



Central Hyperthermia Due to Intracerebral Hemorrhage Treated with Baclofen: A Case Report

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We report the treatment of a rare case of central hyperthermia due to intracerebral hemorrhage (ICH) in the basal ganglia with baclofen. Central hyperthermia is associated with a high mortality rate and poor prognosis among patients with failure of the thermoregulation system. A 35-year-old man arrived at the emergency room with the sudden loss of consciousness and right-sided hemiparesis. Computed tomography revealed an ICH in the left basal ganglia with a midline shift. Following craniotomy and evacuation of the ICH, the patient developed persistent hyperthermia. Laboratory investigations for fever did not aid in determining the origin, and the fever did not respond to any antibiotics or antipyretics. Oral baclofen was started at a dose of 30 mg/day, which was increased to 90 mg/day. The patient's temperature markedly decreased to the normal range. Baclofen can be considered for treating suspected central hyperthermia in patients with ICH.

Key Words: Baclofen; Basal ganglia; Cerebral hemorrhage; Hyperthermia, induced

INTRODUCTION

Central hyperthermia is defined as high body temperature usually caused by stroke, and it responds poorly to antipyretic treatments. Prolonged central hyperthermia that develops from stroke is associated with a high risk of morbidity and mortality^{2,4,6,10,16-18}. We report a rare but successful case of management of a patient with central hyperthermia, which occurred after intracerebral hemorrhage (ICH) in the basal ganglia with baclofen.

CASE REPORT

A 35-year-old man with no medical history presented to the emergency room with sudden loss of consciousness (Glasgow Coma Scale, E1V1M4) and right-sided hemiplegia on neurologic examination.

Non-contrast computed tomography (CT) demonstrated acute left basal ganglia hemorrhage with a midline shift (Fig. A). The patient was treated with emergency decompressive craniectomy and hematoma evacuation (Fig. B). Post surgery, he was admitted to the intensive care unit and managed with mechanical ventilation with monitoring systems and medication. On postoperative day (POD) 12, he presented with intermittent fever and sudden muscle rigidity. Despite thorough diagnostic evaluation to rule out the focus of infection and full coverage of broad-spectrum antibiotics, the fever persisted and fluctuated in the range of 38.2°C to 39.6°C. Routine biochemistry and hematological tests showed no evidence of inflammation with a normal white blood cell count (7,900/mL), C-reactive protein level (5.3 mg/L), and negative blood culture results. The anticoagulation tests and lumbar puncture cerebrospinal fluid analysis on POD 16 were normal (red blood cells, 220/mm³; white blood cells, 5/mm³; glucose, 71 mg/dL; and protein, 51 mg/dL). He showed no signs of active inflammation, and his coagulation test results

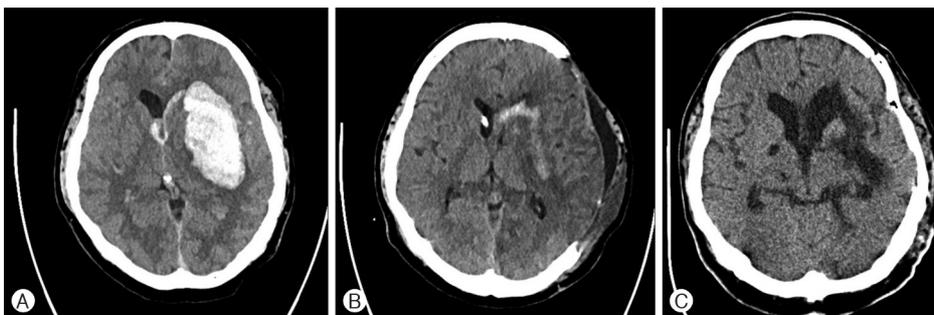


Fig. 1. (A) Computed tomography axial image demonstrating intracerebral hemorrhage (ICH) in the left side basal ganglia with a midline shift. (B) Extensive left frontoparietal craniectomy with resolving state of ICH. (C) Cranioplasty with scanty subdural fluid collection.

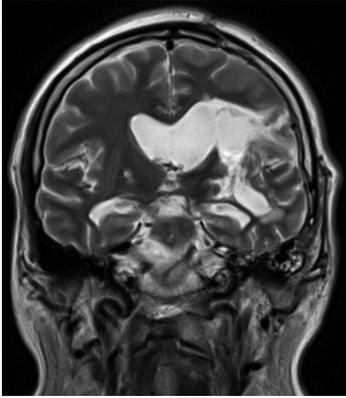


Fig. 2. Magnetic resonance imaging demonstrated that encephalomalacia due to intracerebral hemorrhage in left frontotemporoparietal lobe, basal ganglia, external capsule.

were normal; therefore, it could be concluded that central hyperthermia was the likely cause of the prolonged fever. Central hyperthermia was treated with baclofen at a dose of 30 mg/day on POD 18, and the dose was increased to 60 mg/day on POD 22. Hyperthermia did not subside when the dose of baclofen was 30 mg/day; however, the body temperature fluctuated between 39°C and 37°C on POD 23 but did not reach the normal level. On POD 30, we increased the baclofen dose to 90 mg/day, and the body temperature was reduced to normal levels. The neurological state showed gradual improvement with a reduction in stupor and muscle rigidity. Postoperative CT demonstrated resolved ICH without any midline shift (Fig. 1C). Postoperative magnetic resonance imaging demonstrated encephalomalacia due to ICH in the left frontotemporoparietal lobe, basal ganglia, external capsule (Fig. 2).

