaint.

In March 1993 the patient developed pneumonia and mounted a fever to 39.2 °C (102.5 °F) orally.

In April 1993 the patient presented to a local hospital with hypothermia. As his oral temperature was 33.9 °C (93.1 °F), he was treated with warm blankets and his next oral temperature was 35.1 °C (95.1 °F), with subsequent variable measurements as high as 36.1 °C (97.0 °F). Physical examination was normal except for cool, pale skin. Multichannel chemistry, electrolyte profile, and complete blood count (CBC) were normal except for hematocrit 0.384 (reference values: 0.42–0.52), random glucose 7.76 mmol/L (3.58–5.78), cholesterol 6.01 mmol/L (2.77–5.18), and triglycerides 2.68 mmol/L (0.40–1.69). Thyroid stimulating hormone (TSH) and free thyroxin index were normal. Aerobic and anaerobic blood cultures were negative. Chest X ray (CXR) revealed a shallow inspiratory effort, crowding of the basilar lung markings, peripheral pulmonary vessels at the upper limits of normal, but no definite infiltrate or cardiac decompensation. Magnetic resonance imaging (MRI) of the brain 7 days later revealed mild generalized cortical atrophy, left maxillary antral sinusitis, and an intact corpus callosum.

In June 1993 the patient presented to a local hospital with another episode of hypothermia. Vital signs included an oral temperature of 34.4 °C (93.9 °F), pulse 68 beats per minute, respirations 16 per minute, and blood pressure 112/72 mmHg. He was noted to appear ill, with pale, cool, and diaphoretic skin with sweat beading on his face and chest. Apart from an unstable gait, the examination was otherwise normal. Warm blankets were applied, and his oral temperature was then measured at 34.7 °C (94.5 °F). Laboratory studies revealed a normal amylase, lactate dehydrogenase (LDH), and CBC. Multichannel chemistry and electrolyte profiles were unchanged except for mild elevation of aspartate aminotransferase (AST) 0.83 μ kat/L (0.08–0.67). Serial creatinine kinase (CK) levels ranged from 7.60–8.55 μ kat/L (0.58–6.23) with 1%–2% CK-MB (0–4). The erythrocyte sedimentation rate (ESR) was elevated to 50 mm/hour (0–15). CXR was normal. Urinalysis (U/A) revealed a specific gravity of 1.021 (1.016–1.022), no glucose, and trace ketones. Urine, fecal, and blood cultures were without pathogens. The stool was negative for heme, white blood cells, and ova and parasites. Abdominal ultrasound and computed tomography of the abdomen and pelvis were non-contributory.

Subsequent 24-hour urine studies revealed 5-hydroxyindole acetic acid (5-HIAA) 37.8 and 55.4 μ mol (0–31.4), with normal epinephrine, norepinephrine, dopamine, and vanillylmandelic acid (VMA). A malaria smear was negative. Biopsy of a 5–6 mm by 3–4 mm sessile nodular elevation of the ascending colonic mucosa noted at colonoscopy demonstrated intramucosal lymphoid aggregates. Distal rectal and anal canal mucosa revealed mild to moderate proctitis. Esophagogastroduodenoscopy (EGD) revealed diffuse mild to moderate gastritis with a very prominent prepyloric antral region mucosal fold. Histologic evaluation demonstrated chronic duodenitis, and the gastric antrum revealed chronic gastritis with organisms consistent with *Helicobacter*. Five-hour oral glucose tolerance testing revealed a fasting glucose

of 5.72 mmol/L with a glucose curve diagnostic of diabetes mellitus, and no subsequent hypoglycemia. The glycohemoglobin A_{1c} was 0.059 SI (<0.067) with a height of 172.7 cm and weight of 98.4 kg. Repeat 24-hour urine studies demonstrated normal VMA, norepinephrine, epinephrine, metanephrine, normetanephrine, and 5-HIAA.

