DOI: 10.7860/JCDR/2023/59699.17539

Case Report

Internal Medicine Section

# Quad Fever after Acute Traumatic Spinal Cord Injury

MARUTEESH MALLAPPA[1], PRADEEP RANGAPPA[2], IPE JACOB[3], LAKSHMAN THIMMEGOWDA[4], KARTHIK RAO[5]



## ABSTRACT

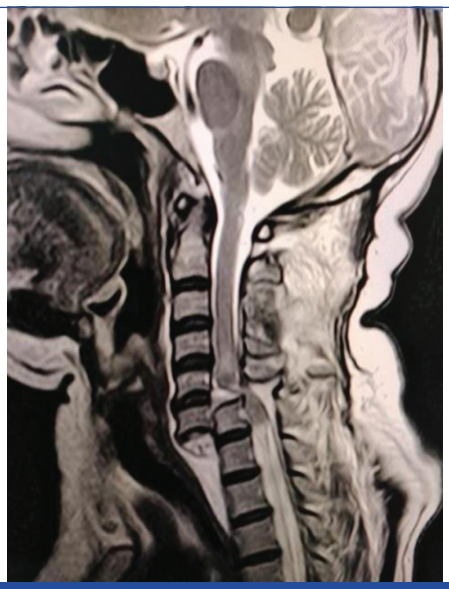
Quad fever is a rare and sometimes fatal condition characterised by sustained high temperatures of 40.8°C (105.4°F) and above, in spinal cord injury patients. Patients are often unresponsive to routine antipyretics and diagnosis is usually one of exclusion after other causes of fever are ruled out. This condition is understood to be secondary to autonomic dysfunction leading to thermoregulatory impairment. In the present case report, a 53-year-old male patient developed a fever of 104°F two days after a traumatic spinal cord injury involving C6-C7 segments. The fever did not respond to paracetamol, empirical broad-spectrum antibiotics or thromboprophylaxis. After ruling out both infectious and non infectious causes of fever, the hyperthermia was attributed to quad fever, a type of neurogenic fever. The patient continued to have non relapsing high fever and died five days after presentation. The case highlights the need to be aware of this differential in cases of high fever following traumatic spinal cord injury, in order to better prognosticate and also avoid unnecessary antimicrobial usage.

**Keywords:** Autonomic dysreflexia, Pyrexia, Quadriplegia, Spinal cord transection, Thermoregulation

## CASE REPORT

A 53-year-old male presented to the emergency room about one hour after falling from a two-wheeler, followed by inability to move all four limbs. He had a Glasgow Coma Scale (GCS) score of 15/15, blood pressure of 85/40 mmHg, heart rate of 108 beats per minute, respiratory rate 32 breaths per minute and oxygen saturation of 96% on room air and was afebrile. His co-morbidities included diabetes mellitus and hypertension.

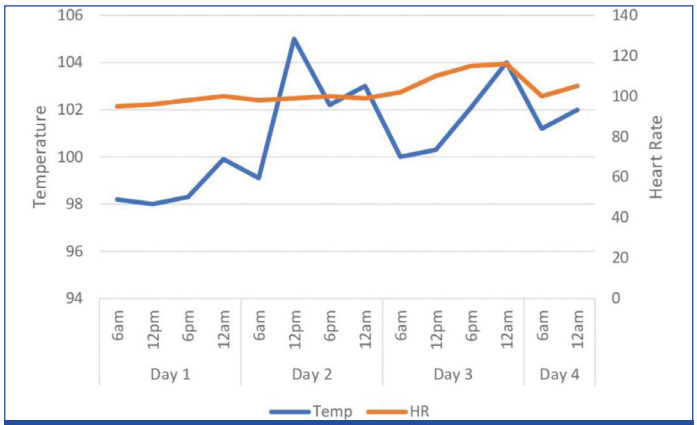
Motor power in all limbs was 0/5, deep tendon reflexes were absent and plantar reflexes were non responsive bilaterally. Laboratory investigations were normal. After immobilising the neck with a hard collar and resuscitation with intravenous fluids, he underwent Magnetic Resonance Imaging (MRI) of head and neck. He was diagnosed with American Spinal Injury Association (ASIA) grade A spinal cord injury (SCI) with complete transection of spinal cord at C6-7 with extensive cord oedema, and overriding of the body of C6 over C7, as shown in [Table/Fig-1] [1]. He was electively intubated with cervical manual in-line stabilisation, as he remained tachypnoeic and hypotensive despite adequate resuscitation.



