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SHORT REPORT

Non-infectious fever in the neurological intensive care unit: incidence, causes and predictors

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Background and objective: Non-infectious causes of fever are often considered in critical neurological patients but their true significance has not been formally studied. The aim of this study was to evaluate the incidence, causes and predictors of fever in patients with acute neurological/neurosurgical disease and no documented infection.

Methods: Prospective data collection of consecutive patients admitted to the neurological intensive care unit (NICU) of an academic medical centre for more than 48 h was carried out. Fever was defined as body temperature ⩾101˚F (38.3˚C) documented on at least one measurement for 2 consecutive days. Patients were enrolled only if a diagnostic workup, including cultures of ⩾2 body samples, was performed before antibiotic use. Febrile patients with no proven evidence of infection were considered to have non-infectious fever.

Results: 93 patients were included in the final analysis. Fever was non-infectious in 31 patients (33%). There were no differences between the infectious and non-infectious fever groups in terms of age, use and duration of invasive catheters, daily duration of fever and number of days with fever. Documented infections tended to be more common among febrile patients with traumatic brain injury (52% vs 36%; p = 0.06). Non-infectious fever was more frequent among patients with subarachnoid haemorrhage (48% vs 18%; p = 0.01) in whom it was associated with vasospasm (p = 0.03) and symptomatic vasospasm (p = 0.05). Non-infectious fever started earlier (mean 2.6 vs 4 days; p = 0.007) and onset of fever within the first 72 h of admission predicted negative evaluation for infection (p = 0.01). Subarachnoid haemorrhage and fever onset within the first 72 h were independent predictors of non-infectious fever on multivariable analysis.

Conclusions: Fever in the absence of documented infections occurs commonly in the NICU, especially among patients with subarachnoid haemorrhage and vasospasm. Early onset of fever predicts a non-infectious cause.

Between one-quarter[1] and more than one-half[2–4] of patients admitted to the neurological intensive care unit (NICU) develop fever. The cause of fever in these patients often remains unexplained. As hyperthermia is strongly detrimental for the recovery of the acutely injured brain[5–9] and contributes to an increase in the length of stay in the NICU,[4 10] timely and accurate diagnosis of the cause of fever in the NICU is crucial.

Infections are the most common causes of fever in the NICU population but they are only documented in half of all febrile patients.[1] Central fever related to loss of the physiological regulation of body temperature by the hypothalamus is often proposed as a possible cause for persistent fever in acute neurological patients with no evidence of infection. There are no current means to confirm the diagnosis of central fever. Thus we can only assess its frequency by studying patients in whom fever remains unexplained after thorough investigations for infectious and other non-infectious causes.

The objective of this study was to determine the incidence, causes and predictors of non-infectious fever in patients with acute neurological disease.

PATIENTS AND METHODS

All patients admitted for more than 48 h to the 24 bed NICU of Jackson Memorial Hospital (Miami, Florida, USA) between June 2004 and April 2005 were screened for the presence of fever. In all patients, body temperature was measured continuously by bladder sensors and documented hourly throughout their NICU stay. Fever was defined as body temperature ⩾101˚F (38.3˚C) documented on at least one measurement for two consecutive days. Clinical data were prospectively collected in all febrile patients during the study period. If more than one episode of fever occurred, only the first episode was analysed.

Documented infectious fever was defined according to the following criteria[11 12]: (1) positive culture of body fluids, tissue samples or indwelling catheters by recognised pathogenic microorganisms, (2) sinusitis documented by CT and transnasal puncture, (3) diarrhoea and positive *Clostridium difficile* toxin in stools, (4) lung, abdominal or pelvic abscess documented by CT, (5) complicated surgical wound or (6) clinical evidence of cellulitis. Cultures of ⩾2 body samples before antibiotic use were required to enter the study.

Patients without documented infection were categorised as having non-infectious fever. All possible non-infectious causes of fever, excluding central fever, were noted using predefined diagnostic criteria.[11 12] All febrile patients were uniformly treated according to a practice protocol with acetaminophen and mechanical cooling measures (cooling blankets, ice packs). Induced hypothermia was not routinely used in our NICU during the study period.