The patient was instructed to record his oral temperature in the morning and at night daily while asymptomatic, and more frequently should an episode occur. At 11:50 AM December 2, 1993, the patient noted the onset of a mild episode of hypothermia (Figures 2 and 3). He presented to the hospital where his oral temperature was measured by the nursing staff. The patient vomited 5 times before the nausea and hypothermia resolved at approximately 2:30 PM (160 minutes total). Vital signs included a blood pressure of 155/80 mmHg without orthostatic changes. His pulse rate was 60–68 beats/min. The skin was of normal thickness, cool and clammy, with no violaceous striae or hyperpigmentation. Neurologic examination was normal. Laboratory evaluation revealed a normal CBC except for $7.6 \times 10^9/L$ neutrophils (2.0–7.5), and platelets of $193 \times 10^9/L$ (200–400). Electrolyte and chemistry profiles were unchanged except for the elevation of alanine aminotransferase (ALT) 1.15 $\mu\text{kat/L}$ (0–0.75). U/A, CK, urinary 5-HIAA, human pancreatic polypeptide, urine and serum serotonin, and serum neuron specific enolase were normal. Brain positron emission tomography (PET) 22 hours after the onset of symptoms (patient was no longer hypothermic) with ^{18}F -2-fluorodeoxyglucose was normal. Sympathetic skin responses of

the wrist and foot were normal to volitional (inspiration) and extrinsic (startle) stimuli. There was no evidence of small fiber neuropathy or significant peripheral sympathetic dysfunction. Electroencephalogram (EEG) during wakefulness and drowsiness, 26 hours after symptom onset, suggested a mild focal disturbance of cortical neuronal function over both temporal regions with occasional bitemporal theta slowing in the 5–6 Hz range of low-to-moderate amplitude. No epileptiform activity was seen, and no seizures were recorded. Approximately 48 hours after the onset of symptoms the patient reported resolution of his generalized weakness and gait unsteadiness.

Subsequent laboratory testing included a low baseline free testosterone of 33 pmol/L (34.6–104) with a normal total testosterone of 10.1 nmol/L (8.7–32.9), luteinizing hormone (LH) of 3.1 IU/L, follicle stimulating hormone (FSH) of 3.3 IU/L, and prolactin of 6.2 $\mu\text{g/L}$. Repeat free and total testosterone values 6 weeks later were normal at 34.9 pmol/L and 10.2 nmol/L, respectively. Simultaneous samples sent to another laboratory revealed total testosterone of 10.9 nmol/L (10.4–41.5), and free testosterone of 163 pmol/L (311–1,038). Insulin-induced hypoglycemia evoked symptoms of drowsiness, sweating, and heart palpitations with normal responses of growth hormone (GH), adrenocorticotropic hormone (ACTH), cortisol, and arginine vasopressin (AVP, antidiuretic hormone) (10).

Repeat MRI of the brain, before and after gadolinium administration, revealed mild brain volume loss based on the prominent ventricular system and subarachnoid spaces for age. The corpus

FIG. 2. Patient's oral temperature over 57 days. Small square = patient's oral temperature; unfilled circle = hypothermia; large square = 5th percentile oral temperature lower limit; filled circle = 95th percentile oral temperature upper limit.

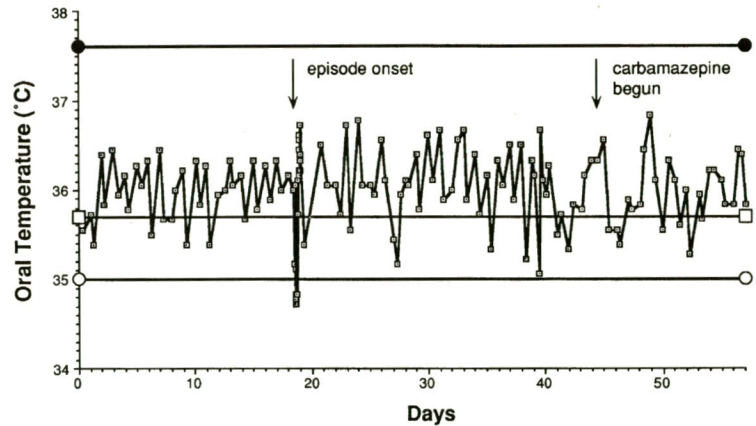
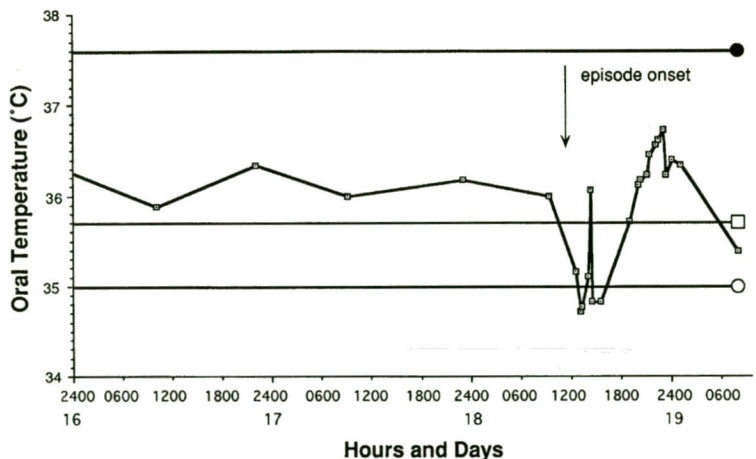


FIG. 3. Detailed view of patient's oral temperature during hypothermic episode seen in Figure 2. (See Figure 2 legend.)



callosum, hypothalamus, and pituitary were normal.

