Chinese Journal of Traumatology 26 (2023) 27–32

Contents lists available at ScienceDirect

Chinese Journal of Traumatology

journal homepage: http://www.elsevier.com/locate/CJTEE

Original Article

Unraveling quad fever: Severe hyperthermia after traumatic cervical spinal cord injury

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ARTICLE INFO

Article history:
Received 22 February 2021
Received in revised form
5 December 2021
Accepted 2 January 2022
Available online 21 January 2022

Keywords:
Spinal cord injuries
Fever
Quadriplegia
Therapeutic hypothermia

ABSTRACT

Purpose: There are many infectious and inflammatory causes for elevated core-body temperatures, though they rarely pass 40 ℃ (104 ℉). The term "quad fever" is used for extreme hyperpyrexia in the setting of acute cervical spinal cord injuries (SCIs). The traditional methods of treating hyperpyrexia are often ineffective and reported morbidity and mortality rates approach 100%. This study aims to identify the incidence of elevated temperatures in SCIs at our institution and assess the effectiveness of using a non-invasive dry water temperature management system as a treatment modality with mortality.

Methods: A retrospective analysis of acute SCI patients requiring surgical intensive care unit admission who experienced fevers ≥ 40 ℃ (104 ℉) were compared to patients with maximum temperatures < 40 ℃. Patients ≥18 years old who sustained an acute traumatic SCI were included in this study. Patients who expired in the emergency department; had a SCI without radiologic abnormality; had neuropraxia; were admitted to any location other than the surgical intensive care unit; or had positive blood cultures were excluded. SAS 9.4 was used to conduct statistical analysis.

Results: Over the 9-year study period, 35 patients were admitted to the surgical intensive care unit with a verified SCI. Seven patients experienced maximum temperatures of ≥ 40 ℃. Six of those patients were treated with the dry water temperature management system with an overall mortality of 57.1% in this subgroup. The mortality rate for the 28 patients who experienced a maximum temperature of ≤ 40 ℃ was 21.4% ($p = 0.16$).

Conclusion: The diagnosis of quad fever should be considered in patients with cervical SCI in the presence of hyperthermia. In this study, there was no significant difference in mortality between quad fever patients treated with a dry water temperature management system versus SCI patients without quad fever. The early use of a dry water temperature management system appears to decrease the mortality rate of quad fever.

Introduction

While fever is common in the intensive care unit (ICU), the presence of temperatures exceeding 40 ℃ is uncommon.[1] In many cases, an infectious etiology is the culprit. However, there are other non-infectious reasons for elevated core temperatures, including malignant hyperthermia, neuroleptic malignant syndrome, thromboembolism, medication-related fever and autonomic thermoregulatory dysfunction.[1–3] These types of high-temperature elevations in the presence of a cord injury are rare phenomena and have been termed "quad fever". Quad fever was first described by Sugarman[4], as an idiopathic rise in core temperature above 38.6 ℃ (101.5 ℉), and later by Lee-Chiong et al.[5], as a temperature above 40.7 ℃ (105.4 ℉) in patients with spinal cord injury (SCI).

Quadriplegia has a higher risk of developing hyperpyrexia than paraplegia.[4,6] The etiology of quad fever has yet to be elucidated, but various pathophysiological hypotheses exist including a hyperadrenergic hypermetabolic state, spinal thermoreceptor afferent dysfunction, and dysautonomia.[3,4,7,8] The onset of this

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Peer review under responsibility of Chinese Medical Association.

https://doi.org/10.1016/j.cjtee.2022.01.006

extreme hyperpyrexia is from as early as hospital day (HD) 1 to as late as HD 23.[3,9,10] Of the surviving patients, there is an indolent course of elevated body temperatures that self-resolve over time with no specific timeline. Early recognition and aggressive treatment is important to reduce mortality.[3,11]

Antipyretics are used as the mainstay treatment for fever but are less effective in severe hyperthermia. In instances where temperatures persist even after the use of antipyretics, external cooling devices such as cooling blankets and ice packs are often employed. Although commonly used to induce hypothermia after cardiac arrest, newer external cooling devices are useful when conventional approaches to central fever are ineffective.[12,13] In this study, we sought to identify the incidence of elevated core-body temperatures in acute SCI at our institution and describe our experience using a dry water temperature management system (Arctic Sun ®, Medivance, Louisville, Colorado) in the presence of extreme hyperthermia refractory to antipyretic treatment.

