Original article:

Neurogenic fever after traumatic brain injury: an epidemiological study

Gour R, Chourasia AK* , Shivhare J, Songra MC

Department of General Surgery, Government Gandhi Medical College, Bhopal (M.P.)

Corresponding author: Dr Rajneesh Gour, Neurosurgeon in GMC Bhopal.

Abstract:

Aims and Objectives: To determine incidence of neurogenic fever(NF) after severe traumatic brain injury (TBI) and To identify factors associated with development of NF in severe TBI in adults

Methods: Charts of patients admitted from January 2015 to December 2017 with severe TBI at a tertiary care teaching hospital in central India were retrospectively evaluated based on diagnostic criteria for each episode of fever 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 and final outcome of the patient.

Results: Out of 375 patients with TBI, 88% were males. 18 (4.8%) patients developed NF. Frontal lobe injury of any type, diffuse axonal injury and sub arechnoid haemorrhage are good predictors of increased risk of development of NF following severe TBI. The presence of a skull fracture and lower initial Glasgow Coma Score (GCS<5) were individual predictors of development of NF and contribute to the adverse final outcome. Neurogenic fever as such is an indicator of poor prognosis in TBI patients with 100% mortality in our study if occur within first 48 hours of admission.

Conclusions: These findings suggest the role of new clinical and radiological predictors for identifying TBI patients who are at increased risk of developing NF. Earlier diagnosis and appropriate intervention for fever in these patients may lead to improved outcomes in future.

Key words: Neurogenic fever (NF), traumatic brain injury (TBI)

Introduction:

Fever is a commonly-encountered diagnostic and management dilemma in patients with traumatic brain injury. Neurogenic fever (NF) is a non-infectious source of fever in the patient with head injury and, which if left untreated, can cause damage to the brain in multiple ways. In the past, NF was thought to be a relatively rare presentation in traumatic brain injury (TBI), but later studies have reported that upto 37 percent of TBI survivors experience this condition. [1] This is a well known fact that fever fever is detrimental in acute neurologic injury. Worse prognosis is reported in cases of acute stroke, subarachnoid hemorrhage, and traumatic brain injury. NF mainly occurs in subarachnoid hemorrhage and traumatic brain injury, with hypothalamic injury being the underlying mechanism.[2] Paroxysmal sympathetic hyperactivity is another source of hyperthermia commonly seen in the population with traumatic brain injury.[3]

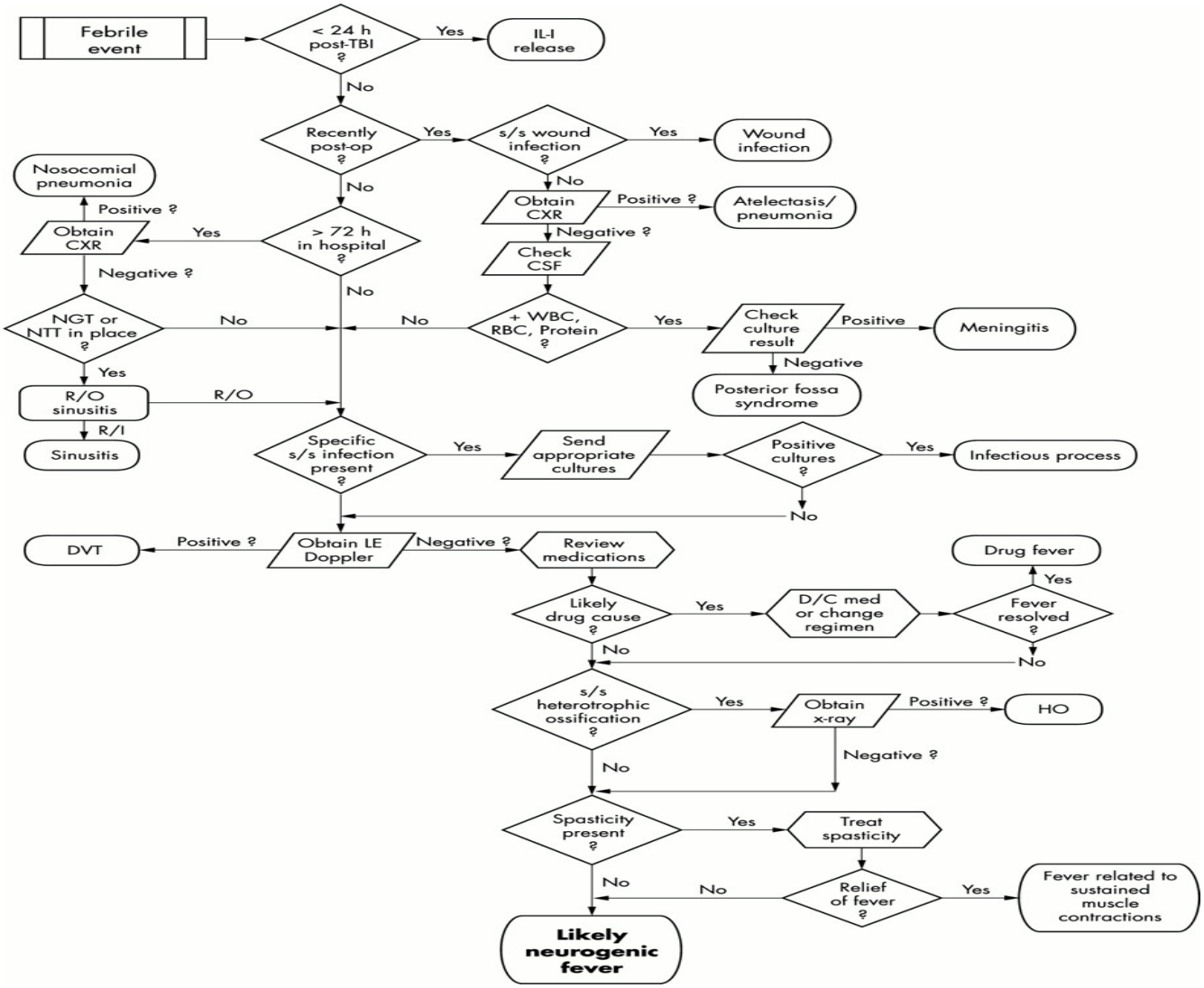
Currently NF is a diagnosis of exclusion and the diagnostic work up of the TBI patient with fever must be thoroughly done before the diagnosis of NF is made but This often leads to expensive, invasive, and often painful tests in order to make the diagnosis. As a result of the time consuming diagnosis for NF, the start of rehabilitation is delayed which can further affect the patient's ultimate functional recovery.[1,3]

