Letter to the Editor

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A stroke patient with persistently intermittent fever treated with gabapentin: A clinical case

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SUMMARY Fever is one of the most common complications in stroke patients and can generally be classified as either infectious or non-infectious. Infectious fevers are commonly caused by pulmonary infections, urinary tract infections, and secondary infections associated with medical interventions such as endotracheal intubation, urinary catheterization, and nasogastric tubes. Non-infectious fevers primarily manifest as central fevers, although in rare cases, they may also result from drug-induced causes. Existing research indicates that the most common cause of central fever is brainstem hemorrhage, followed by hemorrhage in the basal ganglia and thalamus, then cerebellar hemorrhage, large cortical infarction, and basilar artery occlusion, with intraventricular hemorrhage being relatively rare. Stroke patients' body temperatures can rise to 39°C within 12 hours after onset and peak within 24 hours. In this case, a stroke patient with acute cerebral infarction and secondary thalamic hemorrhage developed new sensory abnormalities in the left limbs and intermittent fever during hospitalization. Despite the use of antibiotics targeting a pulmonary infection, the patient's fever did not show significant improvement. Gabapentin was added to the treatment regimen to address the sensory abnormalities. Surprisingly, within four hours of gabapentin administration, the patient's body temperature normalized and remained stable during subsequent monitoring. This observation led us to hypothesize that gabapentin may have a potential role in alleviating central fever.

Keywords stroke, infection, thalamic fever, gabapentin, central fever

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The typical manifestation of central fever is a significant fluctuation in body temperature over a short period, characterized by a rapid rise followed by a gradual decline, and is often associated with high mortality rates (*1,2*). Additionally, studies have suggested that dysphagia may also be linked to fever (*3,4*). Paroxysmal sympathetic hyperactivity can also cause fever, with clinical symptoms including paroxysmal hyperthermia, tachycardia, rapid breathing, hypertension, and generalized muscle rigidity (*5,6*). Common treatments for such fevers include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (*7-9*). Traditional pharmacological interventions, such as diclofenac sodium, are widely used, while bromocriptine and dantrolene are frequently prescribed for patients with malignant hyperthermia (*10*). Furthermore, the literature mentions the adjunctive use of non-pharmacological therapies and physical cooling methods, such as warm compresses, ice packs, and alcohol wipes (*11,12*).

The thalamus not only functions as the brain's primary sensory relay center but also plays a critical role in temperature regulation, as the hypothalamus, which is responsible for thermoregulation, is closely linked to central fever symptoms (*13*). Central fever is not uncommon in clinical practice, particularly among stroke patients. A review of the literature and case reports reveals that treatment for central fever primarily focuses on anti-infective and anti-inflammatory therapies. However, to date, no reports have documented the use of gabapentin for treating central fever following a stroke.

Here, we report a novel case: A 70-year-old patient initially presented with persistent dizziness, vomiting, and urinary incontinence, without any clear cause. Upon admission, her symptoms included drowsiness, slowed responses, cognitive impairment, poor speech fluency, and reduced motor function in both limbs, with more pronounced symptoms on the right side, including

sensory deficits in the right lower limb. Muscle strength assessment revealed 2/5 in the right upper and lower limbs, 4/5 in the left upper limb, and 3/5 in the left lower limb.

An initial evaluation at the local hospital included a brain MRI, which showed medullary infarction. Due to the severity and complexity of her condition, the patient was transferred to our hospital for further evaluation and treatment. Upon admission, we developed a comprehensive treatment plan to address her medical issues. According to stroke management guidelines, the patient received dual antiplatelet therapy with aspirin and clopidogrel to prevent stroke recurrence. In addition, atorvastatin was prescribed to regulate lipid levels and stabilize plaques. Butylphthalide was introduced to improve cerebral circulation and metabolism. Urokinase was used to promote collateral circulation, and betahistine was administered to prevent vertigo episodes. Fibrinolysin was also used to manage the patient's hypercoagulable state.

During hospitalization, the patient developed additional complications, including signs of upper gastrointestinal bleeding, prompting the introduction of omeprazole to protect the gastric mucosa. The patient also experienced intermittent fever, leading to immediate laboratory tests and imaging studies. Subsequent imaging revealed a hematoma in the right thalamus with rupture into the ventricle. A chest CT also showed patchy shadows in the right upper lobe and left lower lobe, suggestive of pulmonary inflammation. Based on these findings, standard antibiotic therapy was initiated with cefoperazone-sulbactam. However, despite treatment, the patient's temperature continued to rise, and infection markers did not improve as expected. Cefoperazone-sulbactam was then combined with linezolid, but the results remained unsatisfactory. Antibiotic therapy was escalated to meropenem, and after detecting *Legionella*, moxifloxacin was added for targeted treatment. Despite these anti-infective interventions and improvement in infection markers, the patient's intermittent fever persisted, and her clinical condition remained complex and challenging (Figures 1 and 2).

