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CASE REPORTS

Taming the Neurogenic Storm: Targeted Pharmacotherapy for Central Fever in Neurointensive Care: A Case Report

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ABSTRACT

Central fever is a non-infectious, neurogenic hyperthermia arising from thalamic injury. It complicates the clinical course of patients in neurointensive care units by closely mimicking infectious sepsis, often leading to diagnostic dilemmas and the inappropriate overuse of broad-spectrum antimicrobials.The underlying mechanism involves the disruption of hypothalamic thermoregulatory pathways and secondary neuroinflammation. Emerging advanced neuromonitoring techniques further assist in differentiating autonomic dysregulation from infection.

We present the clinical course of two neurocritically ill patients who developed refractory central fever. The report discusses successful resolution of fever in these patients. Maintaining a high clinical suspicion for central fever following the systematic exclusion of sepsis is paramount. Prompt intervention with targeted therapies like diclofenac rapidly controls temperature, safeguards the brain from secondary metabolic stress, and prevents antimicrobial abuse.

KEYWORDS

• Fever • Diclofenac • Brain Injury • Bromocriptine

INTRODUCTION

Central fever is a non-infectious, high-grade, persistent fever that is unresponsive to antibiotics and mimics sepsis.[1] Accurate identification is essential to avoid antibiotic overuse and to implement effective symptom control. Management relies on targeted non-steroidal anti-inflammatory drugs like diclofenac, which blocks central prostaglandin synthesis. Refractory cases, or those presenting with paroxysmal sympathetic hyperactivity (PSH), may benefit from secondary agents such as bromocriptine, chlorpromazine, baclofen, propranolol, or clonidine to modulate specific central adrenergic, dopaminergic, or GABAergic pathways.[2] This report of two cases

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adheres to the CARE (Case Report) guidelines of EQUATOR network.

CASE DESCRIPTION 1

A 66-year-old female with type 2 diabetes, a 15-year history of uncontrolled hypertension, and a 3-year history of hypothyroidism presented with a right thalamic infarct and aspiration pneumonitis. Severe hypoxia (SpO_2 70%) necessitated endotracheal intubation and mechanical ventilation on SIMV-PC mode.

She subsequently developed extreme hyperthermia (up to 105°F) that failed to respond to broad-spectrum antibiotics, including piperacillin-tazobactam, meropenem, vancomycin, clindamycin, and levofloxacin. Serial imaging and cultures revealed no definitive infectious source. Neuroimaging demonstrated a right lentiform infarct, cerebellar atrophy, periventricular ischemic changes, and bilateral white matter demyelination. After thoroughly excluding infection, a diagnosis of central fever was established. The initiation of a continuous intravenous diclofenac infusion achieved gradual and sustained resolution of her fever.

CASE DESCRIPTION 2

A 60-year-old male presented with a severe traumatic brain injury following a motor vehicle accident. Neuroimaging revealed an acute subarachnoid hemorrhage (SAH) involving the right frontoparietal and occipital regions and the mesencephalic cistern. Associated polytrauma included multiple facial fractures, a rib fracture, a vertebral fracture (D12-L1), and left hemiplegia.

Within 36 hours of admission, his Glasgow Coma Scale (GCS) score deteriorated from $E_1V_TM_5$ to $E_1V_TM_4$. He developed a persistent, high-grade fever unresponsive to empiric antibiotics and supportive care. Extensive clinical evaluations and cultures were entirely negative for an active infectious source. He was managed on the lines of central fever, resulting in an immediate positive response and subsequent complete resolution of his hyperthermia.