Methods

After Institutional Review Board approval, the trauma registry at Nassau University Medical Center, a level I trauma center in East Meadow, New York, was queried for all trauma patients with SCIs, paraplegia, and cervical contusions or lacerations based on International Classification of Diseases, Ninth Edition (ICD-9), ICD-10, and Abbreviated Injury Score 2005 coding systems from January 1, 2010 to December 31, 2018.

The electronic medical records were reviewed to extract patient demographics: age and gender. Retrospectively, the following data points were collected: mechanism of injury, American spinal injury association (ASIA) score, level of SCI, Glasgow coma scale (GCS) on arrival, whether surgery performed and on what HD, if applicable. Temperature, leukocyte count, and central venous pressure trends were collected, if recorded. Other variables collected included laboratory results such as thyroid-stimulating hormone levels, albumin levels, blood and respiratory culture results. The in-hospital administration of medication was recorded and these included antipyretics, corticosteroids and antipsychotics. The performance of bedside interventions such as the insertion of an indwelling catheter or the use of an external cooling device were collected. Mortality, surgical intensive care unit (SICU) length of stay and disposition were also collected from the electronic medical records.

Inclusion criteria included patients $\geq$ 18 years old who sustained a traumatic injury with a clinical exam of acute SCI who also had a CT or MRI of the neck that demonstrated an acute SCI. Those patients who expired in the emergency department, had a spinal cord injury without radiologic abnormality, or had neuropraxia were excluded. Patients were excluded if they were dispositioned from the emergency department to any destination other than the SICU. To eliminate the possibility that fever was due to infection, patients who had positive blood cultures were excluded. Due to the poorly defined definition of quad fever, a temperature of 40 ℃ was used as our threshold, as the literature describes different temperature setpoints for this phenomenon.[4,5] Patients were further classified into levels of spinal injury based on the highest anatomical spinal level.

The study cohort was stratified into two groups: those who experienced a maximum temperature during their hospital stay $\geq$ 40 ℃ (QF+), and those who did not (QF−). Furthermore, an in-depth review of three cases where extreme temperature elevations above 42 ℃ was performed.

Patients with SCI that experienced a maximum temperature of $\geq$ 40 ℃ during their SICU stay were compared with those who did not. Descriptive statistics were reported as means ± standard deviation and median. To compare the means of the two groups, a Student's *t*-test or a non-parametric alternative, the Wilcoxon Rank-Sum test was used. A x^2 test or Fisher's exact test was performed for comparison of categorical variables (mechanism of injury, SCI level, ASIA score, and mortality). A Cochran-Armitage trend test was used to assess the ASIA score by temperature level. To compare SICU length of stay, survival analysis, specifically the Kaplan Meier method was utilized. A p value less than 0.05 was considered to be statistically significant. SAS 9.4 was used to conduct statistical analysis.

Results

Over the 9-year study period, 84 patients were identified from the trauma registry as having a cervical SCI. After implementing our inclusion and exclusion criteria, 35 patients were included in our study. Comparative demographics and clinical data were collected, analyzed and summarized in Table 1. The study cohort consisted of 26 males and 9 females with a mean age of 54 (range 21–95) years. The average temperature maximum in the QF + group was 41.3 ℃, and 38.1 ℃ in the QF− group. Mechanism of injury varied, with a higher rate of motor vehicle crashes and falls, 40.0% and 28.6%, respectively. There was no statistically significant variation in the subgroups based on the mechanism of injury (p = 0.1335). The highest level of SCI was present at the $C_5 - C_7$ range in 65.7% of the patients, $C_1 - C_4$ range in 20% of patients, and below C_7 in 14.3% of patients. Among QF + patients, 85.7% had an injury in the lower cervical range ($C_5 - C_7$) (p = 0.6866) (Fig. 1).

