Neurogenic fever after traumatic brain injury: an epidemiological study

H J Thompson, J Pinto-Martin, M R Bullock

Objectives: To determine the incidence of neurogenic fever (NF) in a population of patients in the acute phase following severe traumatic brain injury (TBI); to identify factors associated with the development of NF following severe TBI in adults.

Methods: Charts of patients admitted from 1996 to 1999 with severe TBI at a large, urban mid-Atlantic teaching hospital were retrospectively evaluated based on diagnostic criteria for each episode of hyperthermia to determine the diagnosis of NF. Data were collected regarding mechanism and area of injury, severity of injury, and demographic factors to determine potential predictors of NF.

Results: Diffuse axonal injury (DAI) [OR 9.06, 95% CI 0.99 to 82.7] and frontal lobe injury of any type [OR 6.68, 95% CI 1.1 to 39.3] are independently predictive of an increased risk of development of NF following severe TBI. The presence of a skull fracture and lower initial Glasgow Coma Score (GCS) were individual predictors of development of NF, but did not contribute to the final model.

Conclusions: These findings examine known and novel risk factors for this phenomenon in comparison to previously published literature on NF. A set of predictor variables was identified to help clinicians target patients at high risk for development of NF following severe TBI. It is hoped that earlier diagnosis and appropriate intervention for fever in the TBI patient will lead to improved outcomes.
incidence in the acute phase of injury and to identify factors associated with the development of NF following severe TBI in adults.

METHODS
Design
A retrospective analysis of chart data was used for this exploratory study. Subjects for this study were patients diagnosed with NF identified from the head injury databank for years 1996–99 at the Medical College of Virginia Hospital/Virginia Commonwealth Health System. The comparison group was patients with a diagnosis of severe TBI without a diagnosis of NF. For each patient, the entire chart was reviewed for episodes of hyperthermia/fever and for each episode of hyperthermia, a determination of aetiology was made. The diagnosis of NF was made based on reviewing available patient data following the diagnostic algorithm (fig 1).

Sampling criteria
The potential sample consisted of adult patients with severe TBI admitted to a large, urban, teaching hospital located in the mid-Atlantic area, designated as a level I trauma centre for years 1996–99. Exempted Institutional Review Board approval was obtained prior to study initiation.

Inclusion criteria for both cases and controls in this study were: (1) patient who required hospitalisation for an admitting diagnosis of severe TBI who was alive at least two weeks after initial injury; and (2) patient must be over 18 years of age. According to the limited data available, TBI patients experience NF more frequently than patients with other neurological deficits such as non-traumatic subarachnoid haemorrhage, and are more vulnerable to the metabolic consequences of fever. Neurogenic fever generally does not develop in the hyperacute phase of TBI, thus the two week survival criteria.

Exclusion criteria included patients with a history of malignant hyperthermia as they have an altered baseline thermoregulatory mechanism. Of the 167 patients admitted in 1996–99 with severe TBI, 87 patients met criteria; full medical records were not available on all of the remaining subjects, thus the final enrolment was 76 (see table 1 for summary of excluded patients).
Instrumentation
The mechanism of injury was collected from the chart, and checked for congruence with the trauma registry and head computed tomography (CT) and/or magnetic resonance imaging (MRI) films. The presence of hyperthermia in the six hours immediately following the TBI as a predictor for development of NF was determined by chart review of vital sign recordings. Hyperthermia is defined to be a temperature of 1°C or more above patient baseline if normothermic at time of initial assessment, or any temperature of 38.5°C or above. The presence of hypothalamic-pituitary (HP) dysfunction was determined by chart review for the diagnosis of diabetes insipidus, evidence of abnormal prolactin secretion, or secretion of inappropriate antidiuretic hormone during the hyperacute phase of care.

Initial head injury severity was measured by the GCS. The ISS was measured by the Injury Severity Score (ISS). The ISS is the sum of the squares of the most severe injury in each of the three most severely injured body regions. The six body regions on which the ISS is based are head/neck, face, chest, abdomen/pelvic contents, extremities/pelvic girdle, and external. The ISS is scored on a scale of 1 (least severe) to 75 (most severe).