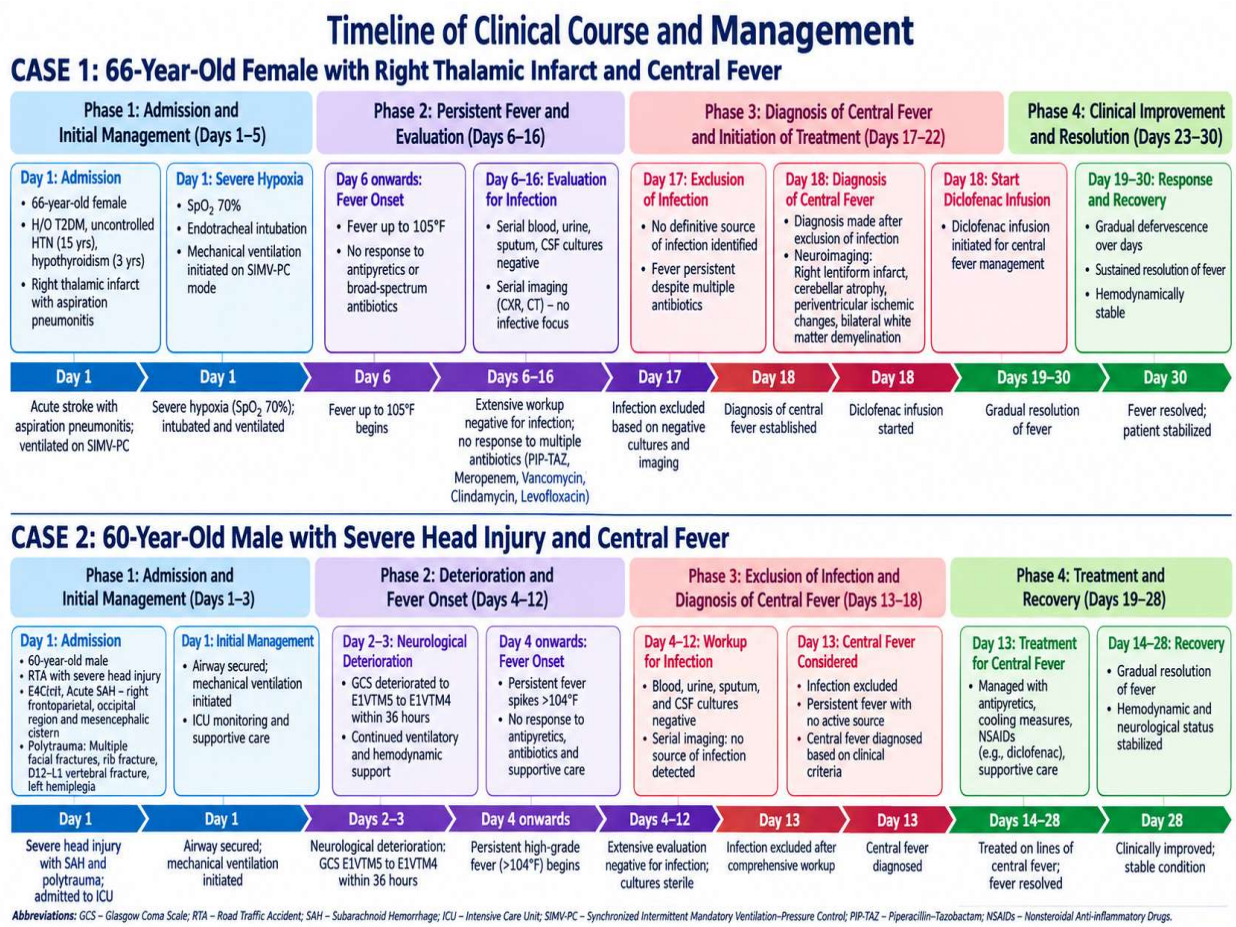

Figure 1: Timeline of clinical course of the two patients

DISCUSSION

Central fever remains a diagnosis of exclusion in neurosurgical intensive care units, occurring most commonly after traumatic brain injury, SAH, intracerebral hemorrhage, hypothalamic injury, or major cranial surgery. The underlying pathophysiology involves the disruption of hypothalamic thermoregulatory pathways, neuroinflammation, localized cytokine release, autonomic dysfunction, and impaired central temperature control. Differentiating central fever from infectious causes is highly challenging because both conditions frequently coexist in critically ill neurosurgical patients.

Central fever affects 23–37% of patients with acute brain injury, particularly traumatic brain injury (TBI), SAH, and large ischemic strokes. It typically presents with a sudden onset, high-grade temperature (>39°C), and an absence of diurnal variation.[3]

While frequently confused with nosocomial infections, key diagnostic indicators supporting central fever include: (i) A normal or non-rising white blood cell (WBC) count, (ii) sterile cultures across all sites, (iii) non-responsiveness to broad-spectrum antibiotics, (iv) neuroimaging evidence of CNS injury, especially involving the hypothalamus, brainstem, or basal ganglia.

