Baclofen Successfully Abolished Prolonged Central Hyperthermia in a Patient with Basilar Artery Occlusion

Yung-Sung Huang, Ming-Chang Hsiao, Meng Lee, Ying-Chih Huang, and Jiann-Der Lee

Abstract- Hyperthermia, not uncommon in severe brainstem stroke, is frequently difficult to control and associated with a poor prognosis and high mortality. Successful treatment of central hyperthermia in patients with brainstem infarction by baclofen has not been described. Following basilar artery occlusion, a 68-year-old female developed prolonged hyperthermia. Her hyperthermia did not respond to any antipyretic treatments. A water-cooling blanket was utilized to control her hyperthermia; however, body temperatures fluctuated at a range of 35.5~40.0˚C. After given baclofen 30 mg/day, her body temperatures returned to a normal range and remained stable. Hyperthermia following severe brainstem infarction without any sign of infection or inflammatory sources usually comes from a central origin and is likely associated with dysfunctions of the thermoregulatory system. Baclofen may be one of the treatment choices in patients with neurogenic central hyperthermia.

Key Words: Stroke, Critical care, Hyperthermia, Baclofen

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INTRODUCTION

Hyperthermia is usually associated with a marked increase in morbidity and mortality in stroke patients[1]. It may be caused by severe brainstem dysfunction in patients with basilar artery occlusion[2]. There is clinical evidence indicating a strong correlation between fatal hyperthermia and the compromise of pontine structures and functions[3]. Central hyperthermia is usually associated with a high temperature and does not respond to common antipyretic treatments[4]. We report a patient who experienced prolonged central hyperthermia following basilar artery occlusion. Central hyperthermia was successfully controlled by baclofen. The probable mechanisms of central hyperthermia in patients with brainstem infarction are reviewed and discussed in detail.

CASE REPORT

A 68-year-old right-handed female with a history of hypertension and coronary heart disease presented with an acute-onset dizziness, nausea, and vomiting. Neurological examination showed dysarthria, binocular diplopia, and truncal ataxia. Magnetic resonance imaging (MRI) demonstrated infarction involving the right

From the Department of Neurology, Chang Gung Memorial Hospital, Chiayi, and Chang Gung Institute of Technology, Taiwan.
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Reprint requests and correspondence to: Jiann-Der Lee MD. Department of Neurology, Chang Gung Memorial Hospital, Chiayi, No. 6, W. Sec., Jiapu Rd., Puzih City, Chiayi 613, Taiwan.
E-mail: jdlee540908@yahoo.com.tw

occipital area and bilateral cerebellum; magnetic resonance angiography identified nonvisualization of the distal intracranial vertebral and basilar arteries (Fig. 1A), presumably due to atherothrombotic occlusion. Echocardiogram and electrocardiogram results were normal. Following initial evaluation, the patient was treated with systemic heparinization. However, this treatment was discontinued 2 days later due to diffuse and multiple petechiae of her abdomen; clopidogrel 75 mg/day was then administered. Unfortunately, neurological symptoms deteriorated 4 days later with the lowest Glasgow Coma Scale (E1V1M1). Neurological examination showed apneustic breathing, pinpoint pupil, absent oculocephalic reflex, and bilateral positive Babinski's signs. An emergent computed tomography scan demonstrated infarcts of bilateral pons and cerebellum (Fig. 1B-C). The patient was placed on mechanical ventilation, and tracheostomy was performed later. She had intermittent high fever since admission. Despite a complete fever workup and a full course of antibiotic treatments, her fever persisted with a normal white blood cell count (WBC), C-reactive protein (CRP) and negative blood cultures (WBC: 6800/μL, segment: 46.3%, CRP: 8.3 mg/L). We tried common antipyretic treatments such as acetaminophen and non-steroidal anti-inflammatory drugs for prolonged fever initially; however, the results were unsatisfactory. Under the diagnosis of "neurogenic central fever", a water blanket was employed for cooling and hyperthermia control. However, the patient's fever rose again when the cooling blanket was removed. The patient's body temperature fluctuated at a range of 35.5~40.0˚C, and the cooling blanket was only used when body temperature was > 38˚C. A beta-blocker of propranolol was also given to decrease sympathetic activity with unreliable fever control. At 16 weeks after stroke onset, she was administered baclofen 30 mg/day for fever control. Her body temperature became stable, and the cooling blanket was seldom needed after one week of baclofen treatment. Finally, this patient became normothermia and was discharged.

