Diagnosis and management of periodic hypothermia

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Summary

Hypothermia, defined as a core temperature below 35°C, can occur in a variety of clinical settings, including environmental exposure, shock, infection, metabolic disorders (such as hypothyroidism, adrenal insufficiency, and Wernicke encephalopathy), malnutrition, and alcohol or drug toxicity. Typically, hypothermia should resolve with treatment of the underlying disorder. However, in rare cases patients experience recurrent episodes of hypothermia in the context of a stereotyped syndrome due to a hypothalamic lesion, which can be either congenital or acquired. The episodes are characterized by progressive confusion and a decreased level of arousal, hypothermia, and eventual resolution with a return to baseline. Additional clinical findings during episodes may include diaphoresis, asterixis, bradycardia, and thrombocytopenia. These recurrent episodes represent periodic hypothermia.

In healthy individuals, several mechanisms exist to prevent hypothermia from occurring. When a reduced body temperature is detected by peripheral temperature receptors, several reflexes are activated: skin vasoconstriction and contraction of erector pili muscles reduce heat radiation, shivering produces heat, and sympathetic excitation and thyroxine production increase the basal metabolic rate. Control of these reflexes occurs in the preoptic nucleus of the anterior hypothalamus and adjacent regions of the septum, which is referred to as the pre-optic area.^{e1} In this region, thermoafferent signals are mediated by a variety of neurotransmitters, including catecholamines, serotonin, melatonin, peptides, and cytokines.

Dysfunction, injury, or destruction of the preoptic area, whether congenital or acquired, can lead to the development of periodic hypothermia. The cognitive impairment and other neurologic symptoms seen during hypothermia may be due to the reduction in cerebral blood flow that occurs once the body temperature falls below 33°C.^{e2} EEGs performed during episodes

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demonstrate diffuse slowing without other abnormalities. Focal seizure activity in the preoptic area is difficult to exclude definitively, as routine surface EEGs may not detect hypothalamic seizures, but empiric anticonvulsants do not appear to be effective in the prevention of recurrent episodes.

Currently, only case reports or small case series exist describing patients with periodic hypothermia. However, a comprehensive review of these reported cases reveals that periodic hypothermia occurs in the context of several underlying conditions, and the recognition of these syndromes may have implications for successful treatment of the disorder.

Case 1

Starting at age 7, a boy developed episodes of profuse sweating followed by the progressive development of lethargy and decline in body temperature over the next 30 minutes. After several hours the episode would resolve with severe shivering and his temperature and mental status would return to normal. He had no recollection of events during the episodes. They could occur daily or near-daily for days to weeks and then remit for years at a time. There was no clear pattern to the episodes, although they often occurred in the morning or 1–2 hours after a meal. Stress or heightened emotional states also may have served as triggers. He was otherwise healthy, and after graduating high school he served in the United States Marines. He married, had children, and worked as a city maintenance employee. At age 45 (in the 1980s), a CT scan revealed agenesis of the corpus callosum and a diagnosis of Shapiro syndrome was made. He was hospitalized in 2004 during a cluster of episodes where his temperature would fall to 32°C, and an MRI was performed (figure 1, A and B). The hypothalamic region was normal in appearance. An EEG performed during an episode demonstrated moderate generalized slowing with no epileptiform activity. The episodes occurred daily for 3 weeks and then remitted spontaneously. During his life, empiric trials of phenobarbital, phenytoin, valproic acid, and oxybutynin were all ineffective as abortive therapy or prophylaxis against future episodes. At age 70 he developed progressive bradykinesia and rigidity, and he died at age 74 from complications of parkinsonism.

Case 1 discussion Shapiro, Williams, and Plum were the first to describe periodic hypothermia in 2 patients with agenesis of the corpus callosum.^{e3} Since their initial report, there have been more than 50 published cases of periodic hypothermia in patients with agenesis of the corpus callosum, which is now known as Shapiro syndrome.^{1–7} In these patients, episodes can begin at any age, occur for hours, are often associated with diaphoresis, and can spontaneously remit for years. Periodic hypothermia can also occur in patients with partial agenesis of the corpus callosum, with a similar clinical presentation as patients with complete agenesis.^{8–10} These cases represent the syndrome of periodic hypothermia in the context of a congenital structural lesion. While the clinical syndrome has been well described, successful treatment has been only sporadically reported. In these patients, clonidine may be an effective agent for prophylaxis against further episodes (table).

