



Episodic Hypothermia Related to Autonomic Dysfunction Improved on Cyproheptadine and Pyridostigmine

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Abstract

Hypothermia is quantified by a basal core temperature that is below 35°C and can have a variety of causes, most of which are self-limited or resolve when the underlying cause is treated. Some patients may exhibit episodic hypothermia. There are several reports of cyproheptadine being beneficial in the treatment of episodic hypothermia in children and young adults. This case report discusses a 62-year-old woman with underlying autonomic dysfunction who had multiple episodes of neuropathic pain, hypothermia and diaphoresis, all of which responded to cyproheptadine and pyridostigmine treatment. In this patient, the hypothermia was attributed to her autonomic system dysfunction.

Keywords: Autonomic dysfunction; Hypothermia; Cyproheptadine; Pyridostigmine; Case Report

Introduction

Hypothermia is quantified by a basal core temperature that is below 35°C and is often self limited once the underlying cause is treated. Some patients have episodic hypothermia. A variety of causes can lead to this type of thermoregulatory dysfunction such as injury or destruction of the hypothalamus, agenesis of the corpus callosum (Shapiro's syndrome), multiple sclerosis, or other autonomic dysfunction [1,2]. Patients who experience episodic hypothermia can have physical and cognitive manifestations during an episode. Some of these symptoms can severely hinder a patient's ability to continue with their activities of daily living. Temperature regulation is maintained by a hippocampal circuit including ventrolateral preoptic GABAergic neurons, and the neural activity of dorsomedial neurons leading to reflexive response temperature dysregulation [3]. Activation of GABAergic vLPO neurons reduce body temperature [3].

This case report reviews a patient diagnosed with autonomic

dysfunction, which contributed to her recurrent episodic hypothermia. This patient responded well to treatment with cyproheptadine and pyridostigmine with improvement of her hypothermia [4]. Reports have indicated that cyproheptadine may be beneficial in the treatment of episodic hypothermia in children and adults summarized in Table 1 [2,5]. Pyridostigmine at a dose of 30 mg twice a day has been reported to optimize thermoregulatory regulation by minimizing the susceptibility to hypothermia, and by maintaining basal body temperature via a peripheral cholinergic mechanism [6]. Pyridostigmine can be used on a long-term basis safely in patients with neurological conditions [7]. Pyridostigmine displays the ability to suppress the activation of GABAergic postsynaptic currents, thus possibly affecting the hypothalamus' role in lowering body temperature [8]. Cyproheptadine appears to affect the hypothalamic 5HT_{2A} receptors linked with thermoregulation [9]. There have been no reports of the concomitant treatment of pyridostigmine and cyproheptadine for hypothermia.

Table 1: Reported Treatment of Episodic Hypothermia with Cyproheptadine.

Case Report	Age of Onset	Cause of Hypothermia	Dose of Cyproheptadine	Results
LeWitt et al.	21	Agenesis of Corpus Callosum	16 mg	No episodes
Arroyo et al.	1.5	EHH without agenesis	0.2 mg/kg/day	No episodes
Sheth et al.	2.5	Varicella induced thermoregulatory dysfunction	1mg/kg	No episodes
Arroyo et al.	3	EHH without agenesis	0.2 mg/kg/day	No episodes
Greenberg, Rittchier	5	ESHH	Not Specified	No episodes

Case Presentation

A 62 year-old woman with a history of degenerative disc disease, arthritis, neuropathic pain, and a nonruptured 4 mm left M2 aneurysm who presented to the neurology clinic with a reported history of hypertensive crises, lightheadedness with position changes, and a feeling of being cold. The patient's hypothermic episodes usually began in the evenings, lasted through the night, and she would wake in the early morning hours shivering. These episodes could last between 8 and 12 hours. During the hypothermic episodes the patient reported an experience of "unawareness" of her body. EEG testing was negative for seizures. The patient's self temperature monitoring on a standard oral thermometer revealed a temperature that was often below 98 degrees F (36.67 degrees C). She frequently reported temperatures of 96 degrees F (35.56 degrees C) and occasionally as low as 94 degrees F (34.44 degrees C) temperature changes summarized in Table 2. Triggers to the hypothermic episodes included stress and infection. The patient also had difficulties with orthostatic hypotension (drop of SBP >20 when changing positions) with her systolic blood pressure dropping below 100 mmHg when she stood up. Tilt table testing provided no evidence of predisposition to neurally mediated syncope or exaggerated postural tachycardia, however tilt testing revealed