DISCUSSION

In patients with ischemic stroke, fever was detected in more than 60% of patients during the first 72 hours[5]. In one study, fever appeared approximately in a fourth of stroke. The percentage of fever without documented infection (probably fever of central origin) was 33%[4]. Approximately one third of patients with pontine hemorrhage developed extreme high fever during the early

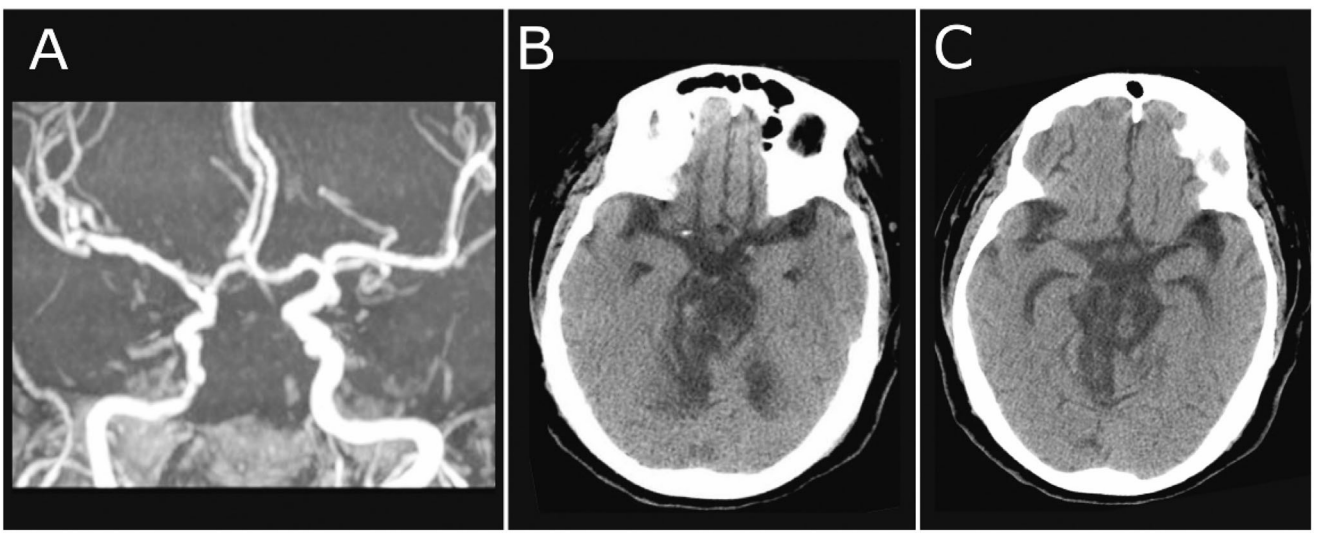

Figure 1. Neuroimaging studies of the stroke involving the brainstem and cerebellum. (A) Magnetic resonance angiography (MRA) showed the absence of filling in the territories of the distal intracranial vertebral and basilar arteries. (B-C) Computed tomography demonstrated infarcts in bilateral pontine structures and the cerebellum.

stage after the onset of stroke[3]. Most of these studies focused on early fever after brain insults. Prolonged central fever after stroke has not been carefully studied. The precise mechanism of central fever in ischemic stroke, especially in brainstem infarct, is still unknown.

Body temperature is strictly controlled in humans at approximately 37˚C. Several physiologic mechanisms are involved in temperature homeostasis, all of which are coordinated through the hypothalamus. Heat production in normal adults is through shivering, an increase in the metabolic rate, and, to a lesser degree, sympathetically mediated nonshivering thermogenesis[6]. We propose a hypothesis that nonshivering thermogenesis may play an important role in a quadriplegic patient with severe brainstem infarct who suffers from prolonged central hyperthermia. Brown adipose tissue (BAT) is the principal effector of nonshivering thermogenesis in humans by transferring energy from food to heat. The central pathway for control of thermoregulatory thermogenesis and innervations of BAT is complex[6]. The pathway described here must be considered a simplistic and tentative one (Fig. 2). Preoptic chiasma/anterior hypothalamic nuclei (POAH) is accepted as the center for body temperature control[7]. Cooling of this area activates BAT [8], whereas warming suppresses activation of BAT and nonshivering thermogenesis[9]. The efferent from the POAH