Oral carbamazepine (Tegretol, Basel Pharmaceuticals, Ciba-Geigy, Summit, NJ) was initiated, and the dose titrated upward. With serum trough levels below 31 $\mu\text{mol/L}$, the patient twice experienced mild episode onset symptoms with the sensation in his head, nausea, minimal or no vomiting, weakness, mild diaphoresis, and an urgent sense to lie down. The temperature declined only mildly (always above 36.1 $^{\circ}\text{C}$ [97.0 $^{\circ}\text{F}$]), and each episode resolved within 30 to 60 minutes. The patient had never before experienced such "abbreviated" episodes, the last of which occurred January 15, 1994. With carbamazepine 800 mg/d, the patient had mild CNS side effects, no further hypothermic episodes, and a trough serum level of 29 $\mu\text{mol/L}$. The patient was intolerant of 1,000 mg/d with increased CNS side effects including mild confusion and impaired judgment, slight speech disturbance, drowsiness, incoordination/unsteadiness, and feelings he described as "woozy" and a sense of being "in another place." At the patient's request, alternative therapy with clonidine 0.1 mg po bid was begun March 10, 1994, and subsequently converted to the Catapres-TTS-2 transdermal system (Boehringer Ingelheim, Ridgefield, CT). A hypothermic episode occurred July 20, 1994, with an oral temperature nadir of 35.0 $^{\circ}\text{C}$, and clonidine therapy was discontinued. Further carbamazepine therapy and a trial of phenytoin (Dilantin, Extended Phenytoin Sodium Capsules USP, Parke-Davis, Morris Plains, NJ) were refused. The patient had no further episodes since discontinuation of clonidine.

Discussion

Clinical presentation

This case is consistent with previously reported cases of spontaneous periodic hypothermia. In those cases, the periodicity of hypothermic episodes ranged from hours to years, and episodes lasted hours to weeks (Tables 1 and 2). Frequent body temperature measurements below the normal 5th percentile were recorded while this patient was asymptomatic, and a normal diurnal variation was present (Figures 2 and 3). Some patients have maintained interval body temperatures in the frankly low to low-normal range (24, 37, 75, 106, 121). Hyperhidrosis has been a frequent and prominent feature, and is consistent with stimulation of the anterior hypothalamic thermoregulatory center (2-4, 16, 22, 52, 55). However, Slotki et al reported the absence of diaphoresis (116), Sheth et al reported the onset of sweating towards recovery (114), and 2 other reports (75, 107) noted no consistent relationship between the profuse sweating and temperature changes. Yet, when warming was attempted in 2 of these cases, both patients "defended" their lowered set points. The patient presented here was not formally tested to demonstrate defense of a temporarily lowered set point. The fact that he did not complain of being cold during the acute phase of the hypothermia, however, argues strongly for a temporarily lowered set point. Further, while application of warming blankets was twice followed by mildly increased temperatures,

one may argue that this patient's episodes were usually of short duration, and that he may have been in the process of spontaneously recovering and beginning to employ systemic heat conservation measures such as those he described with his spontaneous recoveries when he would feel cool and his face would turn white. This possibility is supported by the fact that with the first warm blanket intervention, the patient was noted to be pale, and not diaphoretic. On the second occasion, he was no longer diaphoretic before the repeated temperature determination.

Urine specific gravity measurements during acute episodes have ranged from 1.021 to 1.025; this documents the presence of AVP. Potential causes for AVP stimulation in this setting may include nausea/vomiting, adrenergic stimuli, emotional stress, and hypovolemia secondary to profound diaphoresis. The stimulatory effect of opiates on AVP release, the effects of AVP on thermoregulation, and the potential role toward hypothermia are discussed below. Of note, this patient reported diaphoresis with codeine ingestion. No abnormality of thirst or water metabolism was noted during or between episodes, however.