When we were struggling to control the patient's fever, the patient's family reported the recent onset of pain in the left limbs. Given that the patient's pain likely

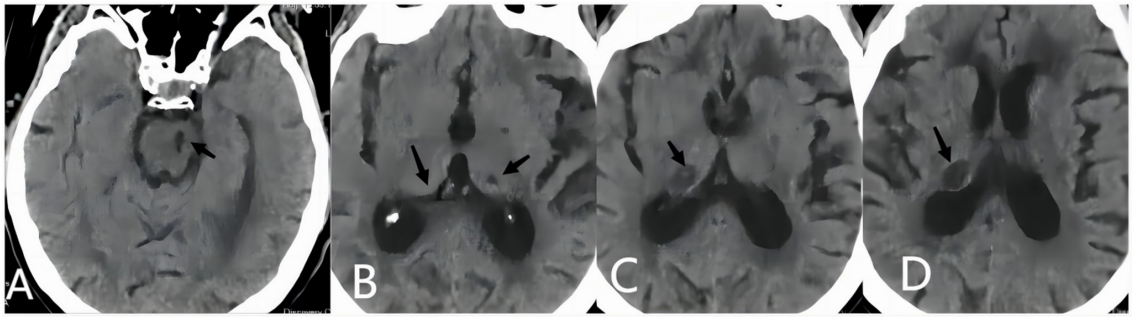

Figure 1. Clinical imaging of stroke indicators at initial presentation. (**A** and **B**) Suspected areas of ischemia and infarction are observed in both the basal ganglia, frontal and parietal lobes, the left thalamic region, and the brainstem, with associated softening. (**C** and **D**) A slightly hypodense area is visible in the right thalamic region.

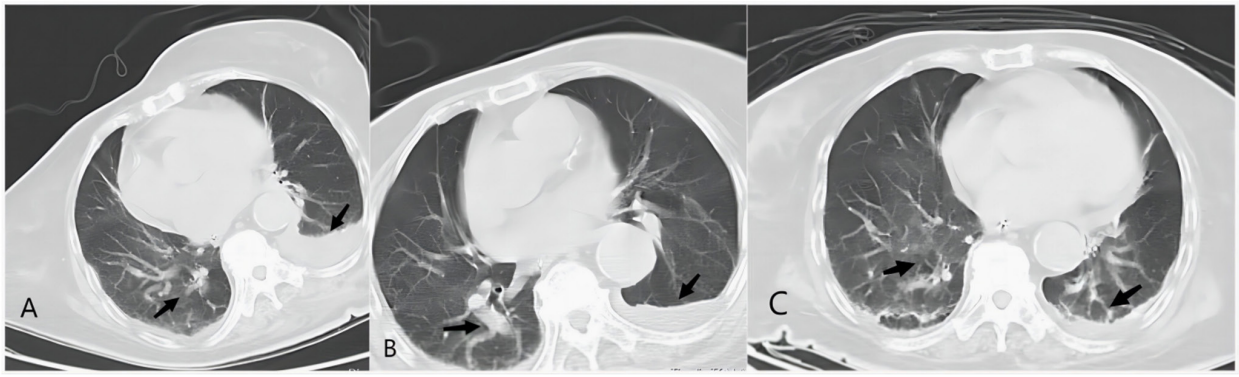

Figure 2. Imaging examinations on days 13, 17, and 25 of hospitalization. (**A**) Infectious lesions are considered in both lungs, with left pleural effusion and partial left lung collapse. (**B**) Inflammatory changes in both lungs, with partial absorption compared to the previous scan. Both pleurae are thickened, with left pleural effusion and partial left lung collapse or consolidation. (**C**) Inflammatory changes in both lungs. Both pleurae remain thickened, with left pleural effusion and partial left lung collapse or consolidation, showing slight improvement compared to the previous scan.

Table 1. Temperature variations following medication use during hospitalization

Pre-medication temperature (℃)	Post-medication temperature (℃)	Drugs
	37.5-38.5 (+5d*)	sulperazone
	37-38.9 (+3d)	Sulperazone + linezolid
	36.5-38.5 (+5d)	Sulperazone + linezolid + azithromycin
	36.2-38.4 (+4d)	meropenem
	36.4-37.9 (+5d)	Meropenem + moxifloxacin
38-39	36.4-38.1 (+2d)	Sulperazone + aspirin-dl-lysine
	36-36.8 (+5d)	Sulperazone + gabapentin
	36-36.9 (+10d)	Sulperazone + gabapentin + tigecycline + fluconazole
	36.1-36.8 (+8d)	Gabapentin + tigecycline + fluconazole + meropenem
	36-36.6 (+2d)	Gabapentin + tigecycline + meropenem
	36.2-36.6 (+2d)	Gabapentin + meropenem