**[Table/Fig-1]:** MRI (sagittal view) of spinal cord showing complete transection of cervical cord at C6-C7.

He also underwent cervical traction with a 4 kg weight and was started in intravenous (i.v.) methyl prednisolone 2 g. Initial laboratory investigations were normal.

The following day, he developed a fever of 104.8°F, for which he was empirically started on cefoperazone and sulbactam. Prior to this, leucocyte count and cultures were ordered. The fever did not subside with i.v. paracetamol 1g 6$^{th}$ hourly and other measures including tepid sponging and external cooling with a fan. Further tests were ordered that included C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and procalcitonin. Leucocyte count was 8000 cells/mm$^3$, CRP 7 mg/L (normal 0-5 mg/L), ESR 55 mm/hr (normal 0-22 mm/hr), procalcitonin level 0.4 ng/mL (normal 0.15-2 ng/mL). He remained febrile on the third day in Intensive Care Unit (ICU), with the highest temperature reaching 104°F. Blood, urine and endotracheal secretion cultures were sterile with repeated leucocyte count and procalcitonin levels remaining normal. [Table/Fig-2] shows the trend of daily temperatures along with the corresponding maximum pulse rate.




**[Table/Fig-2]:** Trend of daily temperatures along with the corresponding maximum pulse rate.

All drugs except enoxaparin for Deep Vein Thrombosis (DVT) prophylaxis were stopped. 2D echocardiogram, D-dimer and thyroid function tests were normal. History of usage of neuroleptics, tricyclic antidepressants and selective serotonin reuptake inhibitors was ruled out. After ruling out other infectious and non infectious causes for fever, a diagnosis of quad fever was made. Over the next

two days, he became comatose and progressively hypotensive, requiring multiple vasopressors, eventually succumbing on the fifth day of admission.

## DISCUSSION

Quad fever, initially termed so as it was seen in quadriplegic SCI patients, is characterised by temperatures beyond 40°C (101.5°F) [2]. Fever is reported to occur in 47-85% of patients with SCI, and is significantly higher in patients with complete SCI ASIA grade A), as in the present case, than those with incomplete SCI [3]. Quad fever is usually seen in cervical and rarely in high-/mid-dorsal spinal injuries, and is characterised by its unresponsiveness to antipyretics and other standard treatment modalities [4]. It is non infectious in origin, thought to occur due to hypothalamic injury, and carries a high mortality of upto 88% [5].

Neurogenic fever (NF) is a non infectious source of fever seen in 2.6-27.8% of patients with traumatic brain injury or SCI, and may be an early sign of autonomic dysfunction [6,7]. It is notable for hyperthermia, usually above 102°F (38.9°C), and resistance or partial response to antipyretic medications, and having a plateau-like temperature curve that may persist for days to weeks. Additional features of autonomic dysfunction may be seen including shock, bradycardia and the loss of sweating. In the case series on quad fever, patients had a course of events similar to the present report, including high-grade fever unresponsive to antipyretics, haemodynamic instability and cardiac arrhythmias coinciding with the fever and rapid deterioration culminating in death [2].