A periodic hypothermia syndrome with similar clinical characteristics to Shapiro syndrome has been reported in children with a normal MRI of the brain, in some cases referred to as episodic spontaneous hypothermia with hyperhidrosis (ESHH).^{11–16} In these cases, children experience recurrent, spontaneous episodes of hypothermia below 35°C that last for hours, are associated with lethargy and diaphoresis, and terminate spontaneously with return to

Supplemental Data

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Figure 1 MRI findings in patients with periodic hypothermia

(A) T1 sagittal and (B) coronal MRI of a 70-year-old man with agenesis of the corpus callosum and periodic hypothermia. (C) T1 sagittal and (D) T2 fluid-attenuated inversion recovery axial MRI of a 54-year-old man who had rupture and clipping of an anterior communicating artery aneurysm 6 months prior. C demonstrates an area of encephalomalacia in the anterior corpus callosum (arrow). Metal artifact obscures the hypothalamic region. D demonstrates encephalomalacia of the genu of the corpus callosum (arrow), with gliosis of the frontal paraventricular white matter due to wallerian degeneration. (E) T1 sagittal and (F) coronal postcontrast MRI of an 82-year-old man with a suspected renal cell carcinoma metastasis to the hypothalamic region. The tumor appears as a homogeneously enhancing mass lesion (arrow).

baseline. Single cases have reported patients with decreased levels of serotonin metabolites in the CSF or increased serum melatonin levels, implicating a neurotransmitter disorder as the cause of the syndrome.^{13,e4} Cyproheptadine has been reported to be effective in several of these cases as prophylaxis against further episodes (table).

Case 2

A 53-year-old man experienced sudden onset of severe headache while at home and lapsed into a coma. He was taken to the hospital and found to have a subarachnoid hemorrhage due to a ruptured right anterior communicating artery aneurysm. He underwent an emergent craniotomy and surgical clipping of the aneurysm, and levetiracetam was started for seizure prophylaxis. Over the next 3 weeks he made steady improvement and was discharged to a rehabilitation facility, although he had persistent severe anterograde amnesia and impaired thirst. During his first week of rehabilitation, he developed recurrent episodes of lethargy associated with hypothermia. The episodes occurred every few days, with stereotyped clinical features. Starting midmorning, he would develop increasing disorientation and confusion. His body temperature would decrease

Table Reported treatment of periodic hypothermia

Syndrome	Patient age at onset, y	Sex	Treatment	Outcome	Duration of follow-up	Reference
Congenital with structural lesion	NR	F	Clonidine 0.1 mg twice daily	No episodes	3 mo	1
	21	M	Cyproheptadine 16 mg daily	Fewer episodes	NR	2
	34	F	Chlorpromazine 150 mg daily	No episodes	2 y	2
	21	M	Oxybutynin 5 mg twice daily	No episodes	3 mo	3
	66	F	Clonidine 0.3 mg daily	Fewer episodes	NR	4
	34	M	Clonidine 0.3 mg daily	No episodes	NR	5
	12	M	Clonidine 0.3 mg daily	No episodes ^a	NR	6
	68	F	Chlorpromazine 150 mg daily	No episodes	4 y	7
	5	M	Cyproheptadine	No episodes	1 mo	8
	6	F	Glycopyrrolate 2 mg 3 times daily	No episodes	NR	9
Congenital without structural lesion	NR	M	Clonidine	No episodes ^a	NR	10
	2.5	F	Cyproheptadine 1 mg/kg	No episodes ^a	1 y	11
	1.5	F	Cyproheptadine 0.2 mg/kg/day	No episodes	2.5 y	12
	3	F	Cyproheptadine 0.2 mg/kg/day	No episodes	1.5 y	12
	6	F	Propranolol	No episodes	1 y	13
	4	F	Carbamazepine 20 mg/kg	No episodes	NR	14
	5	F	Cyproheptadine	No episodes	8 mo	15
Acquired and stereotyped	4	M	Clomipramine 125 mg twice daily	No episodes	4 y	16
	44	M	Clomipramine 35 mg daily	No episodes ^a	2 y	17
	39	M	Clonidine 0.1 mg twice daily	No episodes	2 mo	18
	48	M	Clonidine 0.2 mg 3 times daily	Fewer episodes	NR	19
	48	M	Clonidine 0.2 mg 3 times daily	Fewer episodes	NR	19

Abbreviation: NR = not reported.