Previous authors (6, 75, 121) have noted abnormal liver function tests in patients with periods of hypothermia, which may be accounted for by hypoperfusion of the liver due to reduced splanchnic blood flow. Another possible explanation of this patient's mild hepatic transaminase abnormalities is fatty infiltration of the liver secondary to obesity and diabetes mellitus. Abnormalities of sex hormones and gonadotropins in similar cases from the literature are discussed below. Interpretation of this patient's low free testosterone is complicated by his normal LH and FSH, advanced age compared to that of subjects used for assay normalization (testosterone levels normally fall with aging), and normal sexual function. A gonadotropin releasing hormone stimulation test has not been performed. Ataxia has been mentioned by previous authors (24, 29, 75, 121). Of note, this patient's altered gait appeared to persist temporarily despite resolution of the hypothermia.

While this patient's diagnosis of type II diabetes mellitus is the most likely explanation for his randomly elevated glucose values at the time of hypothermia, decreased glucose utilization and impaired insulin release as a cause of impaired oral glucose tolerance testing during hypothermia has been demonstrated (72, 101, 111, 122). Further, vasopressin has been found to increase hepatic glucose production (14, 15, 44, 56, 119, 126), and to stimulate pancreatic glucagon release (31, 32). Glucagon in turn rapidly stimulates hepatic glucose production (15, 95).

Bradycardia and decreased cardiac output are well recognized consequences of hypothermia, and may explain why this patient's peripheral pulmonary

TABLE 2. Cases of periodic hypothermia with insufficient CNS imaging

Reference Year	Sex	Age at Onset	Seizures	Abnormal EEG	Frequency of Episodes	Episode Duration	CNS Imaging Modality	Drug Tried	Drug Response
59 1934	M	12 yr	No	Not done	Annually for 4-6 wk with multiple episodes/d	Approximately 2 hr	Skull X rays	Sodium amyltal	Complete
63 1942	M	33 yr	No	Not done	Annually for 2-3 mo with episodes each morning	2-3 hr	Skull X rays	Amytal	Complete
29 1961	M	10 yr	No	Yes	Variable, daily morning attacks for 16 d recorded	Approximately 1/2 d	Skull X rays	None	None tried

vessels on chest X ray were deemed at the upper limits of normal during 1 hypothermic episode (5, 101). The patient's exhaustion and abnormal EEG (while he was no longer hypothermic) are consistent with cases previously reported.

This is the first case of spontaneous periodic hypothermia to have a PET evaluation of cerebral glucose metabolism; no functional abnormality was demonstrated. This is the first case of spontaneous periodic hypothermia to respond possibly to carbamazepine, however, a temporary spontaneous remission is not excluded. Although Hines and Bannick (59) reported a prodrome of nausea and vomiting, this is the first reported case of nausea and vomiting occurring consistently at the episode onset. Interestingly, 2 cases (35, 130) of recurrent *hyperthermia* have been reported with nausea and vomiting as part of the episodic symptomatology. Of note, gastrointestinal effects have been demonstrated (41, 42) in animals with stimulation of the anterior hypothalamus.

Pathophysiology

There is general agreement among authors that an altered central thermoregulatory mechanism is the determining factor for the fluctuating body temperatures of both Shapiro syndrome and spontaneous periodic hypothermia. In the 1934 report of Hines and Bannick (59), atropine sulfate alleviated the sweating but did not affect the temperature curve. Rather, the patient developed a prolonged "hot period," most likely representing a decreased ability to dissipate heat via sweating to accommodate the new thermoregulatory set point. In most cases (5, 29, 75, 111, 121), attempts to warm these hypothermic patients have resulted in profuse sweating. There is evidence to suggest decreased heat generation in the setting of spontaneous periodic hypothermia despite the low core body temperature (5, 75, 114). Attempted cooling while patients were hypothermic has resulted in shivering and body heat conservation. Several patients, including the present case, have demonstrated a febrile response to infection or diagnostic challenge (114); some during a hypothermic episode (40, 50, 111, 116, 121). Taken together, this evidence supports a "reset thermostat" concept with coordination between heat loss and conservation mechanisms, and the presence of an intact autonomic nervous system regulating the efferent vasomotor pathways (29, 75, 89, 111). Sheth et al (114) reported that immediate external warming altered the course in 2 of 3 patients, however, and proposed an abnormal anterior hypothalamic extrapyramidal shivering mechanism rather than an alteration of set point.