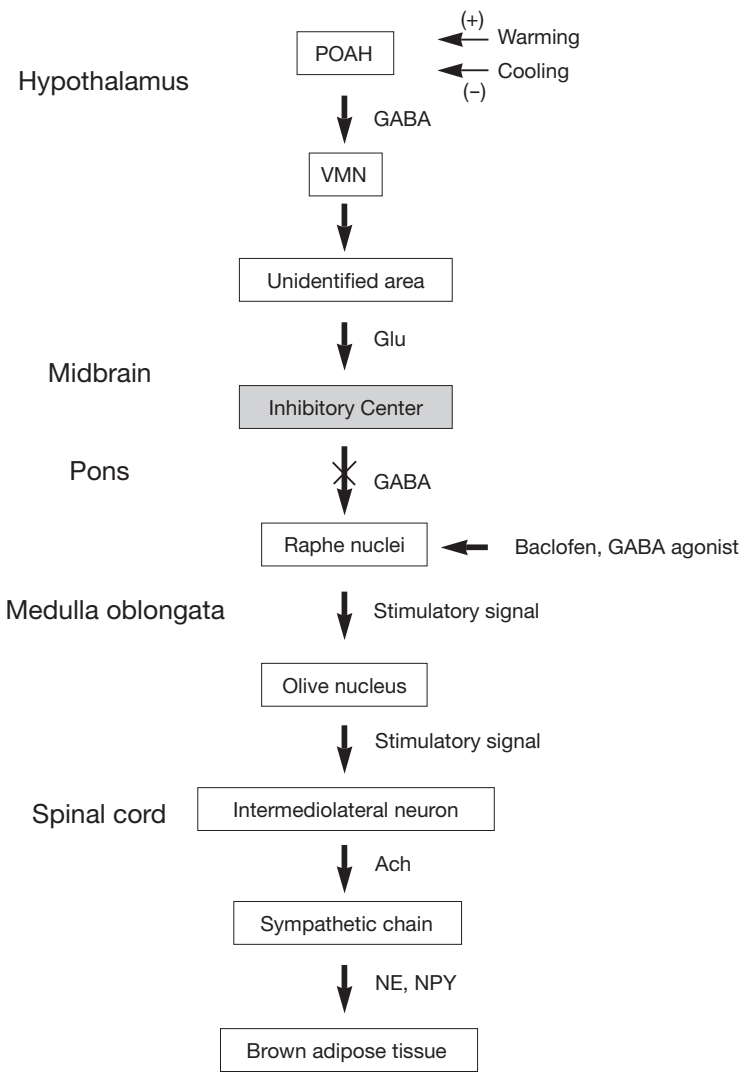

Figure 2. Neurogenic control of the thermoregulatory system. In a normal physiological condition, the warmth activates POAH to suppress BAT and nonshivering thermogenesis; whereas cooling releases this inhibition and activates BAT. In the patient with an infract involving bilateral pontine structures, the inhibitory signal (i.e. GABA) from the inhibitory center is eliminated and BAT is activated, which in turn increases the body temperature. Baclofen functions as GABA acting directly on the raphe nuclei to suppress BAT activation, which in turn suppress the body temperature.
POAH: preoptic chiasma/anterior hypothalamic nuclei, VMN: ventromedial hypothalamic nucleus, GABA: gamma-aminobutyric acid, Ach: acetylcholine, Glu: glutamate, NE: norepinephrine, NPY: neuropeptide Y.

is an inhibitor gamma-aminobutyric acid (GABA) to reach ventromedial hypothalamic nucleus (VMN)[10]. The signal from the VMN probably passes through the periaquaductal gray[11] and is further mediated via an "inhibitory center" in lower midbrain[12]. The output from the inhibitory center may reach the raphe nuclei and release GABA in this area[13]. The thermoregulatory signal is further mediated by inferior olivary nucleus and intermediolateral neurons that connect to the sympathetic chain. The sympathetic chain then controls the BAT for nonshivering thermogenesis[14]. This mechanism is tonically inhibited at thermoneutrality, but this inhibition is released in the cold. According to this model and previous animal studies[15,16], a transection between the pons and medulla eliminates the decending inhibitory signal, i.e. GABA. The decerebration can release this inhibition and cause an excessive rise in body temperature because of an increment in the thermogenesis of the BAT. This may explain the marked hyperthermia in this patient with infarction involving bilateral pontine structures. Baclofen, a GABA agonist, may function as an inhibitory signal acting directly on the raphe nuclei in the medulla and successfully abolished prolonged hyperthermia in this patient.

Marked hyperthermia with significant fluctuations in patients with brainstem stroke usually suggests a poor prognosis and high mortality. Pharmacological management of central hyperthermia is difficult and antipyretic agents are usually of no use. A number of medications have been reported to be beneficial in dysautonomia (heart rate, respiratory rate, blood pressure, temperature, and sweating) following traumatic brain injury but the efficacy is often unpredictable or incomplete. These include, in order of available evidence, intravenous morphine, midazolam, drugs with sympathetic activity (alpha-adrenergic agonist and some beta-adrenergic blockers), bromocriptine and intrathecal baclofen[17]. However, febrile reaction to subarachnoid baclofen administration was reported in a patient with thoracic syringomyelia[18]. We hypothesize that different neurologic insults associated with fever may need different strategies for fever management. Cerebrospinal fluid studies for neurotransmitters (GABA, glutamate) may be warranted in the patients with central hyperthermia. The correlation between the neurotransmitter and the infarct location may give us a better guide for fever management. Through this interesting case, we explore possible thermoregulatory mechanisms. Further research is needed to improve understanding of central hyperthermia in brainstem infarct.

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