Overall, ASIA grade A classification was 35.5% with a higher rate observed in the QF + patients (71.4% *vs.* 25.0%, p = 0.0346). Compared to the QF− group, the QF + group was more severely injured: injury severity score (medians: 21 *vs.* 18, p = 0.3029) and required a longer SICU stay (24 days *vs.* 5 days, p = 0.0008). The non-invasive dry water temperature management system was used in 10.7% of QF− patients, and in 85.7% of QF + patients. There was no statistical difference in mortality between the two groups (57.1% *vs.* 21.4%, p = 0.1554).

The baseline ICU characteristics of QF + patients are summarized in Table 2. On average, temperature maximums were experienced 7 days after admission and were accompanied by an unsustained elevation in white blood cell count. Respiratory cultures were positive in 6 of the 7 patients but were not associated with temperature or white blood cell count elevations. Surgical intervention was performed within 72 h of admission. An in-depth review of 2 patients with different mechanisms of injuries and quad fever with extreme temperature elevations of > 42 ℃ is as follows. These patients had the highest recorded temperatures in our review; 2 patients were treated with the non-invasive dry water temperature management system, whereas 1 did not.

Illustrative cases

Case 1

A 59-year-old male unrestrained driver presented after a motor vehicle crash with a GCS of 15 and an ASIA grade A. MRI of the cervical spine revealed a $C_6 - C_7$ fracture, spinal canal stenosis and cord contusion (Fig. 2).

On HD 3, he underwent a $C_5 - C_7$ decompressive laminectomy with $C_4 - T_1$ fusion. Later that evening, the patient experienced his first fever of 38.8 ℃. Blood cultures, urinalysis, arterial blood gas, and chest radiograph were performed. Blood cultures and urinalysis were subsequently negative. Antipyretics were administered in addition to external cooling measures (i.e., ice packs to the axillary and inguinal regions, dry-water temperature management system). The patient's core temperature normalized.

Table 1
Comparison of QF + to QF− spinal cord injury patients.

Variables	Total ($n = 35$)	QF− ($n = 28$)	QF+ ($n = 7$)	p value
Age (year), mean ± SD (median)	54.0 ± 20.1 (55)	56.7 ± 20.1 (57.5)	43.3 ± 17.5 (47)	0.115[b]
Male/Female	26/9	19/9	7/0	0.153[c]
Temperature max (°C), mean ± SD (median)	38.8 ± 1.7 (38.5)	38.1 ± 1.1 (37.8)	41.3 ± 1.1 (41.7)	< 0.001[d]
Mechanism of injury, *n* (%)				0.134[c]
MVC	14 (40.0)	12 (42.9)	2 (28.6)	
MCC	1 (2.9)	1 (3.6)	0 (0)	
Fall	10 (28.6)	8 (28.6)	2 (28.6)	
Diving accident	2 (5.7)	0 (0)	2 (28.6)	
Other	8 (22.9)	7 (25.0)	1 (14.3)	
SCI highest level, *n* (%)				0.687[c]
$C_1 - C_4$	7 (20.0)	6 (21.4)	1 (14.3)	
$C_5 - C_7$	23 (65.7)	17 (60.7)	6 (85.7)	
Lower SCI	5 (14.3)	5 (17.9)	0 (0)	
ASIA score[a], *n* (%)				0.035[e]
A	11 (35.5)	6 (25.0)	5 (71.4)	
B	3 (9.7)	3 (12.5)	0 (0)	
C	3 (9.7)	2 (8.3)	1 (14.3)	
D	4 (12.9)	3 (12.5)	1 (14.3)	
E	10 (32.2)	10 (41.7)	0 (0)	
GCS, mean ± SD (median)	12.5 ± 4.7 (15)	12.3 ± 4.8 (15)	13 ± 4.5 (15)	0.835[d]
ISS, mean ± SD (median)	20.4 ± 10.8 (20)	19.4 ± 10.9 (18)	24.4 ± 10.2 (21)	0.303[d]
SICU LOS, median (95% *CI*)	8 (3, 15)	5 (2, 10)	24 (15, -)	0.001[d]
DWTMS, *n* (%)	9 (25.7)	3 (10.7)	6 (85.7)	< 0.001[c]
Overall mortality, *n* (%)	10 (28.6)	6 (21.4)	4 (57.1)	0.155[c]