In addition, the TBI patients are at increased risk of secondary injury from fever as for every 1°C rise in body temperature, there is a 13% increase in the metabolic rate. This utilizes the stressed energy reserves of the

severely brain injured, catabolic patient. The higher metabolic demand of fever exacerbates this problem, and can lead to additional loss of muscle and fat stores. The neurologic 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. Patients who are at risk of intracranial hypertension may also be significantly affected by temperature rise because the intracranial blood volume increases with temperature. This reduces compliance and puts the brain at risk for further injury. The aims of this study were to determine the incidence of NF in the acute phase of TBI and to identify factors associated with the development of NF following severe TBI in adults.[4]

Material & Methods:

This prospective observational study was conducted in the department of General Surgery in Government Gandhi Medical College Bhopal(M.P.) during January 2016 to December 2016. Patient who were more than 13 year of age and had significant acute craniocerebral injury, who were admitted for more than 24 hours were included in the study. For each patient, the entire monitoring and treatment chart was reviewed for episode of hyperthermia and fully investigated for NF . The diagnosis of neurogenic fever was made based on reviewing available patient data following the diagnostic algorithm.



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Observation & Results:

375 patient of different age group were studied & their age ranged from 13 years to 80 years with highest prevalence in 3rd decade of life with male preponderance in all age groups i.e 330(88%) out of total cases. As in our circumstances mainly males are involved in occupation & travelling while females are generally housewives. All the patients of neurogenic fever were male and all were involved in high velocity road traffic accidents.

Unconsciousness (70.4%) was the commonest positive findings in cases of traumatic brain injury which was followed by vomiting.(56%), headache(29.6%) and ENT bleeding (25.6%).

Table :1. Signs In Patients With Traumatic Brain Injury

S NO	SINGS	NO OF CASES	PERCENTAGE(%)
1.	High Temperature(>38.2^0 C)	75	20
2.	Abnormal Pulse (Bradycardia/Tachycardia)	330	88
3.	Pupillary Abnormality	165	44
4.	Tachyponea	228	60.8
5.	Decerabrate Rigidity	30	8

Table : 2. Distribution Of Patients Developing Fever In Traumatic Brain Injury (N=75)

S NO		NO OF CASES	PERCENTAGE (%)
1.	No. of Cases Temp>38.2^{0}C	75	100
2.	No. of Fever of infectious origin	36	48
3.	No. of Fever of Unknown origin	39	52
	a. No of Fever Determined to be PTH b. No. of fever responded to measures	18 21	24 28

Percentage of neurogenic fever among all fever = 24% (18/75)

Table:3.Radiological Type Of Craniocerebral Injury And Gcs In Neurogenic Fever (N=18)

SIDE	NO OF CASES	PERCENTAGE (%)
Frontal injury	18	100
Subarachnoid haemorrhage	18	100
Mid brain injury	6	33.33
GCS on admission a. ≤ 5 b. > 5	 18 0	 100 0

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Table:4.Area Of Brain Injured In Traumatic Brain Injury (n=375)

AREA	NO OF CASES	PERCENTAGE (%)
FRONTAL	156	41.6
TEMPORAL	126	33.6
PARIETAL	156	41.6
OCCIPITAL	39	10.4
CEREBELLUM	9	2.4
BRAINSTEM	15	4

Frontal lobe is the most vulnerable part of brain involved in cases of traumatic brain injury.