Structural lesions affecting critical neurovascular and hypothalamic-adjacent areas further exacerbate thermoregulatory failure. For instance, Rao et al. documented a tuberculum sella meningioma causing vascular compression and neurological deficits, demonstrating how pathology in the sellar and suprasellar regions disrupts neighboring neural architectures. Although fever was not a presenting feature in that specific case, lesions near hypothalamic pathways reinforce the neuroanatomical foundation of central thermoregulatory dysfunction.[4]

The paradigm for understanding recovery from severe neurological injury continues to evolve. Recent shifts in coma management emphasize advances in neurocritical care, multimodal neuromonitoring, and the mechanisms governing consciousness recovery. These developments are highly relevant because central fever often occurs in patients with impaired consciousness, where precise neurological tracking is vital to differentiate fever-induced deterioration from the progression of primary brain injuries.[5]

Once infection is ruled out, targeted antipyretic therapy is paramount. Diclofenac demonstrates consistent efficacy in central fever due to its potent cyclooxygenase (COX) inhibition and central prostaglandin synthesis blockade. Continuous intravenous diclofenac infusion is well-documented in neurocritical care literature when alternative methods fail; conversely, acetaminophen monotherapy is often insufficient, and external cooling devices serve only an adjunctive role.

While prophylactic antipyretics remain under investigation, Giaccari et al. described a protocol utilizing an initial diclofenac sodium bolus (0.2 mg/kg over 30 minutes), followed by a continuous infusion of 75 mg in 50 ml of normal saline at 2–3 ml/hr to achieve effective fever suppression.[6]

For refractory cases, or those associated with specific clinical syndromes, alternative agents target distinct pathways. Bromocriptine is a dopamine agonist that acts on hypothalamic thermoregulation via D2 receptor stimulation. Central dopamine depletion is hypothesized to drive brain injury-induced hyperthermia, making bromocriptine highly effective in neuroleptic malignant syndrome (NMS) and central fevers tied to basal ganglia or hypothalamic injuries.[7] It serves as a valuable second-line option if NSAIDs fail, particularly in patients with thalamic or basal ganglia insults (as seen in Case 1) or during paroxysmal sympathetic hyperactivity (PSH).

Chlorpromazine is a phenothiazine antipsychotic that acts on central dopamine, serotonin, and histamine receptors. Its anticholinergic and sedative properties help dampen hyperactive hypothalamic pathways, serving as a second-line option for severe central fevers or NMS.[8] While beneficial for managing concurrent agitation, its potential to cause detrimental systemic hypotension limits its utility in neurocritically ill patients.

Baclofen is a $GABA_B$ receptor agonist and central muscle relaxant that reduces excitatory neurotransmission, blunting sympathetic overactivity.[9] It is particularly useful when central fever coexists with the spasticity and rigidity of PSH, or in spinal cord injuries, though risks of hypotonia and respiratory depression at high doses limit its intensive care application.

Propranolol is a beta-adrenergic blocker that mitigates peripheral sympathetic activation (e.g., tachycardia, hypertension), indirectly supporting temperature regulation. It serves as an excellent adjunct when central fever is accompanied by autonomic dysregulation in severe neurotrauma or SAH, and has demonstrated a mortality benefit by blunting catecholamine surges. The patient in Case 2 may have benefited from propranolol if systemic sympathetic overdrive had emerged.[10]

Clonidine is a central alpha-2 agonist that reduces sympathetic outflow, thereby dampening central thermoregulatory overdrive. It is highly effective in managing PSH presentations involving fever, tachycardia, diaphoresis, and hypertension, preventing recurrent febrile spikes. Clonidine provides additional benefits to patients with marked autonomic instability by modulating sympathetic storms.[11]

While diclofenac successfully managed the patients in this series, adjuncts like bromocriptine, clonidine, and propranolol should be reserved for NSAID-refractory cases, PSH, or neurotrauma involving autonomic centers. Integrating these therapies can optimize autonomic control, reduce ICU length of stay, and minimize complications from sustained hyperthermia. We summarize these pharmacological options in the table below.