SD: standard deviation; MVC: motor vehicle crash; MCC: motorcycle crash; ASIA: American spinal injury association; GCS: Glasgow coma scale; ISS: injury severity score; SICU LOS: surgical intensive care unit length of stay; DWTMS: dry water temperature management system.
[a] 11% missing ASIA score.
[b] Student's *t*-test.
[c] Fishers exact test.
[d] Wilcoxon rank-sum test (mean and standard deviation shown for illustrative purposes).
[e] Cochran-Armitage trend test.
-: not mentioned.

On HD 6, the patient became febrile to 42.2 ℃. Cooling methods with additional antipyretics were implemented. There were several episodes of waxing and waning in the patient's core body temperature with aggressive cooling methods initiated each time. Despite antipyretic and antibiotic treatment, and hemodialysis the patient experienced several days of temperatures above 40 ℃ until he ultimately expired on HD 20.

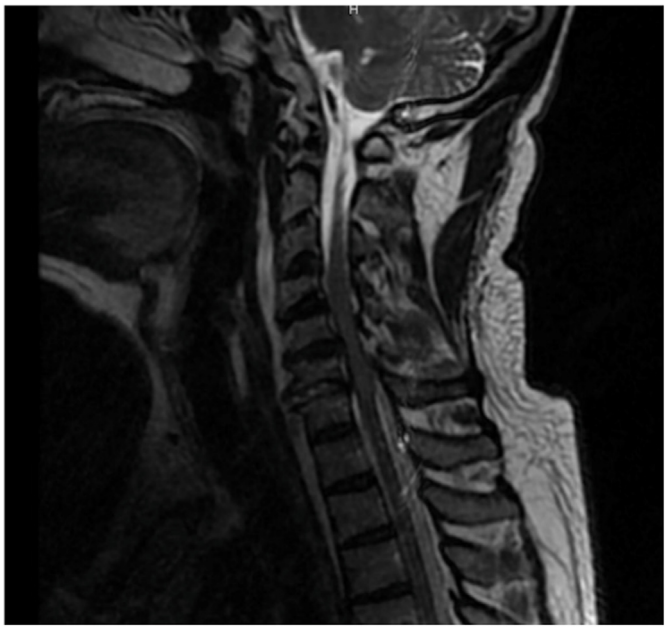

Fig. 1. T2-weighted MRI revealed a ligamentous injury along with spinal stenosis at the $C_5 - C_6$ spinal level.

Case 2

A previously healthy 30-year-old male presented with a GCS of 14 and an ASIA grade A SCI after a diving accident. MRI studies revealed a complete $C_5 - C_6$ translocation injury (Fig. 3) for which he underwent a $C_5 - C_6$ posterior decompression and fusion.

On HD 4, the patient became febrile to 38.8 ℃. He was pan cultured to localize a source of infection while metronidazole was started empirically for loose stools. Intravenous acetaminophen was given as needed for temperature control. On HD 10, he became hemodynamically unstable and was found to have a temperature of 41.6 ℃. In addition to axillary and inguinal ice packing, the dry water temperature management system was implemented and acetaminophen was administered. He began to normalize, and sources of potential infection were explored again and found to be negative. The patient became febrile to 42.2 ℃ again on HD 17. The same treatment modalities were utilized and resulted in repeat stabilization.

During the remainder of his SICU stay, he had persistent fluctuations in his core body temperature, despite unremarkable culture results. The patient was dispositioned to a lower level of care with occasional low-grade fevers.

Discussion

Despite of varying definitions, an unclear etiology, and few reported cases, quad fever carries a high rate of mortality.[3,9,10] Given that several small case-studies demonstrated poor outcomes related to quad fever, we conducted a review to identify the incidence of quad fever among our SCI patients, and scrutinize their hospital course to determine if the use of a non-invasive dry water

Table 2
Baseline characteristics and ICU data for QF + spinal cord injury patients.