Quad fever is a NF seen in SCI, usually involving the lower cervical segments, from C5 to C7, and is more common in quadriplegic than paraplegic patients, similar to this case report [8]. It is usually diagnosed after ruling out infectious causes of fever, as well as non infectious causes, enumerated in [Table/Fig-3] [6,7,9-11]. Common non infectious causes of fever include Acute Myocardial Infarction (AMI), acute pulmonary embolism, acute pancreatitis, gastrointestinal bleeding and uncomplicated phlebitis while infectious causes include catheter-associated bacteriuria and uncomplicated wound infections. However, these rarely lead to temperatures above 102°F (38.9°C) [9]. Temperatures of ≥102°F associated with a steady temperature curve, as well as relevant clinical findings such as lack of tachycardia or sweating, may point to a non infectious fever [4,9]. Once diagnosed with NF, empirical antibiotics can be stopped. It should also be noted that extreme hyperpyrexia of ≥106°F (41.1°C) is always non infectious and should not be empirically covered with antibiotics.

| Aetiology of fever | Mode of diagnosis |
|---|---|
| Drug reactions | Stop all possible medications |
| Intracerebral haemorrhage | Computed tomography |
| Malignant hyperthermia | Elicit history of usage of volatile anaesthetic gases such as halothane or depolarising muscle relaxants such as succinylcholine |
| Neuroleptic malignant syndrome | Elicit history of usage of antipsychotics and antinauseant medications such as metoclopramide |
| Serotonin syndrome | Elicit history of usage of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, triptans, etc |
| Thyrotoxicosis | Measure Thyroid Stimulating Hormone (TSH) levels along with clinical signs such as tachycardia, sweating and agitation |
| Pheochromocytoma | Measure plasma or urinary metanephrines and imaging studies to rule out pheochromocytoma |
| Adrenal crisis | Rule out hyponatremia, hyperkalemia, hypoglycemia, hypercalcemia and low adrenocorticotropic hormone levels |
| Deep vein thrombosis | Rule out by lower limb venous Doppler studies |
| Pulmonary embolism | Rule out by CT-pulmonary angiogram/2D-Echocardiogram |
| Atelectasis | Rule out by chest roentgenogram and chest auscultation |

**[Table/Fig-3]:** Aetiology of early onset of hyperthermia in spinal cord injury [6,7,9-11].

Autonomic dysregulation is more common in SCI cases affecting the spine above T6 [5]. In these patients, the afferent input from sensors in the skin to the thermoregulatory centre located in the hypothalamus, from below the lesion level, is disrupted [8]. Consequently, the response of the hypothalamus to fever in the form of cutaneous vasodilatation as well as sweating is impaired, leading to a pattern of sustained high fever. Also, SCI at a higher level such as the cervical cord leads to greater impairment of thermoregulation than in injury at lower segments such as thoracic, lumbar or sacral cord injury. Other theorised pathophysiologies leading to hyperthermia include a hyperadrenergic hypermetabolic state or elevation of Cerebrospinal Fluid (CSF) prostaglandin E2 seen after SCI, presence of blood in CSF, accelerated free radical production and increased intracellular glutamate concentration [5,8].

Hyperthermia may lead to increased muscle metabolism, muscle rigidity, rhabdomyolysis, acidosis, hypovolemia, reduced cardiac output, coagulopathy, acute tubular necrosis, increased liver enzymes and bone marrow suppression, leading to pancytopenia, which together may worsen the central thermal dysregulation [2,4]. In addition, hyperthermia may also lead to increased local cytokine activity, increased infarct size, and poorer outcomes in the acute phase of injury [6].

Brain temperature is often higher than centrally (rectal or oesophageal) measured temperatures, and prolonged hyperthermia ≥40°C may alter brain structure and functioning, hence prompt treatment is required [6,11]. Routine measures such as antipyretics, tepid sponging, cold gastric lavage, and axillary/inguinal ice packs may be ineffective as seen in the present case, due to cutaneous vasoconstriction, which diminishes the capacity for heat loss. Other methods of quickly lowering body temperature include drugs such as bromocriptine, amantadine, dantrolene, and propranolol, phenothiazines, which reverse vasoconstriction and benzodiazepines, which block muscle contractions. Patients unresponsive to these measures may require invasive procedures such as continuous veno-venous haemofiltration (CVVH) or thermoregulatory devices such as the Arctic Sun 2000® [12].

## CONCLUSION(S)

Patients presenting with unrelenting high fever following a high SCI may be considered to have NF, when other infective and non-infective causes have been ruled out. This can help in both prognosis as well as avoiding the unnecessary use of antibiotics.