measure of parasympathetic and sympathetic adrenergic function is abnormal, with normal sympathetic cholinergic function. Her neurological exam revealed normal cognitive testing, cranial nerve function, motor strength, reflexes, coordination and gait. Her sensory exam revealed a small fiber neuropathy; sensory polyneuropathy with a stocking/glove deficit in pinprick sensation. The results of a skin biopsy of PGP9.6 immunolabeled sections showed severe distal small fiber neuropathy with reduction of epidermal innervation with the retention of the dermal and dermal gland innervation. Morphometric quantitation of epidermal nerve ending yielded epidermal neurite density of 14 neurites/mm² skin. This is below the 5th percentile threshold resulting in a diagnosis of small fiber neuropathy. Diabetes mellitus was ruled out due to the lack of supporting lab results. The diagnosis of multiple system atrophy was also excluded due to a lack of parkinsonism features, cerebellar ataxia and lack of significant imaging such as atrophy of the putamen pons or cerebellum, and no indication of MSA on TILT table testing. An MRI of the brain did not reveal any structural issues and a full endocrine panel including T3,T4, ferritin, B12 and Vitamin D were normal. An EMG ruled out large-fiber peripheral neuropathy. There was no infectious or pharmacological causes identified for the autonomic insufficiency.

Table 2: Total Daily Dose of Cyproheptadine and Pyridostigmine with Self Reported Temperature data in F.

Date	Total Daily Dose of Cyproheptadine	Total daily Dose of pyridostigmine	Self Reported Temperature in F
May 2020	0mg	0mg	94.4
Jun 2020	0mg	60mg	95.3
Oct 2020	0mg	120 mg	94.7
Nov 2020	0 mg	180mg	95.5
Dec 2020	0mg	240 mg	94.4
Dec 2021	24mg	180mg	96
Jan 2022	8mg	120 mg	97.6
Feb 2022	4mg	120mg	97.8

Her orthostatic hypotension improved with pyridostigmine treatment starting at 30mg PO BID and titrating it up to effect. Her hypothermia improved further with the addition of the pyridostigmine. The patient developed gastrointestinal side effects on the pyridostigmine. Once her orthostatic hypotension stabilized, the pyridostigmine was lowered slightly to reduce gastrointestinal side effects. She was maintained at a low level of 30mg twice daily.

Cyproheptadine was started for hypothermia with some improvement.

Gradually, the dose of cyproheptadine was increased to 8mg three times a day. On this regimen, the patient had a reduction in the number and intensity of episodes. They decreased from daily episodes to an episode once every few weeks. She did experience some side effects of cognitive slowing 3 months following the in-

crease of the cyproheptadine dosage. Repeat cognitive testing and MRI of the brain to rule out central causes of hypothermia, provided normal results. Cyproheptadine was gradually tapered without return of her severe hypothermia episodes with the maintenance dose of pyridostigmine. She subsequently moved to a warmer climate that allowed the complete resolution of the hypothermia.

Discussion

This case report discusses a patient with autonomic dysfunction with autonomic neuropathy including hypothermia who had reduction in the severity and frequency of hypothermic episodes on a combination of pyridostigmine and cyproheptadine. Hypothermia can be due to a variety of causes that can include metabolic derangements, neurotransmitter disorders, or brain lesions to the hypothalamus due to tumors, multiple sclerosis, or trauma [10]. The mechanism of temperature regulation is due to a combination of neuroregulatory signals that maintain the reflexes designated to regulate temperature. The most common cause of episodic hypothermia is related to medication side effects. Hypothermia has sometimes been observed with agenesis of the corpus callosum (Shapiro's syndrome).

The most common treatment for episodic hypothermia is dependent on the cause. Medications that have been reported to help in the treatment of episodic hypothermia include clonidine, clomipramine and cyproheptadine [11]. To our knowledge, this is the first case reported with concomitant use of pyridostigmine and cyproheptadine with beneficial effects for episodic hypothermia. Cyproheptadine acts at a serotonin 2A and histamine receptor antagonist, thus may be useful in regulating temperature modulation via the regulation of the neurotransmitters responsible for temperature modulation. Pyridostigmine may be combined with cyproheptadine in the management of autonomic patients with thermoregulatory dysfunction to optimize recovery (Table 1 & 2).

Statement of Ethics

This study protocol was reviewed and determined to be exempt by the St. Elizabeth's Medical Center IRB, on February 15th, 2022. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest

The authors have no conflict of interest to declare.

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Author Contributions

Conceptualization: A.H; Writing of manuscript: L.M; Data Collection: L.M, A.H; Formal Analysis: L.M; Review and Editing: A.H.

Data Availability

Details are found in the patient's medical record and on no other publicly accessible website. All data generated or analyzed during the study are included in the article. Further enquiries can be directed to the corresponding author.

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