No.	Age (year)	Gender	Level of injury	ASIA score	Max temperature (℃)/HD	WBC ($\times 10^9$/L)	Surgery /HD	Cultures	Arctic sun	Outcome
1	65	Male	$C_3 - C_4$	D	40.1/14	15.42	Yes /1	+ respiratory	Yes	Died
2	55	Male	$C_3 - C_6$	C	40.2/11	18.21	Yes	–	No	Died
3	26	Male	$C_2 - C_6$	A	40.4/9	16.8	Yes/1	+ respiratory	Yes	Survived
4	47	Male	$C_6 - C_7$	A	41.7/3	12.3	Yes	+ respiratory	Yes	Died
5	30	Male	$C_5 - C_6$	A	41.7/10	13.65	Yes/1	+ respiratory	Yes	Survived
6	59	Male	$C_6 - C_7$	A	42.3/6	8.82	Yes/3	+ respiratory	Yes	Died
7	21	Male	C_5	A	42.7/8	19.48	No	+ respiratory	Yes	Survived

ICU: intensive care unit; QF: quad fever; ASIA: American spinal injury association score; HD: hospital day; WBC: white blood cell count.

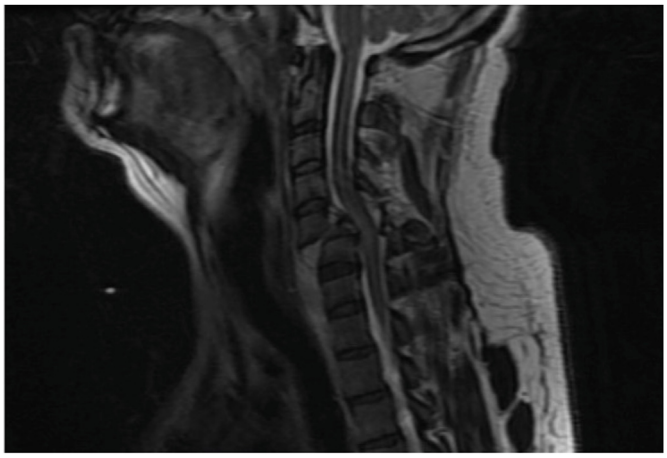

Fig. 2. T2-weighted MRI revealed a $C_5 - C_6$ translocation injury with associated cord compression and surrounding edema.

management system produced favorable outcomes. In our study, we observed an incidence of 8.3% (7/84) and a recorded maximum temperature of 42.7 ℃, which is comparable to the systematic review on neurogenic fever of unknown origin conducted by Savage, that reported an incidence of 8.0% and recorded maximum temperature of 44 ℃ (111.2 ℉).[14,15] The 2 cases detailed portray the variable and indolent course of quad fever as well as the positive

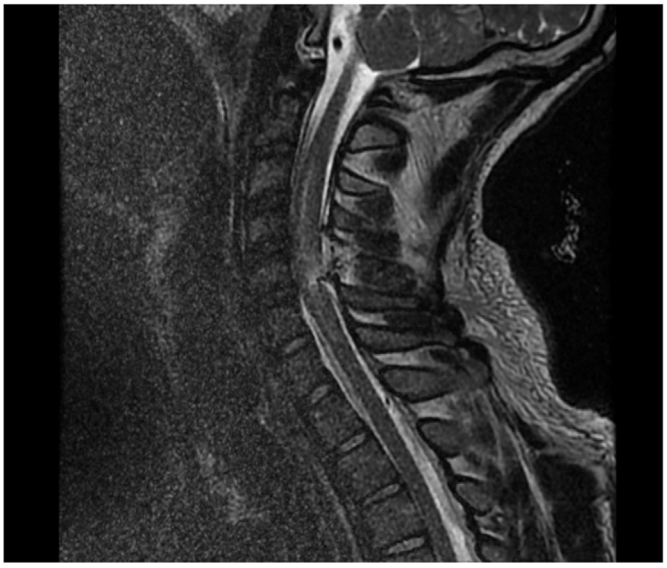

Fig. 3. T2-weighted MRI revealed a comminuted fracture at the C_5 vertebrae along with bullet fragments resulting in cord compression and surrounding edema.

outcomes when the combination of both dry water-cooling systems and antipyretics are used.