In cases of congenital periodic hypothermia with a structural lesion, clonidine has most often been reported as successful treatment. Oxybutynin, chlorpromazine, and glycopyrrolate have been reported as successful in isolated cases. Congenital periodic hypothermia without a structural lesion has been reported to respond to cyproheptadine. Acquired, stereotyped periodic hypothermia has been reported to respond to clomipramine or clonidine. No successful treatment has been reported in any cases of acquired, nonstereotyped periodic hypothermia.

^a Indicates that episodes recurred when the treatment was temporarily withdrawn.

to 33°C from a baseline of 36°C, and he would become obtunded. The episodes would always remit spontaneously by late afternoon, with a return to his baseline mental status. After recovery, he had no memory of any of these episodes. Ultimately he returned to the hospital for evaluation. Imaging revealed an ischemic stroke of the anterior corpus callosum, suspected to be due to injury of a pericallosal artery during aneurysm rupture or surgical clipping (figure 1, C and D). An EEG performed during an episode demonstrated mild generalized slowing, with no seizures or focal abnormalities seen. He was started on clomipramine 50 mg once daily and had no further episodes. Levetiracetam was discontinued, as he had no evidence of seizures. He was discharged home and has not had any subsequent episodes over the past 2 years while remaining on clomipramine.

Testing should include an MRI of the brain with contrast to evaluate for agenesis of the corpus callosum, a tumor in the hypothalamic region, or other structural abnormalities.

Case 2 discussion Periodic hypothermia has been reported in cases of subarachnoid hemorrhage or traumatic injury to the brain, in which the lesion to the preoptic area is acquired rather than congenital. These cases represent an acquired, stereotyped periodic hypothermia syndrome that may respond to treatment. As in Case 2 above, the 4 reported cases of periodic hypothermia after subarachnoid hemorrhage all occurred in the setting of a ruptured anterior communicating artery aneurysm.^{e5–e8} Treatment was not reported in any of these cases.

Three cases of periodic hypothermia following a traumatic brain injury have also been reported, with the onset of episodes 3–10 years after the injury.^{17,18,e9} In one case, treatment with clomipramine resulted in cessation of the episodes, leading to the selection of clomipramine to treat the patient described in Case 2.¹⁷ It is important to note that periodic hypothermia must be differentiated from defective thermoregulation occurring within days of an acute traumatic brain injury, as these patients may have rapidly fluctuating hypo- and hyperthermia in the context of autonomic instability.^{e10} A stereotyped periodic hypothermia syndrome has also been described in the context of chronic HIV infection and may respond to treatment with clonidine.^{19,e11}

Case 3

An 82-year-old man was admitted to the hospital with 1 week of worsening confusion and dizziness. He was found to be mildly hypothermic at 35°C and hyponatremic due to syndrome of inappropriate antidiuretic hormone secretion (SIADH). An MRI of the brain demonstrated an enhancing mass lesion in the hypothalamic region (figure 1, E and F). A CT scan of the abdomen revealed a mass in the right kidney suspicious for renal cell carcinoma. No biopsies were performed, and he was started on dexamethasone. On the sixth day of his hospitalization, he developed increasing lethargy and was found to have a temperature of 33.5°C. Comprehensive laboratory studies and an infectious evaluation were unremarkable. An EEG revealed diffuse generalized slowing. His temperature gradually returned to 37°C over a 5-day period, with normalization of his mental status. He was discharged to a rehabilitation facility. Three weeks later he again developed confusion and dizziness, which progressively worsened over 12 hours. He returned to the hospital, where he was found to have a temperature of 34.2°C. He was started on clomipramine 50 mg once daily. However, over the next 3 months he continued to have recurrent episodes of confusion and lethargy associated with periods of hypothermia. In successive episodes the hypothermia gradually became more severe, ultimately to 29°C. He became increasingly frail and was discharged from the hospital to a hospice facility, where he died 2 weeks later.

