Neurogenic fever
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ABSTRACT
Fever in patients with severe head injury is a commonly-encountered diagnostic and management problem. Neurogenic fever (NF) is a non-infectious source of fever in the patient with head injury and, if untreated, can cause damage to the brain in many ways. Until recently, NF was thought to be a relatively rare consequence of traumatic brain injury (TBI), but other studies have reported that four to 37 percent of TBI survivors experience this sequela. Patients with TBI are immunocompromised to a certain extent and this predisposes them to sepsis, which should be a primary concern particularly in comatose patients. NF is essentially a diagnosis of exclusion. It is only when sepsis is excluded, can we consider NF. Though in the acute phase of severe TBI, brain temperature is indeed higher than the core temperature, but that significance is uncertain with regard to outcome prediction, since there has been a paucity of work on the use of direct methods of brain temperature monitoring. In summary, the pathophysiology and management of NF is not well understood and needs more research and understanding for better management and a favourable outcome.

Keywords: brain injury, head injury, neurogenic fever, trauma

INTRODUCTION
Fever in the severely-injured head injury patients is a commonly-encountered diagnostic and management problem, and these episodes may be of infectious or non-infectious origins.4,12 Neurogenic fever (NF) is a non-infectious source of fever in the patient with head injury. Until recently, NF was thought to be a relatively rare consequence of traumatic brain injury (TBI), but other studies have reported that 4%–37% of TBI survivors experience this sequela.5,14

RISK FACTORS
Many patients experience early hyperthermia (at least one episode of body temperature > 38.5°C within the first two days) after traumatic brain injury.5,6 In a retrospective study, there was an increased risk of development of NF among patients with severe TBI who had experienced either diffuse axonal injury (DAI) or frontal lobe injury of any form.17 Other risk factors predicting early hyperthermia include Glasgow Coma Scale score in the emergency department ≤ 8, paediatric trauma score ≤ 8, cerebral oedema or diffuse axonal injury on initial head computed tomography, admission blood glucose > 150 mg/dL (8.2 mmol/L), admission white cell count > 14,300 cells/mm³, and systolic hypotension.6,8

PATHOPHYSIOLOGY
Cerebral temperature has been recognised as a strong factor in ischaemic brain damage.9,13 Fever is extremely frequent after acute cerebral damage, and cerebral temperature is significantly higher than body core temperature.13 Body core temperature may markedly underestimate cerebral temperature, especially during the phases when temperature has the greatest impact on the central nervous system (CNS).13 TBI results in many different types of injury, and at this point, it is unclear if one particular type is associated with an increased incidence of NF. NF results from a disruption in the hypothalamic set point temperature, which results in an abnormal increase in body temperature, and is thought to be caused by injury to the hypothalamus.5,14,15 From cadaveric studies, it is known that hypothalamic injury is common in patients after TBI as 42.5% of the brains prosected had evidence of hypothalamic injury.16

NEUROLOGICAL EFFECTS
The neurological effects of fever are significant as increased temperature in the post-injury period has been associated with increased local cytokine activity, increased infarct size, and poorer outcomes in the acute phase of injury.17,18 This is, in part, related to the fact that patients at risk of intracranial hypertension may be significantly affected by a rise in temperature because the intracranial blood volume increases with temperature. This reduces compliance and puts the brain at risk for further injury.13 Hyperthermia, from fever or other sources, when high enough (> 43°C), has been reported to cause neuronal injury in normal brains, and lengthy periods of moderate (40°C) hyperthermia have been reported to alter brain structure and function.19,20 Additionally, the TBI patients are at risk of secondary injury from fever because for every 1°C rise in body temperature, there is a 13%
increase in the metabolic rate. This taxes the stressed energy reserves of the severely brain injured, catabolic patients. The higher metabolic demand of fever further exacerbates this problem, and can lead to additional loss of muscle and fat stores.\(^{29}\)

**CLINICAL FEATURES**

Currently, NF is a diagnosis of exclusion and the diagnostic work-up of the TBI patient with fever must be exhaustive before the diagnosis can be made.\(^{21,22}\) Most reports characterise the patient with NF as being relatively bradycardiac, having a notable absence of perspiration, having a plateau-like temperature curve (no diurnal variation) that persists for days to weeks, the temperature being characteristically very high, and resistant to antipyretic medications.\(^{3,13,22,24}\) NF may be associated with the presence of prolonged unawareness or coma state and diabetes insipidus.\(^{23}\) This often leads to expensive, invasive, and often painful tests in order to make the diagnosis.\(^{22}\) Differentiating a patient of NF from a patient who is having a true infectious or inflammatory source of the fever is a critical diagnostic decision for the clinicians caring for the TBI patients. The two treatment regimens differ significantly; thus rapid and proper diagnosis and treatment are essential for control of fever and optimisation of patient outcome following TBI.\(^{7}\)

**MANAGEMENT**

Rapid control of the hyperthermia associated with fever is essential as it is associated with worsened outcome in both experimental and clinical studies.\(^{5,25-27}\) The treatment of NF includes use of both external cooling methods until the diagnosis is made and appropriate drug therapy.\(^{7}\) Many drugs which have successfully been used either anecdotally, or in case reports, to treat NF include: bromocriptine, amantadine, dantrolene, and propranolol.\(^{3,9}\) As each of these drugs has significant potential side effects (for example, hypotension and gastrointestinal bleeding), routine use without a relatively firm diagnosis of NF is not prudent.\(^{7}\)

**THE FUTURE**

It is hoped that earlier diagnosis and appropriate intervention for fever in the TBI patients will lead to improved outcome.\(^{7}\) Further research is required to understand the mechanisms of this response and to identify appropriate preventive or therapeutic interventions.\(^{5,6}\) Prevention of secondary insults caused by hyperthermia is a major management goal after traumatic brain injury.\(^{5,6}\)

**CONCLUSION**

NF is a well-recognised entity that if untreated, can cause damage to the brain in many ways. Patients with TBI are immunocompromised to a certain extent and this predisposes them to sepsis which should be a primary concern, particularly in comatose patients. NF is essentially a diagnosis of exclusion. It is only when sepsis is excluded can we consider NF. Though in the acute phase of severe TBI, brain temperature is indeed higher than the core temperature, that significance is uncertain with regard to outcome prediction since there has been a paucity of work on the use of direct methods of brain temperature monitoring. In summary, the pathophysiology and management of NF is not well understood and needs more research and understanding for better management and a favourable outcome.

**REFERENCES**


U.S. ACCREDITED POSTGRADUATE TRAINING IN INTERNAL MEDICINE

The University of Hawaii welcomes inquiries from physicians seeking postgraduate training in Internal Medicine. Ours is a high quality, fully accredited training program that features a full array of clinical material, research opportunities and teaching responsibilities. Several Singaporean physicians have completed training with us, and are now fully certified by the American Board of Internal Medicine. Our graduates have also secured prestigious fellowship positions at the NIH, Mayo Clinic, Barnes, etc., in various subspecialties.

Professor SY Tan (author of the Medicine in Stamps series in the SMJ) will be in Singapore in August 2007 to conduct on-site Q/A sessions and interviews. If you are interested in an appointment, kindly send a brief resume to siang@hawaii.edu. You do not need to have completed all of your qualifying exams (USMLE parts 1 and 2K and 2CS) to meet up with Prof. Tan.