Bromocriptina y su efecto antipirético en la hipertermia central

Bromocriptine and its antipyretic effect in central hyperthermia

Sérgio Costa Monteiro, Bárbara Paracana, João Fonseca, Jorge Henriques
Internal Medicine Service. Unidade Local de Saúde da Região de Aveiro. Aveiro (Portugal)

ABSTRACT

Central hyperthermia is marked by rapid onset of elevated temperatures, resistant to antibiotics and antipyretics. Diagnosis requires exclusion of infectious sources and identification of an underlying neurological condition. As it is linked to poor prognosis, early intervention is critical. Therapeutic options for temperature control are limited, with few supported by strong clinical evidence. Bromocriptine, which modulates dopaminergic transmission, has been used in some cases, although its use remains off-label and based on limited case reports.

The case involves a 72-year-old male with traumatic brain injury, including an acute subdural hematoma and subarachnoid hemorrhage. Hyperthermia refractory to antipyretics developed within 24 hours. After ruling out infection, central hyperthermia was diagnosed. Bromocriptine was initiated and titrated, leading to sustained temperature control after 72 hours. Upon discontinuation, hyperthermia recurred but resolved with reintroduction of bromocriptine. This case highlights the complexity of central hyperthermia management, suggesting bromocriptine may offer benefit despite limited evidence.

Keywords: Bromocriptine, trauma brain injury, central hyperthermia.

RESUMEN

La hipertermia central se caracteriza por un inicio rápido de temperaturas elevadas, resistentes a antibióticos y antipiréticos. El diagnóstico requiere excluir causas infecciosas y confirmar una condición neurológica subyacente. Dado que se asocia a un peor pronóstico, el control temprano es fundamental. Las opciones terapéuticas para el control de la temperatura son limitadas, con pocas respaldadas por evidencia clínica sólida. La bromocriptina, que modula la transmisión dopaminérgica, se ha utilizado en algunos casos, aunque su uso sigue estando fuera de indicación y basado en informes de casos aislados.

Se presenta el caso de un hombre de 72 años con traumatismo craneoencefálico, incluyendo un hematoma subdural agudo y hemorragia subaracnoidea. En las primeras 24 horas, desarrolló hipertermia refractaria a antipiréticos. Tras descartar una infección, se diagnosticó hipertermia central. Se inició bromocriptina, que fue titulada, logrando un control sostenido de la temperatura tras 72 horas. La interrupción del tratamiento provocó recurrencia de la hipertermia, que se resolvió con la reintroducción del fármaco. Este caso subraya la complejidad del manejo de la hipertermia central y sugiere un posible beneficio de la bromocriptina pese a la escasa evidencia.

Palabras clave: Bromocriptina, traumatismo craneoencefálico, hipertermia central.

INTRODUCTION

Central hyperthermia is characterized by a rapid onset with high temperatures that response poorly to antibiotics and antipyretics. To assume this diagnosis is essential the exclusion of an infectious focus and assure a neurological context that justifies it[1,2]. There are currently no clinical guidance guidelines for their approach[2]. Bromocriptine has been considered as a therapeutic option for these situations, however there is no formal indication for its use, and most of the current evidence of this off-label use is limited to fewer case reports.[1-3]

CASE REPORT

A 72-year-old male, with a history of cerebrovascular disease, diabetes *mellitus*, hypertension, and prior smoking habits, was admitted to the emergency department following a fall from height, resulting in traumatic brain injury (TBI). On admission, the patient was prostrate with a Glasgow Coma Scale of 13. Neurological examination didn't reveal any motor deficits or focal findings. Physical examination showed a small contusion in the frontal region, with a core body temperature of 36.2°C, blood pressure of 129/65 mmHg, heart rate of 86 beats per minute, and peripheral oxygen saturation of 99% in ambient air. No additional abnormalities were observed.

An electrocardiogram was normal and a chest X-ray was unremarkable. Computed tomography, illustrated in Figure 1, revealed an acute left temporo-parieto-occipital subdural hematoma, which caused distortion of the surrounding parenchyma, with a mild midline shift to the right. Subarachnoid blood was present within the cerebral sulci, particularly in the right occipital horn. Additionally, there were multiple clastic lesions. Surgical intervention was deemed unnecessary, and the patient was managed medically.