In addition to episodes of frank hypothermia and evidence suggesting a reset thermostat (in most

cases), subtle abnormalities of thermoregulation have also been documented. Duff et al (29), in their second case, reported a delayed response to intravenous pyrogen and suggested a temperature-regulating mechanism abnormality beyond a lowered set point. Shapiro et al (111) noted impaired shivering and a delayed recovery from hypothermia in their second case. Slotki and Oelbaum (116) documented mild abnormalities of central thermoregulation between attacks in a patient with spontaneous periodic hypothermia. The patients reported by Maehle (81) and Duff et al (29) had reversed diurnal temperature rhythms during attacks.

Possible causal mechanisms

The inciting pathophysiologic mechanism(s) leading to the hypothermia and generally apparent "resetting of the thermostat" remains unknown. It would be challenging to explain these recurring events, often beginning well into adult life and with intervals between "attacks" spanning hours to years, based solely on some mechanism which is continually present (that is, a degenerative, irritative, neurochemical, or structural abnormality). Given the episodic nature of the syndrome, it seems logical that the overriding mechanism(s) is itself most likely intermittent.

Degenerative processes: An intermittent, slowly progressing degenerative process might account for the progressive increase in frequency or severity of episodes seen in some cases (40, 59, 63, 75, 92, 111). Duff et al (29) reported that mental deterioration occurred in a patient with spontaneous periodic hypothermia with continued periods of hypothermia, despite control of generalized seizure activity. Shapiro et al (111) noted that in both their cases the body temperature between episodes gradually declined over the years. However, the best evidence for a degenerative mechanism is the severe neuronal loss and nonspecific fibrillary gliosis described by Noel et al (92) in the arcuate nucleus and premammillary formations of the posterior infundibular nuclei at autopsy in their patient with Shapiro syndrome. Conversely, Engel and Aring (35) described a young man without hypothermia but with repeated paroxysms of rhinorrhea, coldness, shivering, chills, pallor of the extremities, fluctuating blood pressure, and spiking temperature, followed by abrupt temperature reduction toward normal with profuse sweating and flushing. Autopsy revealed cystic degeneration of the dorsomedial nucleus, the internal medullary lamina, and the lateral nuclei of the right thalamus: no hypothalamic pathology was mentioned. To my knowledge, no other cases have been reported for which there are histologic data, and

only recently have high resolution imaging modalities become available.

Neurochemical dysfunction: An intermittent neurochemical dysfunction might be another basis for the episodic nature of these attacks. Neurotransmitters in humans known to modulate thermoregulation include dopamine, acetylcholine, serotonin (5, 114), prostaglandins, and several neuropeptides (26, 74). A biochemical agent directly responsible for the alterations of temperature seen in patients with spontaneous periodic hypothermia or Shapiro syndrome, however, is unknown. Catecholamine levels have been found to be elevated in some cases of spontaneous periodic hypothermia (24) and Shapiro syndrome (89, 107). Two such patients have received the catecholamine release inhibitor clonidine, 1 with success (24). A second patient (125) successfully treated with clonidine had normal plasma and urinary catecholamines; the authors of the latter report argued for a central, rather than peripheral, site of pharmacologic action. Catecholamines have multiple effects on heat generation and loss (60). Clonidine is also known to exert a central hypothermic effect mediated by α_2 -adrenoceptors in rats (131), and hypothermia has been noted in humans as a symptom of clonidine toxicity (1). Clonidine has also been reported (87) to suppress paroxysms in a patient with "central autonomic epilepsy" without disordered temperature control.

AVP is known to affect thermoregulation (25, 27, 67, 76, 85, 94, 123). Its secretion is triggered by emotional stress (93, 124), hypoglycemia (10–12, 34, 68, 69, 128), nausea/vomiting (102, 104, 112), adrenergic stimuli (7, 13, 84, 108, 109) (catecholamines), and other stimuli. Infusion of AVP into humans (127) produces peripheral vascular changes similar to those seen during hypoglycemia (128). These changes appear similar, if not identical, to those demonstrated in 1 well-studied case (40) of spontaneous periodic hypothermia. Reactive hypoglycemia was suggested (but not strictly diagnosed) in a previous report (29). Hypoglycemia is accompanied by a fall in body temperature (28), which is thought to be part of a thermoregulatory mechanism to protect the brain from the harmful effects of glucose deprivation (46). In humans, heat loss during hypoglycemia occurs despite an increase in nonshivering heat production (43), and is associated with high skin blood flow due to arteriovenous shunting, sweating, and depressed shivering (128). Further, Brandt et al (17) reported a child with subacute necrotizing encephalomyelopathy (Leigh syndrome) with complex neurologic attacks which included periods of hypothermia. Brain and CSF analysis revealed elevation of endogenous opioids (endorphin fractions, met-enkephalins). Morphine and narcotic ana-