## REFERENCES


[1] Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med. 2011;34(6):535-46. Doi: 10.1179/204577211X13207446293695.

[2] Ulger F, Dilek A, Karakaya D, Senel A, Sarihasan B. Fatal fever of unknown origin in acute cervical spinal cord injury: Five cases. J Spinal Cord Med. 2009;32(3):343-48. Doi: 10.1080/10790268.2009.11760788.

[3] Unsal-Delialioglu S, Kaya K, Sahin-Onat S, Kulakli F, Culha C, Ozel S, et al. Fever during rehabilitation in patients with traumatic spinal cord injury: Analysis of 392 cases from a national rehabilitation hospital in Turkey. J Spinal Cord Med. 2010;33(3):243-48.

[4] Krishnan SS, Nigam P, Bachh O, Vasudevan MC. Quad fever: Treatment through lowering of ambient temperature. Indian J Crit Care Med. 2018;22:43-45.

[5] Ülger F, Küçük PM, Öztürk ÇE, Aksoy İ, Küçük AO, Murat N, et al. Non-infectious fever after acute spinal cord injury in the intensive care unit. J Spinal Cord Med. 2019;42(3):310-17. Doi: 10.1080/10790268.2017.1387715.

[6] Thompson HJ, Pinto-Martin J, Bullock MR. Neurogenic fever after traumatic brain injury: An epidemiological study. J Neurol Neurosurg Psychiatry. 2003;74(5):614-19. Doi: 10.1136/jnnp.74.5.614.

[7] Goyal J, Jha R, Bhatia P, Mani RK. QUAD fever: Beware of non-infectious fever in high spinal cord injuries. BMJ Case Rep. 2017;2017:bcr2017219937. Doi: 10.1136/bcr-2017-219937.

[8] Watson CCL, Shaikh D, DiGiacomo JC, Brown AC, Wallace R, Singh S, et al. Unraveling quad fever: Severe hyperthermia after traumatic cervical spinal cord injury. Chin J Traumatol. 2023;26(1):27-32. https://doi.org/10.1016/j.cjtee.2022.01.006.

[9] Cunha BA. Fever in the critical care unit. Crit Care Clin. 1998;14(1):01-14. Doi: 10.1016/s0749-0704(05)70378-x. PMID: 9448975.

[10] Walter E, Carraretto M. Drug-induced hyperthermia in critical care. J Intensive Care Soc. 2015;16(4):306-311. Doi: 10.1177/1751143715583502.
[11] Niven DJ, Laupland KB. Pyrexia: Aetiology in the ICU. Crit Care. 2016;20:247. https://doi.org/10.1186/s13054-016-1406-2.
[12] Storm C, Gebker R, Krüger A, Nibbe L, Schefold JC, Martens F, et al. A rare case of neuroleptic malignant syndrome presenting with serious hyperthermia treated with a non-invasive cooling device: A case report. J Med Case Rep. 2009;3:6170. Doi: 10.4076/1752-1947-3-6170.

**PARTICULARS OF CONTRIBUTORS:**
1. ICU Registrar, Department of Critical Care, Manipal Hospital, Bengaluru, Karnataka, India.
2. ICU Consultant, Department of Critical Care, Manipal Hospital, Bengaluru, Karnataka, India.
3. ICU Registrar, Department of Critical Care, Manipal Hospital, Bengaluru, Karnataka, India.
4. ICU Registrar, Department of Critical Care, Manipal Hospital, Bengaluru, Karnataka, India.
5. ICU Consultant, Department of Critical Care, Manipal Hospital, Bengaluru, Karnataka, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. Ipe Jacob,
Brigade Gateway, Yeshwantpur, Bengaluru, Karnataka, India.
E-mail: ipe.jacob@gmail.com

**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Aug 26, 2022
- Manual Googling: Oct 12, 2022
- iThenticate Software: Oct 26, 2022 (12%)

**ETYMOLOGY:** Author Origin

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Aug 25, 2022**
Date of Peer Review: **Oct 11, 2022**
Date of Acceptance: **Oct 28, 2022**
Date of Publishing: **Feb 01, 2023**