During the first 24 hours of hospitalization, the patient's temperature increased to >38.5°C, which was refractory to antipyretics and cooling measures. A comprehensive fever workup, including blood cultures, imaging, and laboratory tests, failed to identify any infectious source. Differential diagnoses, such as malignant hyperthermia and neuroleptic malignant syndrome, were excluded based on normal creatine kinase levels and the absence of causative medications.

The diagnosis of central hyperthermia was considered, and treatment with bromocriptine at 5 mg/day (2.5 mg every 12 hours) was initiated, subsequently titrated to 10 mg/day (5 mg every 12 hours). Over 72 hours, gradual control of hyperthermia was achieved, with the patient maintaining a sustained apyretic state. On the sixth day of hospi-

Correspondencia: 71258@chbv.min-saude.pt
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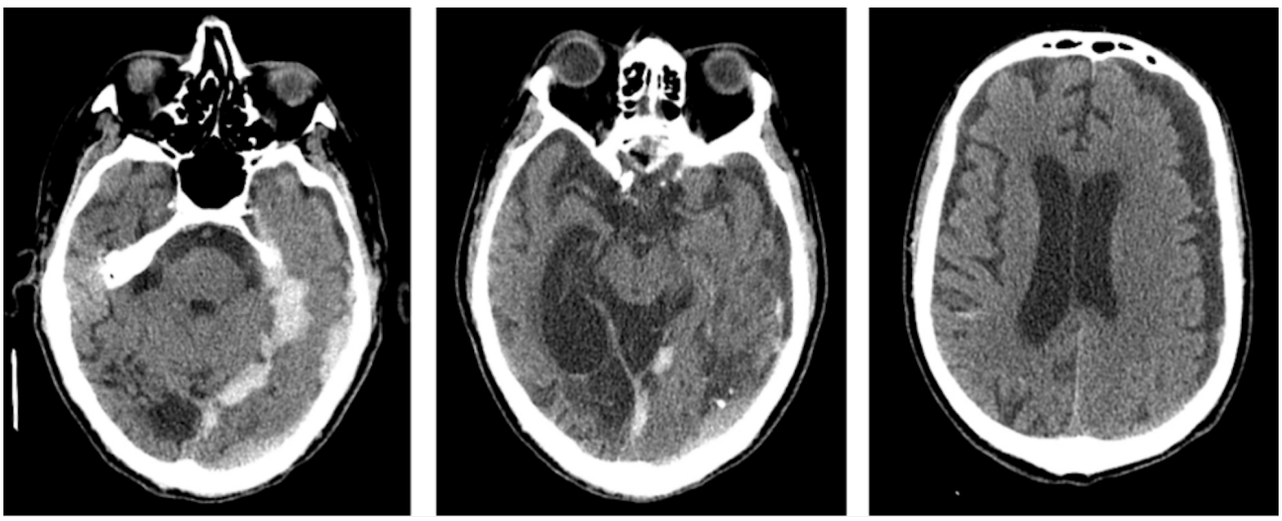

Figure 1. CT scan of the head. CT scan of head showing an acute left temporo-parieto-occipital subdural hematoma that shapes the regional parenchyma, with incipient midline shift to the right; an subarachnoid blood dispersed through the grooves of the hemispheres, settling in the right occipital horn; and multiple clastic lesions.

talization, the patient experienced a loss of oral intake and missed 24 hours of oral medications, including bromocriptine. This interruption led to the recrudescence of hyperthermia, despite a negative septic workup. Upon reintroduction of bromocriptine, temperature control was reestablished. The correlation between temperature fluctuations and bromocriptine administration is illustrated in Figure 2.

The patient remained hospitalized for 24 days and was subsequently transferred to a rehabilitation facility for neurological recovery. Over time, as the subdural hemorrhage reabsorbed, bromocriptine was tapered and eventually discontinued without recurrence of hyperthermia.