logues are known to enhance AVP release (49, 100). Naloxone, a narcotic and endogenous opiate antagonist devoid of agonist properties, dramatically reversed the child's symptoms but only intermittently and for short time periods. Another study (88) reported that naloxone reversed the syndrome of inappropriate antidiuretic hormone (SIADH). This finding suggested that SIADH could be caused by excessive secretion of endogenous opioids in the neurohypophyseal system (88). Naloxone resulted in a temperature increase to normal in a patient with Shapiro syndrome during 1 of 2 trials (89), and a slight temperature increase in another patient (75). Other authors (125) have reported unsuccessful trials. Previous case reports of Shapiro syndrome have suggested possible abnormalities of water metabolism, and previous authors have considered the role of AVP in Shapiro syndrome, but most have found the possibility unlikely (71, 92, 125).

Irritative mechanisms: An etiology based on intermittent irritation could theoretically occur via several mechanisms. An inflammatory process such as an autoimmune disease or immunologic process (61) seems unlikely given the lack of associated systemic manifestations, the failure of exogenous steroids in all attempts, and the absence of diagnostic or suggestive histologic data. An infectious etiology seems equally unlikely given the extensive search by multiple authors for such an agent, prolonged empirical antibiotic trials, and lack of supportive histologic data. An intermittent, irritative process due to nongeneralized seizure activity of the hypothalamic structures, or a resulting postictal period, remains a possibility. However, enthusiasm for this latter mechanism appears to be waning.

Diencephalic epilepsy: In 1907, Gowers (48) observed episodes of behavioral changes, sweating, reduced body temperature, and chills in several patients, and regarded these events as focal seizures of the "vegetative nervous system." In 1929, Penfield (96) reported a patient with a third ventricle tumor, markedly increased intracranial pressure, and a defect through the corpus callosum. He proposed that mechanical irritation lead to "diencephalic autonomic epilepsy"; symptoms included flushing, diaphoresis, and a fall in temperature "well below normal" during the most severe attacks. With an obvious central nervous system structural abnormality, such as in the Penfield case, an epileptic event is clearly possible. One can propose other theoretical mechanisms to account for recurrent thermoregulatory dysfunction in this patient, however, such as recurrent transient local ischemia, pressure, or hypoxia. In Shapiro syndrome and spontaneous periodic hypothermia, the latter mechanisms seem less likely.

Seventeen of 24 cases (5, 24, 37, 75, 81, 107, 114, 125) of Shapiro syndrome or spontaneous periodic hypothermia reported abnormal EEG findings, including nonspecific abnormalities. Five cases (29, 50, 73, 120, 121) are reported to manifest seizures. Twenty-two cases (5, 20, 24, 29, 33, 37, 40, 50, 51, 59, 63, 75, 81, 106, 107, 111, 114, 120, 121, 125) report anticonvulsant drug therapy trials: 5 (24, 50, 59, 63, 111) resulted in resolution, and 3 (51, 75, 81) had partial or temporary improvements. Shapiro et al (111) proposed that the "paroxysmal, involuntary, repetitive and stereotyped neuronal discharges, by all criteria, [fell] within the definition of epilepsy." Further, it was argued that the signs and symptoms of temperature alteration, behavior changes, and EEG abnormalities all fell within the functional domain of the diencephalon.

Should these periodic episodes of hypothermia be of epileptic origin, the lower-than-expected response rate to anticonvulsive medications is unexplained (albeit a relatively narrow range of tested anticonvulsants). Recent studies (83, 117) have documented that carbamazepine is more effective than phenobarbital, phenytoin, primidone, and valproate in controlling partial seizures. Treatment trials with this agent for spontaneous periodic hypothermia (5, 40, 114) and Shapiro syndrome (125) have occurred 5 times previously and failed. However, only a low daily dose of 400 mg was employed in 1 case (40), dose was not specified in the others (5, 114, 125), and none reported trough serum levels achieved. Yet, despite frequent EEG abnormalities, seizure foci have not been identified frequently, and some (29, 111) have speculated that the EEG abnormalities were in part a reflection of the hypothermia. Further, it is difficult to understand how an epileptic event (as well as the other mentioned theoretical mechanisms) would establish a new set point with essentially intact thermoregulatory mechanisms to defend it, and not just thermoregulatory dysfunction.