DISCUSSION

Central hyperthermia is characterized by a cytokine-related elevation setting of the thermoregulatory center that fails to respond to antipyretic treatments. The diagnostic criteria for central fever are not standardized and there are different opinions regarding the time of fever onset, but we used the following criteria to diagnose central hyperthermia: (1) no prior infection or fever for at least one week before onset of stroke; (2) presence of fever ($\geq 38.3^{\circ}\text{C}$) after onset of stroke; and (3) negative workup for infection-originated fever^{5,7,9}. Early diagnosis and treatment of central hyperthermia are crucial. However, in most cases, early diagnosis is difficult because of the time-consuming tests required to rule out infection. Furthermore, the mortality rate is high because of complications related to high fever, including sudden cardiac arrest, rhabdomyolysis, and acute renal failure⁹. The precise mechanism of central fever in stroke remains unknown. Body temperature is strictly controlled in the human body. Multiple physiological mechanisms are involved in thermoregulation, all coordinated with the cutaneous thermal receptors, spinal cord, midbrain, and thermoregulatory center of the hypothalamus¹³. Several possible mechanisms can explain central hyperthermia. First, the central pathway controls thermoregulatory thermogenesis and innervation of the brown adipose tissue (BAT). The BAT is an essential effector organ for nonshivering heat generation

that helps maintains eutherma during exposure to cold¹⁹. Preoptic chiasma and anterior hypothalamic nuclei are the centers of thermoregulation. Lowering the temperature of these areas activates the BAT, while raising the temperature deactivates the BAT and nonshivering thermogenesis^{11,15}. Preoptic chiasma/anterior hypothalamic nuclei generate efferent signals that reach the ventromedial hypothalamic nuclei and act as γ -aminobutyric acid (GABA) inhibitors¹². Signals from the ventromedial hypothalamic nucleus reach the raphe nuclei through the lower midbrain, releasing GABA from this region¹⁴. The thermoregulatory signal is connected to the sympathetic chain, and the nonshivering thermogenesis in the BAT is controlled by the sympathetic chain^{7,9}. Second, dysfunction of the serotonergic or dopaminergic system can also be a possible cause of central hyperthermia; the serotonergic system is associated with heat generation, while the dopaminergic system is associated with autonomic and endocrine regulation¹⁸. Symptoms of central hyperthermia are thought to be related to dopamine or serotonin syndrome, including hyperthermia, altered mental state, muscle hypertonia, and autonomic dysfunction. These symptoms are similar to those of our patient who had hyperthermia, altered mental state, and muscle hypertonia. Lastly, the correlation of the central fever with the ICH volume and third ventricular shift suggests possible hypothalamic compression after ICH. Previous studies found no significant correlation between the ICH location and development of central hyperthermia, although thalamic and basal ganglia involvement showed a trend towards being more common in patients with central hyperthermia^{4,6}.

The precise mechanism of action of baclofen is not fully known; however, thus far, baclofen is an agonist of the beta subunit of GABA receptors on mono- and polysynaptic neurons at the level of the spinal cord and brain¹. Regarding the antipyretic effect, we hypothesized two mechanisms of action by which baclofen possible lowered the body temperature. First, baclofen, a GABA receptor agonist, replaces GABA, thereby directly inhibiting the raphe nuclei and suppressing BAT activation, while GABA is blocked because of the mass effect of ICH⁷. Baclofen lowers the body temperature by affecting the dopaminergic system. According to a previous study, low concentrations of baclofen caused increased activity of dopaminergic neurons in rodent ventral tegmental area slices³. As the symptoms of our patient were related to dopamine deficiency, baclofen's action of increasing the activity of dopaminergic neurons may lower the body temperature of the patient. However, this hypothesis can be controversial because, in this study, higher doses of baclofen inhibited dopaminergic neurons, which usually raises the body temperature, but our patient's body temperature decreased as the dose of baclofen was increased.

CONCLUSION

This case provides guidance for understanding the thermoregulation dysfunction in patients with ICH. Thus, in conclusion, persistent central hyperthermia should be considered as a possible cause of fever in patients with ICH, and baclofen administration should be considered

as a treatment option.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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