Case 3 discussion Periodic hypothermia in patients with tumors has been described in several cases.^{e12–e14} As in Case 3, the hypothermia is recurrent but variable in frequency and duration. In an early reported case of periodic hypothermia, the patient was found to have a tumor in the dorsal medial nucleus of the thalamus, leading to the description of the episode as “diencephalic epilepsy.”^{e15} A more recent case reported periodic hypothermia in a patient found to have gray matter heterotopia in the left frontal lobe, which responded to treatment with sodium valproate, suggesting an epileptic etiology.^{e16} In a single pediatric case, the patient had fewer episodes while being treated with carbamazepine.¹⁴

Seizures originating from the hypothalamus may be difficult to detect with a routine surface EEG due to their deep location. If there is a high clinical suspicion for seizures, extended EEG

Figure 2 Classification of the periodic hypothermia syndromes

Congenital periodic hypothermia with a structural lesion may occur in cases of partial or complete agenesis of the corpus callosum. Congenital periodic hypothermia without a structural lesion is seen exclusively in pediatric cases, where the etiology may be a neurotransmitter disorder. Acquired, stereotyped periodic hypothermia may occur after an intracranial hemorrhage or remote traumatic brain injury. Acquired, non-stereotyped periodic hypothermia may occur in cases of advanced multiple sclerosis or tumors in the hypothalamic region.

monitoring or an empiric anticonvulsant trial may be considered. However, in the majority of cases of periodic hypothermia, the episodes do not respond to treatment with anticonvulsants and EEGs during episodes demonstrate slowing but no epileptiform activity. Treatment with clonidine or clomipramine also does not appear to be effective in patients with tumors of the hypothalamic region, as seen in Case 3.

Many reports also exist of patients with multiple sclerosis (MS) who develop recurrent episodes of hypothermia, but with considerable variability in the associated clinical features and duration of the episodes.^{e17–e22} In all cases, patients have a long-standing history of MS. Patients typically develop hypothermia, lethargy, and worsening of prior neurologic deficits that can last for days to weeks, and in some cases appear to be in the context of new demyelination. These cases represent a syndrome of nonstereotyped, acquired periodic hypothermia. Cases of periodic hypothermia in the setting of sarcoidosis and progressive neurodegeneration due to mitochondrial disease have also been reported.^{e23,e24} No successful treatment has been reported in cases of periodic hypothermia in the setting of tumors or MS.

DISCUSSION

Periodic hypothermia is a rare disorder that can occur in the context of 4 distinct syndromes: congenital periodic hypothermia with or without a structural lesion and acquired periodic hypothermia that is stereotyped or nonstereotyped (figure 2). In patients without agenesis of the corpus callosum, there has been no previously described unifying nomenclature. Although it is rare, periodic hypothermia may be underrecognized. A thorough clinical history and ancillary testing are essential to make the diagnosis.

Testing should include an MRI of the brain with contrast to evaluate for agenesis of the corpus callosum, a tumor in the hypothalamic region, or other structural abnormalities. An EEG should be performed during an episode to evaluate for seizure activity, and a more comprehensive epilepsy evaluation may be considered if there is a high clinical suspicion for seizures. Serum tests should include a complete blood count, sedimentation rate and blood cultures to rule out infection, a comprehensive metabolic panel, thyroid function tests and adrenal function tests to evaluate for metabolic derangements, a serum melatonin level, and CSF and 24-hour urine collection for catecholamine metabolites to evaluate for a neurotransmitter disorder.

The medications reported to have efficacy as prophylaxis against future episodes include clonidine, clomipramine, and cyproheptadine (table). Single case reports have also reported possible efficacy of oxybutynin, chlorpromazine, and glycopyrrolate. Clonidine primarily acts as a central α -2 adrenergic receptor agonist, reducing sympathetic tone. Clomipramine and cyproheptadine both act as serotonin-2A and histamine receptor antagonists. The efficacy of these agents strongly suggests that periodic hypothermia is a neurotransmitter disorder in patients with congenital or acquired and stereotyped periodic hypothermia, although further

study is needed. In patients with acquired, nonstereotyped periodic hypothermia the syndrome appears to be refractory to treatment.

The episodes, by definition, resolve spontaneously without a lasting neurologic deficit. However, patients are bedridden during episodes, placing them at risk for medical complications such as pneumonia and deep vein thrombosis, and patients may require hospitalization. Recognition of a specific periodic hypothermia syndrome can inform treatment decisions, with successful treatment ending the episodes and improving the patient's quality of life. Due to the rarity of the disorder, formal therapeutic trials will be difficult to conduct, but continued case reporting may help guide future treatment recommendations. The goal of treatment should be complete abolishment of the episodes if possible, as well as management of other associated neurologic and medical complications.

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