Table 1: Summary of potential role of drugs mitigating central fever

Therapy	Mechanism of Action	Clinical Context / Indication	Relevance to Present Cases
Diclofenac	Cyclooxygenase (COX) inhibition leading to suppression of prostaglandin-mediated thermogenesis	Considered a first-line pharmacological option for central fever after exclusion of infectious causes	Produced sustained defervescence in **Case 1 (thalamic infarct)** and supported the diagnosis of central fever
Bromocriptine	Dopaminergic agonist that modulates hypothalamic thermoregulatory pathways	Useful in refractory central fever, particularly in patients with basal ganglia or thalamic injury when fever persists despite NSAID therapy	Could be considered as a second-line option if fever recurs or becomes refractory in **Case 1**
Chlorpromazine	Central dopamine antagonism with hypothalamic inhibition and sedative effects	May be beneficial in refractory central hyperthermia, autonomic agitation, or situations overlapping with neuroleptic malignant syndrome-like presentations	Potential rescue therapy for persistent fever unresponsive to conventional treatment
Baclofen	GABA-B receptor agonist reducing central excitatory output	Particularly useful when fever occurs in association with paroxysmal sympathetic hyperactivity (PSH), spasticity, or autonomic dysregulation	May have a role in severe neurotrauma patients exhibiting sympathetic storms
Propranolol	Non-selective β-adrenergic blockade reducing sympathetic overactivity	Effective in fever associated with polytrauma, traumatic brain injury, subarachnoid hemorrhage, and PSH	Particularly relevant to **Case 2 (severe head injury with SAH and polytrauma)** where adrenergic hyperactivity may contribute to persistent fever

Recent advances in neurophysiological monitoring have deepened our understanding of altered brain states in critically ill patients. Anesthetic states are inherently multidimensional and may decouple from conventional electroencephalographic (EEG) indices. For example, paradoxical bispectral index-burst suppression combinations signal neural inertia and complex transitions between states of consciousness. Such phenomena underscore the intricate relationship between cerebral network connectivity and autonomic function—mechanisms that likely participate in the dysregulated thermoregulation of central fever.[12]

The evolving emphasis on objective neurophysiological monitoring has also extended beyond EEG. Photoacoustic detection of propofol in exhaled breath is a novel approach for monitoring anesthetic depth in neuroanesthesia.[13] Continuous multimodal monitoring strategies such as these may contribute to more precise assessment of neurological status and facilitate differentiation between altered consciousness due to infection, metabolic disturbances, drug effects, or primary neurological injury in febrile neurosurgical patients.

Maintaining adequate cerebral perfusion is fundamental, as hyperthermia accelerates cerebral metabolic demand and exacerbates secondary brain injury. Given the physiological nonequivalence of temporary flow-reduction techniques in neurovascular surgery, preserving stable cerebral blood flow and minimizing ischemic insults remains crucial. Because hypothalamic and diencephalic injuries drive central fever, optimizing cerebral perfusion may theoretically shield these sensitive thermoregulatory centers from secondary degradation.[14]

Furthermore, Fourier-based EEG analysis holds promise for predicting anesthetic emergence during non-neurosurgical procedures in neurosurgical cohorts. Advanced signal processing may eventually help characterize the specific cerebral dysfunction that underlies central autonomic disturbances and impaired thermoregulatory control.[15]

Collectively, these contemporary insights emphasize the expanding roles of advanced neuromonitoring, cerebral perfusion management, and brain-state dynamics in neurocritical care. Although direct links to central fever require further investigation, these frameworks illuminate the physiological disruptions underlying thermoregulatory failure and will guide future diagnostic and therapeutic approaches in the neuro-ICU.

Ultimately, managing central fever remains largely empirical, focused on modulating dysregulated central pathways. Diclofenac remains an effective, high-utility first-line agent, as demonstrated by prompt defervescence in our patient with a thalamic infarct. Refractory cases or those with profound sympathetic activation warrant targeted choices: bromocriptine for hypothalamic/basal ganglia injuries, chlorpromazine for central hypothalamic inhibition, baclofen for PSH-associated rigidity, and adrenergic modulators (propranolol/clonidine) for severe neurotrauma or SAH. Our patients' positive responses following the rigorous exclusion of sepsis reinforce the validity of these targeted strategies.

CONCLUSION

These two cases highlight the importance of early recognition of central fever in acute brain injury. Once sepsis is ruled out, targeted therapy with a continuous diclofenac infusion can rapidly resolve hyperthermia, improve patient comfort, and prevent antibiotic overuse. Clinicians must maintain a high index of suspicion for central fever in the neurointensive care whenever high-grade pyrexia persists despite broad-spectrum antimicrobial coverage and sterile cultures.

Conflict of interest: None

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