Collected data included demographics, primary neurological diagnosis, fever onset and duration, presence of persistent fever (operationally defined as continuous fever for more than 6 h over 2 or more consecutive days), presence of central venous catheter, ventriculostomy catheter and endotracheal tube upon fever onset and time from their placement, cultures performed and their results, possible non-infectious causes of fever, use of empiric antibiotics, length of ICU stay and mortality. In patients with subarachnoid haemorrhage (SAH), we documented the presence of vasospasm (ie, mean blood flow velocity >120 cm/s on transcranial Doppler or vessel narrowing on angiography), associated neurological symptoms (symptomatic vasospasm) and timing of vasospasm in relation to fever onset.

We analysed predictors of non-infectious fever using the Fisher exact test for nominal (binary) variables and univariate

Abbreviations: NICU, neurological intensive care unit; SAH, subarachnoid haemorrhage

Table 1 Comparison of patients with documented infectious fever and non-infectious fever in the neurological intensive care unit

Variable	Infectious fever (n = 62)	Non-infectious fever (n = 31)
Age (y) (mean (SD))	48.8 (19)	47.4 (19)
TBI (n (%))	32 (52)	11 (36)
SAH (n (%))	11 (18)	15 (48)*
ICH (n (%))	9 (15)	2 (6)
Other primary diagnosis (n (%))	10 (16)	3 (10)
Ventriculostomy (n (%))	30 (48)	18 (48)
Central venous catheter (n (%))	14 (23)	7 (23)
First day of fever (n) (mean (SD))	4.0 (2.6)	2.6 (1.4)†
Onset of fever before day 3 (n (%))	32 (52)	23 (72)‡
Days of fever (n) (mean (SD))	5.8 (4.1)	6.1 (5.2)
Persistent fever (n (%))	27 (44)	16 (52)
Length of ICU stay (days) (mean (SD))	17.2 (8.8)	15.9 (12.1)
Mortality (n (%))	3 (4.8)	2 (6.5)

ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage; TBI, traumatic brain injury.
*p = 0.01
†p < 0.01
‡p = 0.02

logistic regression for continuous variables. We then tested the independence of the associations using a multivariable logistic regression model. A p value <0.05 was considered significant. The Institutional Review Board of the University of Miami School of Medicine approved the study design.

RESULTS

Ninety-three febrile patients were included in the final analysis. Fever was not associated with documented infection in 31 patients (33%). In only four of these patients, all with head trauma, did we identify potential non-infectious causes for the fever other than the primary brain injury (alcohol withdrawal in three and phenytoin toxicity in one). Hence, 27 patients (29%) had unexplained, non-infectious fever. Positive culture of respiratory secretions, present in 46 patients (49% of the total population and 74% of patients with documented infection), was the most common criterion determining the diagnosis of infectious fever. Possible causes of non-infectious fever were noted in 10 patients with documented infection (16%), including pancreatitis in four, deep venous thrombosis in two, pulmonary contusions in two and drug toxicity/withdrawal in two.

There were no differences between the infectious and non-infectious fever groups in age, sex, rate and duration of use of central venous and ventricular drainage catheters or tracheal tube, number of days with fever and prevalence of persistent fever. Patients with traumatic brain injury tended to have infectious fever more commonly (52% vs 36%; p = 0.06) while non-infectious fever predominated in patients with SAH (48% vs 18%; p = 0.01). Vasospasm was diagnosed in 12/15 (80%) patients with SAH and non-infectious fever (symptomatic in seven; preceding onset of fever in six) and in 4/11 (36%) patients with SAH and documented infection (symptomatic in only one; preceding onset of fever in three) (p = 0.03 for vasospasm and p = 0.05 for symptomatic vasospasm). Neither radiological grade (Fisher score) nor placement of intraventricular catheter was related to non-infectious fever.

Table 2 Multivariable analysis of predictors of non-infectious fever among 93 patients with acute neurological illness admitted to the neurological intensive care unit

Variable	OR	95% CI	p Value
Age	0.96	0.92–1.0	0.06
SAH	11.79	3.0–59.4	0.001
Fever within 72 h of admission	2.21	1.22–4.34	0.01
Fever duration	0.98	0.86–1.11	0.79
Persistent fever	1.04	0.57–1.93	0.88

Median number of sites cultured was 3.5 and 94% of patients had cultures from ⩾3 sites. Empiric antibiotics were used in 72% of cases of non-infectious fever but these treatments were usually stopped when the negative infectious workup was confirmed (mean duration of antibiotic therapy 3.7 days).