Data collection procedures
Once access to the dataset was obtained via exempted Institutional Review Board approval, the head injury registry was reviewed for patients meeting inclusion criteria for the years 1996–99. The identified subject's medical record was reviewed to confirm the presence/absence of NF utilising a diagnostic algorithm (see fig 1) and the subject was allocated to either case or control group. For this study, identification of a case was made on the presence of a diagnosis of NF. The diagnosis of NF is one of exclusion and is based on a multitude of tests and assessment data including negative culture results, ruling out other possible sources of fever in the patient (see fig 1), and the presence of previously discussed clinical symptoms such as relative bradycardia and lack of diurnal variation. As data collection was retrospective, not all patients had all testing required to definitively confirm NF per the algorithm; therefore, any uncertainty in the classification of cases and controls was resolved by discussion with a second clinician. The medical record was reviewed for demographic data (including age, sex, and race) to ensure the sample was representative of the TBI population. Temperature recordings in the patient's medical record for the first six hours after injury were reviewed for the presence of hyperthermia and hypothermia as potential predictive factors for later development of NF. The subject's pertinent head CT and MRI scans and reports were reviewed for type of injury. If necessary, confirmation of radiological findings were sought from a neuroradiologist. Injury severity scores were culled from the trauma registry at the institution.

Statistical analysis
This case-comparison study utilises logistic regression analysis to answer the research questions of interest. All data management and descriptive and inferential statistical analyses were performed using the SPSS 8.0 statistical software package. Initial GCS on admission was classified into one of four levels based on head injury severity: 3–4 (most severe), 5–8 (severe), 9–12 (moderate), and above 13 (mild). The most severe category was used as the referent group in the comparative analysis.

RESULTS
From 1996 to 1999, 76 patients with severe TBI were available for study. Table 2 presents demographics on the patient population. The incidence of NF in this population was 11.8% (9/76). Each of the variables was tested independently for association with development of NF following severe traumatic brain injury using univariate logistic regression (results are presented in table 3). The set of factors that exhibited a significant (p < 0.05) or relatively significant (p = 0.10) association with development of NF remained in the model (GCS, diffuse axonal injury, frontal injury, skull fracture). Both backward and forward Wald model building was used to arrive at the final set of predictor variables (table 4). Of the four patient attributes tested, only two entered the logistic regression model as independent predictors of development of NF following severe TBI. These predictors in order of relative prognostic strength are presence of diffuse axonal injury and frontal lobe injury of any type.

Diffuse axonal injury
Patients with diffuse axonal injury (DAI) present on imaging studies were 9.1 (95% CI 0.99 to 82.7) times more likely to develop NF than TBI patients without DAI, all other factors being equal.
Patients with frontal lobe injuries were at a statistically significantly increased risk for development of NF in comparison to those without frontal lobe involvement, being 6.7 (95% CI 1.1 to 39.3) times more likely to develop this sequela of TBI. This model has good overall correct predictive value (92.0%). Diffuse axonal injury entered into the model despite having a significance value of p = 0.0508. Removal of DAI from the model resulted in a poorer predictive model. Thus, the best predictive model is presented (table 4), and was confirmed with regression modelling.

Attributes not independently predictive
Glasgow Coma Score, as a measure of severity of brain injury, individually predicted the development of NF, but did not contribute to the model after adjustment for the above factors. The severely injured patients with GCS scores on admission of 5–8 were at a statistically significantly increased risk (p = 0.0339) for development of NF in comparison to the reference group. This was likely due to the fact that the majority of subjects (n = 48) fell into this category, thus distribution was not equal throughout. Once adjustment was made for other factors in the overall model, this attribute fell out as a significant independent predictor. Skull fracture was also individually predictive of NF development subsequent to severe TBI, but did not contribute to the overall final model.

**DISCUSSION**
In this retrospective study, there is an increased risk of development of NF among patients with severe TBI who had experienced either DAI or frontal lobe injury of any form. These data are novel in attempting to establish a relation between injury factors and later development of this sequela in survivors of TBI. Additionally, this is thought to be the first study to examine this complication following TBI in a group of acutely injured adults. Limitations of this study include its retrospective nature, the small number of identified cases, and the exclusion of TBI patients less than 18 years of age (related to exempted review requirements).