The presence of fever in the ICU prompts the need for important diagnostic and therapeutic decisions. Before a diagnosis of quad fever can be made, an extensive search for infection and other febrile causes must be investigated. After each febrile episode, leukocyte counts are trended, patients are pan-cultured (i.e., blood, sputum, urine), and diagnostic radiographic studies of the head, chest, abdomen, and pelvis are obtained, as appropriate. Although positive respiratory cultures were observed in several of our patients, Claridge et al.[16] reports that respiratory infections typically do not reach above 40.3 ℃. One patient in our study experienced several episodes of loose stool raising suspicion for clostridium difficile infection which, the leukocyte count, titers and cultures were negative and subsequently ruled out. Other systemic infections such as fungemia can present with temperatures above 40 ℃ but typically are associated with elevated white blood cell counts.[17] Despite of elevation in temperature, a corresponding leukocyte rise, or positive cultures were not observed in our study cohort.

In the presence of non-infectious severe hyperthermia, neuroleptic malignant syndrome and malignant hyperthermia must be considered. Neuroleptic malignant syndrome is a result of an adverse reaction to antipsychotic medications and is characterized by a well-defined set of clinical symptoms (mental status change, rigidity, fever, dysautonomia).[9,18] Three patients received haloperidol during their SICU stay for delirium, but it was used temporarily unrelated to episodes of pyrexia. Malignant hyperthermia is a genetic disorder that manifests itself in susceptible patients after the induction of anesthetic agents. The onset of malignant hyperthermia typically occurs within 1 h of anesthetic induction, whereas fever presented in our patients several hours to days after their initial procedures.[19] The average onset of an elevated temperature in our patients was by HD 4, and there were no reports of antipsychotic medication use, thus eliminating our suspicions of these 2 entities. Additionally, we observed that the performance of surgery does not correlate with the incidence of quad fever. Other causes of non-infectious fever including venous thromboembolism and thyrotoxicosis-induced fever were ruled out as thyroid-stimulating hormone levels were within normal limits, standard venous thromboembolism prophylaxis was administered, and all doppler studies were negative in each patient. Despite the etiology of the fever, early and aggressive treatment is important for survivability.

We established that high temperature elevations were associated with greater severity of the ASIA score. There was no statistical significance for the highest level of SCI. Respectively, 85.7% and 60.7% of QF+ and QF− patients had cord injuries at the level $C_5 - C_7$.

In general, empiric antibiotics are initiated in the presence of fever, especially if temperatures exceed 38.9 ℃.[20] The antipyretic acetaminophen was administered on an as-needed basis throughout each patient's SICU course. Given the failure of

temperature control in Case 1, the dry water temperature management system was subsequently employed promptly for hyperpyrexia in our SCI patients. The induction of therapeutic hypothermia is commonly used in post-cardiac arrest for the preservation of neurologic functioning.[11] Therapeutic hypothermia has not been well documented as an external cooling treatment for hyperthermia but has shown utility in the treatment of heatstroke.[21] The dry water temperature management system produces high flow rates of cold fluid with precise temperature feedback-control mechanisms making it a useful modality for rapid induction of cooling. Two studies demonstrated the temperature normalizing effect of the dry water temperature management system in febrile ($\geq$ 38.3 ℃) critically ill neurologic patients.[22,23] The dry water temperature management system was used in 6 of our 7 quad fever patients and normothermia was achieved within a few hours of activation. We believe we saw success with its use as our threshold for activation was 39.2 ℃ with a target temperature of normal < 37.7 ℃.

In our experience, the aggressive use of the external cooling device regulated body temperatures in a more systematic and closely monitored manner resulting in favorable outcomes. Mayer et al.[12] concluded that the dry water temperature management system is an effective and superior treatment modality for the treatment of hyperthermia in critically ill neurologic patients. A side effect of the dry water temperature management system noted in some studies is the potentiation of hypotension secondary to vasodilation, which increases the need for mean arterial pressure surveillance and vasopressor support.[12,24] We did not encounter these side effects in the 6 patients treated.