*d: days

originated from thalamic lesion stimulation, we decided to administer gabapentin to target the neuropathic pain. The patient was initially given 0.3 g of gabapentin *via* a nasogastric tube. Unexpectedly, by 2 p.m., the patient's body temperature had dropped to 36.3°C, without the use of any other medications during this time. Over the next 29 days of treatment, gabapentin was continued to manage the patient's neuropathic pain. On the second day, the patient received 0.3 g of gabapentin twice daily *via* the nasogastric tube, and from the third day onward, the dosage was increased to 0.3 g three times daily. Encouragingly, not only did the patient's neuropathic pain improve, but her body temperature also remained consistently between 36°C and 36.9°C, with no recurrence of intermittent fever (Table 1).

In clinical practice, managing post-stroke fever involves not only providing antipyretic treatment when necessary but also collecting laboratory and imaging data to assess for the presence of infection or inflammation, as infectious fever is the most common cause in such cases. If infection is confirmed, targeted antibiotic therapy should be administered. However, if the patient's condition does not improve after the use of appropriate antibiotics, other potential causes of fever, such as drug-induced or central fever, should be considered. Central fever, primarily caused by lesions or injury to the central nervous system, can be particularly challenging to manage. In this case, despite the use of broad-spectrum antibiotics and the fact that laboratory indicators and imaging results suggested that the infection was under control, the patient's fever did not significantly improve. This led us to suspect that while the initial fever may have been related to infection, the persistent intermittent fever that followed was likely due to central factors affecting thermoregulation. Considering the location of the patient's lesion and the concurrent thalamic hemorrhage during fever episodes, we hypothesized that the primary cause of the ongoing intermittent fever was not infection or inflammation, but central fever (*14-16*).

Body temperature regulation is primarily managed by the hypothalamus and brainstem, with the hypothalamus playing a central role (*13*). Thalamic fever refers to fever originating from thalamic lesions, as the thalamus is involved in various sensory and motor functions, as well as temperature regulation. Reviewing the patient's medical history, we suspected that the left-sided brainstem infarction may have disrupted the thermoregulatory pathways. Furthermore, the later-stage right thalamic hematoma, which extended into the ventricle, may have stimulated specific areas of the thalamus. The combined influence of these two factors likely increased neuronal excitability, enhancing the sensitivity of the thermoregulatory center to inflammatory stimuli. This heightened sensitivity could lead to significant increases in body temperature, even in response to mild external or internal stimuli.

Gabapentin, an anticonvulsant, is also used to manage neuropathic pain and certain neurological conditions. It works by modulating neural signals in the central nervous system, helping to alleviate abnormal neuronal excitability. In cases of central fever, gabapentin may help stabilize body temperature by reducing the abnormal electrical excitability in the thermoregulatory center triggered by thalamic lesions (Figure 3).

In this case, we observed that gabapentin may have potential efficacy in intervening against central or thalamic fever induced by abnormal neuronal excitation. This suggests that gabapentin could be considered as an alternative treatment when traditional antipyretic therapies fail. Although more scientific research is needed to establish a definitive link, this case highlights the importance of considering central fever in the differential diagnosis of fever in stroke patients, particularly those with complex or severe conditions, and paying close attention to lesion locations.

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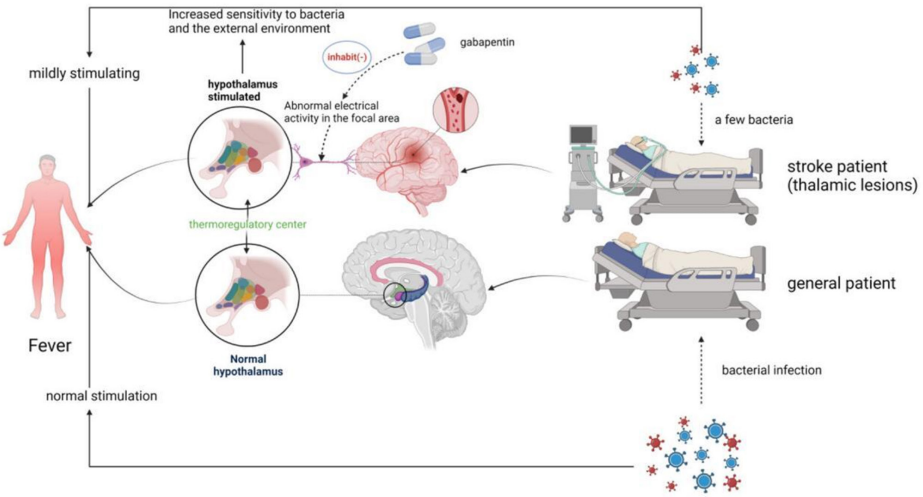

Figure 3. Central fever potential mechanisms and treatment strategies diagram.

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