Approximately 20 000–45 000 patients suffer significant physical or functional deficits as a result of TBI induced DAI in the United States each year, and it is the most common cause of persistent vegetative state in TBI patients. Thus, as previous studies in comatose patients following TBI have found an association between NF and persistent vegetative state, it is not surprising that this study found DAI to be an independent predictor of NF development. Severe DAI is associated with lower GCS scores with midbrain and brain stem injury, and would be a likely mechanism of hypothalamic injury following TBI as the thermoregulatory tracts of the hypothalamus are deep brain structures.

In the original study design, an attempt was made to determine the presence of hypothalamic injury from imaging studies, as no information in surviving patients has been published to date and would likely have been quite useful in this analysis. Determining the presence of hypothalamic injury proved to be extremely difficult based on available studies. Because of the retrospective nature of the study, a decision was made to cease collecting this information following consultation with a radiologist as CT scans of the head for evaluation of traumatic injury generally do not include the precision within the diencephalon required to make this determination.

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate p value</th>
<th>Multivariate p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.3307</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.7103</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>0.3518</td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma score</td>
<td>0.0412*</td>
<td>0.0924</td>
</tr>
<tr>
<td>Injury Severity score</td>
<td>0.3061</td>
<td></td>
</tr>
<tr>
<td>Temperature within 6 hours after injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthermic after injury</td>
<td>0.6151</td>
<td></td>
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<tr>
<td>Hypothermic after injury</td>
<td>0.9418</td>
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<td>HPA axis pathology</td>
<td>0.5359</td>
<td></td>
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<tr>
<td>Side of injury</td>
<td>0.1524</td>
<td></td>
</tr>
<tr>
<td>Type of injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subdural haematoma</td>
<td>0.8868</td>
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<tr>
<td>Epidural haematoma</td>
<td>0.4874</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>0.6885</td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>0.8996</td>
<td></td>
</tr>
<tr>
<td>Laceration</td>
<td>0.5647</td>
<td></td>
</tr>
<tr>
<td>Diffuse axonal injury</td>
<td>0.0568*</td>
<td>0.0508</td>
</tr>
<tr>
<td>Skull fracture</td>
<td>0.0751*</td>
<td>0.2323</td>
</tr>
<tr>
<td>Area injured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>0.0499*</td>
<td>0.0355</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.2729</td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>0.8566</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>0.1515</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.1070</td>
<td></td>
</tr>
<tr>
<td>Brain stem</td>
<td>0.5991</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at p<0.05.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>p value</th>
<th>Odds ratio (OR)</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse axonal injury</td>
<td>2.2038</td>
<td>1.129</td>
<td>0.0508</td>
<td>9.0592</td>
<td>0.9921 to 82.7234</td>
</tr>
<tr>
<td>Frontal lobe injury</td>
<td>1.8998</td>
<td>0.9037</td>
<td>0.0355</td>
<td>6.6843</td>
<td>1.1371 to 39.2936</td>
</tr>
</tbody>
</table>

Frontal lobe injuries
 Patients with frontal lobe injuries were at a statistically significantly increased risk for development of NF in comparison to those without frontal lobe involvement, being 6.7 (95% CI 1.1 to 39.3) times more likely to develop this sequela of TBI. This model has good overall correct predictive value (92.0%). Diffuse axonal injury entered into the model despite having a significance value of p = 0.0508. Removal of DAI from the model resulted in a poorer predictive model. Thus, the best predictive model is presented (table 4), and was confirmed with regression modelling.
Fever in the severely injured TBI patient is a commonly encountered diagnostic and management problem. 

Prospective studies should include provision of analysis of the hypothalamus for damage in the design whenever possible.

Injury to the frontal lobe was an independent predictor for development of NF. As the frontal lobe contains no major thermoregulatory centres, it is possible that frontal lobe injury serves as an indicator of hypothalamic injury in this study given the nature of mechanical forces within the skull during injury and the proximity of the hypothalamus to the ventricles. Skull fracture was also an individual predictor of NF, but was not an independent predictor for development of NF. Skull fracture has previously been associated with other indicators of hypothalamic injury following TBI such as diabetes insipidus. 

Aim: To retrospectively determine if there is a relationship between the presence of NF and various hypnotalamic injuries. This study was supported by United States Public Health Service Grant NR. 7694 and the Neuroscience Nursing Foundation. We thank Charlotte Gilman, RN of the Neurosurgery Division for her assistance with the head injury databank, and the Trauma Registry of the Medical College of Virginia Hospitals, Richmond, VA.