On the other hand, if in fact these periodic episodes of hypothermia are of epileptic origin, one must account for why these patients would be predisposed to recurrent nongeneralized seizure activity involving hypothalamic structures. The presence of a degenerative, irritative, or structural abnormality could serve as such a nidus which may be very subtle and not detected by CT, MRI, PET, or standard postmortem analysis. Consideration was given above to the former 2 theoretical processes. Agenesis of the corpus callosum is a developmental structural anomaly associated with closure of the anterior neural tube (58). Some individuals with agenesis of the corpus callosum appear clinically normal (36); others have associated additional gross midline and random structural abnormalities (18, 53, 77, 86). Severe developmental defects are associated with early

mortality, mental and physical retardation, and generalized and focal seizure activity. Milder anomalies have been associated with a more normal life span, but most patients with milder anomalies have epilepsy (often with adult onset), and many have mild mental retardation (111). The importance of the corpus callosum as a structure linking communication between the 2 hemispheres (118), and not as the center for thermoregulatory function has been well established. Surgical section of the corpus callosum does not result in hypothermia or seizures (47). Patients with agenesis of the corpus callosum do not have deficits in interhemispheric transfer of information, possibly due to compensation by other pathways, although they do manifest defects in perceptuomotor coordination (36, 45, 65, 113, 118). Thus, if structural abnormalities are important in the occurrence of Shapiro syndrome and spontaneous periodic hypothermia, they are likely to be defects that are only associated with agenesis of the corpus callosum, and whose extent and severity account for the presence and variability of the hypothermic episodes (111). Thus, it is likely that while one focuses on the grossly obvious presence or absence of the corpus callosum to distinguish Shapiro syndrome from spontaneous periodic hypothermia, a spectrum of less obvious (and etiologically more important) midline abnormalities may exist. This de-emphasis on the corpus callosum would explain the discrepancy between the not uncommon absence of the corpus callosum (approximately 1-3 per 1,000 CT scans [37, 70]), and the rarity of Shapiro syndrome.

Associated episodic abnormalities

The notion of a temporary focal dysfunction, or even discharge, that encompassed more than the thermoregulatory centers could explain some of the associated abnormalities documented during periods of hypothermia in patients with Shapiro syndrome and spontaneous periodic hypothermia. Although these reports involving facial asymmetry (29), abnormal sex hormones and gonadotropins (106, 116), secondary amenorrhea (121), prolactin (116), and TSH (71, 75) may arguably all be accounted for by acute illness or assay variability, the possibilities of associated hypothalamic-pituitary dysfunction should be noted. This same point is made in the second patient described by Duff et al (29) with spontaneous periodic hypothermia, who, together with periods of hypothermia, had reversed diurnal temperature rhythm and large volumes of dilute urine made at night. This abnormality may imply dysfunction of the hypothalamic-posterior pituitary antidiuretic hormone system, although they stated that diabetes insipidus was not present. It may also be accounted for by abnormal renal tubular reabsorption of sodium and water secondary to hy-

pothemia (90, 110). However, other cases (71, 89) of Shapiro syndrome have had abnormalities of water metabolism reported. Mooradian et al (89) proposed an abnormality of posterior pituitary function in their patient with Shapiro syndrome whose arginine vasopressin failed to rise in response to insulin-induced hypoglycemia, although water deprivation testing was consistent with primary polydipsia. Kovacs et al (71) reported thirst and vasopressin levels typical of downward resetting of the osmostat during hypothermia, and absent thirst and vasopressin responses between attacks. Several authors have reported the association of paroxysmal hypertension with spontaneous periodic hypothermia (5, 24, 114) and Shapiro syndrome (107). These reports are intriguing given the close proximity of the vasomotor center, controlling arterial blood pressure, to the anterior hypothalamic region (57).

Associated baseline abnormalities

The frequent relationship between structure and function raises the question of whether previously reported cases of Shapiro syndrome or spontaneous periodic hypothermia had baseline abnormalities beyond those present during hypothermic episodes. As mentioned earlier, Noel et al (92) described focal abnormalities in the infundibular nuclei in their patient with agenesis of the corpus callosum associated with relapsing hypothermia. The arcuate nuclei are of importance to gonadotropic function (38), and their patient was noted to have testicular atrophy. Gonadotropin levels were not reported, however. Guihard et al (50) reported a child with agenesis of the corpus callosum, primary organic polydipsia with insufficient AVP, craniofacial midline abnormalities, spontaneous relapsing hypothermia, pituitary dwarfism, and precocious puberty. Dutau et al (33) reported a child with Shapiro syndrome, facial-cranial dysraphism, hypotonia, and growth and mental retardation. Sheth et al (114) reported spontaneous periodic hypothermia in a child with moderate mental retardation and developmental aphasia. Arroyo et al (5) reported a child with spontaneous periodic hypothermia with normal serum triiodothyronine (T₃) and thyroxine (T₄) levels but with an inadequate TSH response to thyroid releasing hormone (TRH) stimulation both during and between episodes.