DISCUSSION

Hyperthermia is often considered secondary to an infectious process, but in patients with neurological injuries, it may be a direct consequence of brain injury itself. Central hyperthermia is characterized by a rapid onset of elevated core body temperatures that respond poorly to antipyretics and antibiotics. Diagnosis requires exclusion of infectious causes and appropriate clinical correlation with neurological injury. Central hyperthermia is associated with poorer prognoses in neurologically injured patients, making early temperature control critical in this population.1

The pathophysiology of central hyperthermia likely involves compression or disruption of thermoregulatory centers in the hypothalamus and brainstem due to intracranial pathology. Thermoregulatory areas within the hypothalamus include the lateral parabrachial nucleus at the junction of the pons and medulla, the pre-optic area, and inputs from spinothalamocortical pathways. Brown adipose tissue thermogenesis, regulated by the brainstem, also plays a role in thermoregulation. The complexity of these pathways and their involvement in various neurological injury mechanisms makes central hyperthermia a challenging entity to fully understand and manage.[4]

Given the absence of definitive diagnostic criteria, central hyperthermia remains a diagnosis of exclusion. However, certain clinical features support this diagnosis, such as the development of high core temperatures (>38.5°C) with rapid onset, poor response to antipyretics and antibiotics, absence of infection prior to the onset of hyperthermia, and a negative fever workup[1]. A cohort study of 526 patients with neurological injuries demonstrated that the combination of a negative culture, absence of infiltrates on chest X-ray, appropriate neurological context (such as TBI, subarachnoid hemorrhage, or space-occupying lesions), and onset of hyperthermia within 72 hours of hospitalization had a predictive value of 90% for diagnosing central hyperthermia. Our patient fulfilled all these criteria, supporting the diagnosis.[3]

Treatment of central hyperthermia is challenging and typically requires a multimodal approach. Current therapeutic options are largely based on case reports and small studies, and include pharmacological agents such as bromocriptine, baclofen, and morphine, in combination with surface or intravascular cooling devices. Recently, the use of IL-1 antagonists has been proposed as a potential therapy for central hyperthermia. However, further research is needed to validate this approach.[2-4,5]

In this patient, standard antipyretics were ineffective in controlling core temperature, prompting the addition of bromocriptine. Bromocriptine, a dopamine D2 receptor agonist, acts on the hypothalamus and corpus striatum to enhance dopaminergic transmission. It typically reaches a steady-state concentration 72 hours after initiation, which correlates with the observed timeline of temperature stabilization in our patient. Although bromocriptine is primarily used to treat conditions such as hyperprolactinemia, Parkinson's disease, acromegaly, and pituitary adenomas, its off-label use for central hyperthermia has been described in the literature.[2]

Although the optimal dose for central hyperthermia has not been established, 10 mg/day is often considered effective, with some reports

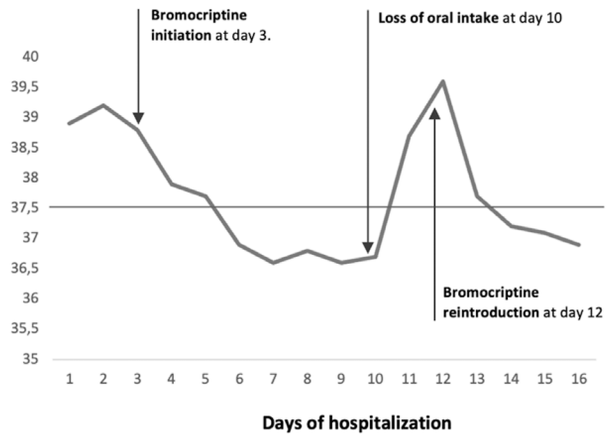

Figure 2. Relationship between bromocriptine and core temperature. Average core temperature for each day during hospital course is graphically shown. Bromocriptine was started at a dose of 2.5mg every 12 hours, titrated up to 5 mg every 12 hours in a 48 hours period. At day 10, patient loss is oral intake and didn't take bromocriptine. Immediately after discontinuation of bromocriptine, there was a significant increase in core temperature. After resuming bromocriptine 5 mg every 12 hours at day 12 of hospitalization, there was a significant decrease in core temperature.

suggesting efficacy at doses as low as 7.5 mg/day. Long-term bromocriptine therapy generally has minimal adverse effects. These can include bradycardia and hypotension and are more commonly seen at higher doses (≥25 mg/day)[4,6]. None were observed in our patient.

Despite the lack of systematic studies evaluating the efficacy and safety of dopamine agonists in traumatic brain injury, available case reports and small sample studies suggest that bromocriptine is effective in controlling central hyperthermia without significant adverse effects. However, further research is warranted to establish formal treatment guidelines for this condition.

CONFLICT OF INTEREST
All authors declare that there are no conflicts of interest in carrying out this work.

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ETHICAL ASPECTS
The patient's written consent was obtained for publication of this case.

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