It was not possible to strictly follow the algorithm in determining the presence of NF, as not all tests were performed on each patient in the study because of the retrospective nature of the data collection. In these cases, any uncertainty in the classification of cases and controls was resolved by discussion with a second clinician. This process generated discussion between investigators regarding the most appropriate history, physical examination, and diagnostic work up for NF. As the diagnosis of NF is currently a diagnosis of exclusion, additional information that may help the clinician in more rapidly identifying the ultimate source of hyperthermia may be a valuable diagnostic aid. While the algorithm presented in fig 1 should remain the standard for diagnostic work up of NF, not every patient will fit an algorithm, nor is it always feasible to strictly follow one.

Conclusions

These findings suggest that clinicians working up patients with severe TBI who are experiencing unexplained fever need to additionally consider the presence of two presenting factors: DAI and frontal injury in their assessment. If the patient experienced either factor, the clinician’s suspicion for the diagnosis of NF should be increased as these data suggest that the patient’s risk is significantly elevated by their presence. It is hoped that earlier diagnosis and appropriate intervention in this patient population will lead to improved outcomes. These initial findings are intriguing; however, due to the small sample size they should be interpreted with prudence. Further work in this area is needed with additional patients and sites, prospective data analysis for confirmation of findings, and specification of site of skull fracture.

**Acknowledgements**

This study was supported by United States Public Health Service Grant NR. 7694 and the Neuroscience Nursing Foundation. We thank Charlotte Gilman, RN of the Neurosurgery Division for her assistance with the head injury databank, and the Trauma Registry of the Medical College of Virginia Hospitals, Richmond, VA.

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**Table 5** Comparison of data based publications regarding development of neurogenic fever

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects/number</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benedek et al</td>
<td>Mixed population: Cranial trauma (n=6) and brain surgery (n=24)</td>
<td>Central medical forebrain involved in all cases. Indomethacin reduced fever in 10/11 patients</td>
<td>First 24 hours post-injury. Likely secondary fever from IL-1 release, not neurogenic fever</td>
</tr>
<tr>
<td>Meyhofer and Stinson</td>
<td>Severe TBI (n=3)</td>
<td>Initial GCS ≤4, prolonged coma in all cases. Intraventricular haemorrhage present in 2/3 cases</td>
<td>Case report. Propranolol was used successfully for treatment</td>
</tr>
<tr>
<td>Whyte et al</td>
<td>Severe TBI patient (n=1)</td>
<td>Patient with known NF in acute post-injury phase had chronic thermoregulatory deficits 3 years post-injury. Basilar skull fracture, brain stem injury, prolonged coma</td>
<td>Case report</td>
</tr>
<tr>
<td>Childers et al</td>
<td>TBI patients admitted to rehabilitation unit within 45 days of injury (n=84)</td>
<td>Incidence: 4% in this population</td>
<td>Retrospective study focused on incidence. Used algorithmic approach to determine presence of NF</td>
</tr>
<tr>
<td>Clinchot et al</td>
<td>Mixed brain injured population: (n=286) on rehabilitation, TBI (n=226)</td>
<td>Unexplained fever occurred in 7% of TBI patients during rehabilitation stay</td>
<td>Retrospective study focused on incidence of fever and determining aetiology</td>
</tr>
<tr>
<td>Sazbon and Grosswater</td>
<td>TBI patients in prolonged coma (&gt;1 month) (n=134)</td>
<td>Presence of NF within first week following injury was significant for predicting non-recovery</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Heindl and Lau</td>
<td>Mixed population of children: TBI (n=82) and hypoxic brain injury (n=45)</td>
<td>Neurogenic fever in patients with TBI was correlated with lower Barthel Index scores at 19 month follow up</td>
<td>Retrospective enrolment</td>
</tr>
<tr>
<td>Thompson et al</td>
<td>TBI patients (n=76)</td>
<td>DAI and frontal lobe injury are independently predictive; skull fracture and lower GCS are individually predictive of development of NF</td>
<td>Retrospective study. Developed predictive model</td>
</tr>
</tbody>
</table>
Neurogenic fever after TBI

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REFERENCES
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