Treatment

It is difficult to evaluate therapy for spontaneous periodic hypothermia and Shapiro syndrome. Limited data are available due to the rarity of identified cases, the intermittent nature of the disorders, the lack of a control population, and the absence of an animal model.

Maneuvers performed at the onset of an episode and reported to abort an attack in 1 case each have included drying the skin (5) and immediate warming (114). Drug therapy with anticonvulsant agents has been discussed above. Two spontaneous remissions have been reported (29, 114); successful clonidine therapy has been reported previously in 2 of 3 trials (24, 107, 125), and preliminary success has been reported (51) in a fourth trial. The serendipitous success of oxybutynin has been reported (73). Chlorpromazine treatment has been successful in 2 of 4 cases of Shapiro syndrome (37, 75, 106). Interestingly, 1 of the 2 successful cases was a patient with episodes of exacerbated hypothermia superimposed on a hypothermic baseline, and both abnormalities resolved (37). Chlorpromazine failed in the 1 case (29) of spontaneous periodic hypothermia in which it was tried. Chlorpromazine, which has been used for the induction of hypothermia for surgery (101), showed transient success in treating a case of periodic pyrexia (130). Chlorpromazine's mechanism of action is unknown. The drug has psychotropic, sedative, and antiemetic activities, as well as antiadrenergic, peripheral anticholinergic, ganglionic blocking, antihistaminic, and antiserotonin effects. It affects all levels of the CNS, primarily the subcortical areas. This drug should be used only with the understanding of the risks of tardive dyskinesia and neuroleptic malignant syndrome, as well as its other side effects (97). The antiserotonergic agent cyproheptadine has been used with partial or complete success in 4 cases of spontaneous periodic hypothermia (5, 114), and with transient success in Shapiro syndrome (75). One case of spontaneous periodic hypothermia was treated with total sympathectomy with symptomatic improvement despite consequent postural hypotension (40).

Summary

Spontaneous periodic hypothermia is a rare syndrome of recurrent, centrally mediated hypothermia without an identifiable systemic cause or brain lesion. Most patients defend a temporarily lowered temperature "set point" during episodes of hypothermia, despite manifesting many well-known systemic consequences of core temperature hypothermia. No case of death directly attributable to an episode of spontaneous periodic hypothermia has been reported, although many of the serious systemic effects of hypothermia have been documented in these cases, so it is not unlikely that death may occur. The syndrome's cause, and that of Shapiro syndrome, remains unknown. Pharmacologic trials to date have been only modestly successful. Anticonvulsant agents, clonidine, and cyproheptadine appear the

most likely to succeed, with cyproheptadine being a reasonable first choice.

Given that the term "spontaneous periodic hypothermia" describes a syndrome, and not a pathophysiologic mechanism, it is likely to encompass a common eventuality, arrived at via several different pathways. One can postulate mechanisms such as structural abnormalities, trauma, infection, irritation, and degeneration involving strategic locations which create a focus for epileptic or other periodic dysfunction whose scope involves the centers for thermoregulation. The existence of 2 distinct, oppositional thermoregulatory centers would allow for speculation of similar mechanisms accounting for cases of both periodic hypo- and hyperthermia (61). Postmortem data regarding the hypothalamic and surrounding areas from future cases of Shapiro syndrome and spontaneous periodic hypothermia would be of great interest. Further, more sensitive *in vivo* testing methods are clearly needed. The role of PET or single photon emission computed tomography (SPECT) with technetium 99m-labeled hexamethylpropylene amine oxime (Tc 99m HMPAO) performed acutely during an episode remains to be characterized (64, 103, 105).

The term "diencephalic epilepsy" may in fact be accurate, given the periodic episodes of the case presented here and similar cases resulting from non-generalized seizure activity, with or without an underlying predisposing lesion. The label diencephalic epilepsy has been merely speculative so far, however, as definitive evidence of seizure activity has not been documented. Further, it is expected that the descriptive terms "spontaneous periodic hypothermia" and "episodic spontaneous hypothermia with hyperhidrosis" will outlive their usefulness as researchers gain greater understanding of this syndrome, and be replaced with a more pathophysiologically meaningful nomenclature.

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