High rates of pyrexia are innately associated with increased mortality. In this review mortality between QF+ group and QF− group was comparable. We believe this is due to a high level of suspicion for quad fever and the early use of the non-invasive dry water temperature management system. We believe this resulted in a mortality rate for quad fever significantly lower than that previously reported.[3,9–11,24]

Although the mechanism behind these extreme temperatures has yet to be established, several hypotheses exist. Autonomic dysfunction is common following cervical and high thoracic SCIs of which thermal dysregulation is a component through unknown mechanisms.[15,25] The body's thermoregulatory center is located in the anterior hypothalamus. Through temperature sensors and chemical mediators (cytokines and interleukins), the hypothalamus can modify body temperature through vasomotor responses.[3] In the presence of central nervous system insults, thermoregulation may be substantially impaired due to the disruption of afferent and efferent hypothalamic pathways.[25] There is speculation that extreme hyperthermia may arise from sympathetic dysregulation resulting in vasodilatory impairment and the inability to perspire at appropriate physiological setpoints. Another hypothesis includes a hyperadrenergic hypermetabolic state that has been observed after traumatic brain injuries and elevation of cerebrospinal fluid prostaglandin E2 that increases after a spinal injury that may stimulate the hypothalamic axis mediating malignant hyperthermia.[8,26] Neither of these studies has been explored further to determine any true association.

We suspect the vagus nerve may play a role in this thermoregulatory dysregulation associated with autonomic dysfunction. The vagus nerve exits the cranial vault via the jugular foramen and commonly lies dorsomedial between the carotid artery and internal jugular vein within the carotid sheath.[27] Although the vagus nerve is located outside the spinal column, patients with acute cervical fractures can have severe inflammation and swelling around injury sites causing both irritation to the nerve and mass effect on surrounding tissue. Such cranial nerve palsies as Collet-Sicard Syndrome after C1 burst fractures demonstrate that neurologic injury is not limited to the spinal cord.[28] Expanding on the same susceptibility to injury of nervous structures in the cervical fracture sites, the vagus nerve would be secondarily irritated to a hyperactive or hyperreactive state. The vagus nerve plays a known role in fever modulation. Hepatic afferent branches of the vagus nerve play a crucial role in stimulating the hypothalamic febrile response to pyrogens such as lipopolysaccharide and IL-8 in the abdomen.[29,30] Thus, if there is irritation of the vagus nerve at the cervical level, it is plausible that this pathway could create an aberrant febrile response.

Limitations of this study include the small sample size of patients who developed quad fever. This is understandable given the low incidence of cervical SCIs and the rare occurrence of quad fever. A multi-institutional study would be necessary to obtain a sufficient number of patients to truly perform a comparative assessment.

In conjunction with the sparse available literature, we have elucidated that quad fever is indeed a phenomenon seen in SCIs, more specifically lower cervical injuries in our experience, and warrants a high level of suspicion in the ICU setting. The pathophysiological mechanisms are not well understood and warrant further investigation. Regardless of etiology, when temperature elevations are extreme and control is unresponsive to conventional treatments, the non-invasive dry water temperature management system should be used early. Despite the clinical history of quad fever as a morbid diagnosis, we observed mortality rates similar to those without hyperpyrexia above 40 °C indicating that our use of the dry water temperature management system in conjunction with antipyretics is associated with a decreased mortality rate.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement

This retrospective study was approved by the Institutional Review Board of Nassau University Medical Center as 19–223 on March 16, 2019.

Declaration of competing interest

The authors aver individually and collectively that they have no conflicts of interest to declare.

Author contributions

Concept and design: Dooniya Shaikh, Jody C. DiGiacomo, Raina Wallace, Shridevi Singh, Sara Cardozo-Stolberg, L. D. George Angus.

Data acquisition: Carlton C. L. Watson, Dooniya Shaikh, Aaron C. Brown, Shridevi Singh, Sara Cardozo-Stolberg, Lisa Szydziak.

Data analysis: Dooniya Shaikh, Lisa Szydziak.

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Critical review and revisions: Carlton C. L. Watson, Dooniya Shaikh, Jody C. DiGiacomo, Aaron C. Brown, Raina Wallace, Shridevi Singh, Sara Cardozo-Stolberg, L. D. George Angus.

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