Fever started significantly earlier in patients without evidence of infection (mean 2.6 vs 4 days; p = 0.007). In fact, onset of fever within the first 72 h of NICU admission was associated with negative results on the evaluation for infection (p = 0.02). Multivariable analysis confirmed that SAH and fever onset within 72 h of admission were strongly associated with non-infectious fever. It also showed a trend towards an inverse association between age and occurrence of non-infectious fever.

Table 1 summarises the comparison between the groups of patients with infectious and non-infectious fever on univariate analysis. Table 2 presents the results of the multivariable logistic regression analysis.

DISCUSSION

Our results indicate that unexplained, non-infectious fever is common in the NICU. Unexplained fever is significantly more frequent among patients with SAH and is associated with the development of vasospasm and symptomatic vasospasm. Non-infectious fever tends to start early (within 72 h of admission) and remains present for several days.

Nearly one-third of our patients had fever with no identified cause other than the primary brain injury. Although central fever cannot be proven, it is the most likely explanation for the hyperthermia in these cases. Impaired central mechanisms of thermomodulation may have also contributed to the occurrence of fever in some patients with documented infection, but this possibility cannot be assessed with our study design. The coexistence of infection and disturbed central thermoregulation in some patients may explain the lack of difference in the duration of fever between the infectious and non-infectious groups.

Early fever onset predicted a non-infectious cause in our population. Thus it may be reasonable to withhold antibiotics within the first 72 h in the absence of other signs of infection until culture results become available. If empiric antibiotics are

prescribed early, they should be promptly discontinued if cultures are negative. Persistent hyperthermia is often regarded as suspicious for central fever, as opposed to the spiking pattern most commonly seen with infections. However, persistent fever, at least as defined for this study, was not a distinctive feature of non-infectious fever. More detailed analyses of the fever curve, including assessment of sustained maximal temperatures, should be part of future studies.

Accurate and timely recognition of non-infectious fever can avoid unnecessary use of antibiotics, thus reducing the risk of toxic effects, drug interactions and emergence of multi-resistant microorganisms. In patients with unexplained or suspected central fever, treatment should be focused on cooling measures to prevent the deleterious effects of hyperthermia on the injured brain.[5–9 13–15] Novel techniques to reduce body temperature, such as surface or intravascular cooling devices, can be particularly useful in these situations.[16–18] The need for more effective treatments to combat hyperthermia is underscored by the prolonged duration of fever in our population.

We found that SAH is associated with unexplained fever and, more specifically, with vasospasm and symptomatic vasospasm, as suggested by previous results.[1 5 13] Fever worsens functional outcome in SAH, thus febrile patients must be treated with cooling therapies early and aggressively.[16] It is unclear if SAH shares a common pathophysiology with vasospasm (such as upregulation of prostaglandin E2)[19] or if it is caused by vasospasm induced damage on the hypothalamus and related structures.[13]

This study has several limitations. We did not include parameters of severity of acute systemic illness in our analysis; however, it is unlikely that including these parameters would have modified our main results. The effects of treatment of hyperthermia on our results cannot be determined, but they represent standard practice. We only collected data on the first episode of fever during the NICU admission. Thus our results do not fully reflect the situation of patients with prolonged admissions who may have multiple episodes of fever from different infectious and non-infectious causes. Reliance on positive cultures to define infectious fever may have led to an overestimate of the frequency of infections; thus the true prevalence of central fever could actually be higher.

Disturbances of central mechanisms of thermoregulation are likely responsible for the common occurrence of non-infectious hyperthermia in NICU patients. The causes of this phenomenon remain speculative. Possibilities include direct damage to thermoregulatory centres, temperature set point elevation induced by cytokines, disruption of mesencephalic–diencephalic physiologically responsible for tonic inhibition of thermogenesis and impairment of peripheral mechanisms of heat dissipation by the overriding effect of sympathetic activation.[1 20]

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