Table:5.Radiological Type Of Craniocerebral Injury(N=375)

TYPE	NO OF CASES	PERCENTAGE(%)
SDH	69	18.4
EDH	87	23.2
SAH	30	8
CONTUSION	144	38.4
DAI	63	16.8
SKULL FRACTURE	90	31.2
INTRAVENTRICULAR BLEED	24	6.4
DIFFUSE CEREBRAL EDEMA	3	0.8
INTRACEREBRAL HAEMATOMA	15	4

DISCUSSION:

Neurogenic fever is non infectious source of fever in the patient with traumatic brain injury and it is a diagnosis of exclusion. Neurogenic fever results from a disruption in the hypothalamic temperature set point which results in an abnormal increase in body temperature & is thought to be caused by injury to hypothalamus. Fever in the severely injured traumatic brain injury patient is a commonly encountered diagnostic and management problem. Rapid control of hyperthermia associated with fever in the traumatic brain injury patient is essential as it is associated with worsened outcome in both experimental and clinical studies. Differentiating a patient with a neurogenic fever from a patient who has true infectious or inflammatory source to the fever is a critical diagnostic decision for the clinician caring for the traumatic brain injury patient to make.

This study includes 375 individuals with TBI out of which 75(20%) developed fever. 18 patients had centrally mediated hyperthermia that was believed to be secondary to hypothalamic injury occurred at the time of traumatic brain injury. Each of these patients were young adults who developed traumatic brain injury after high speed motor vehicle accident.These patients had initial glassgow coma scale<5 & remained comatose during initial period of management. During the course of their hospitalization, these patients developed high fever. In each case, infectious cause were considered and ruled out before centrally mediated fever(NF) was diagnosed.

In our study pulse , temperature, GCS were examined at admission and then continuous monitoring was done. Patients who developed fever were investigated according to algorithm and treated with antipyretics , cold

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sponging and empirical higher antibiotics . Patient found to be of fever of known origin were treated accordingly. Patient with fever of unknown origin were treated by injection paracetamol 6 hourly intravenously and external cooling. 36 patients had fever of infectious origin and they responded to appropriate antibiotics , 18 patients were classified as neurogenic fever after ruling out other possible etiologies.

In our study the mean age of presentation is 36.6 years. This is almost similar to M.K.Childres, J. Rupright & D.W.Smith in their study (1993, mean age 33 years) & H.J. Thompson, J Paito-Mastin, MR Bullock in their study (2002 , mean age 35.4).[5,6]

The patient of NF among all head injury patient in our study were between the age of 25-35 years. All these patients developed severe cranio-cerebral injury following high velocity motor vehicle accidents. This is consistent with the finding of study conducted by J M Meythaler, MD, JD Alvin Macon Stinson III, MD in which all the patients were of young age and the injury was due to motor vehicle accident.[7] In the study by H J Thomson J, Paito-Mastin, MR Bullock(2002) similar results were obtained.[5]

In our study maximum number of Head injury occurred in males. As in our circumstances mainly males are involved in occupation and so in frequent travelling while the females are generally housewives and not exposed to traffic frequently. In M.K.Childres, J .Rupright and D.W.Smith's (1993) study there were 23(28.4%)female & males (71.6%)[6] while in H.P.Thompson, J.Puito-Martin, M.R.Bullock's study there were 12 female(15.8) & males 64(84.2%) with TBI.[5] Talwar et al(1983) in his study 20% patients were females where as the rest 80% were males.[8] Zinmerman et al (1978).26% patients were females. This discrepancy can be explained on the basis of greater outdoor activities of the females in the west as compared to females in India.[9]

Patient with neurogenic fever have persistent hyperthermia , having notably absence of perspiration having a plateau like temp curve (no diurnal variation)that persist from days to weeks. The temperature being characteristically high, resistant to antipyretic drugs and cold sponging.

In our study 18 patient were having neurogenic fever and they had high grade fever at the time of admission which persisted throughout the course of admission. In the rest of the patients temperature was within normal range on the day of injury but developed high grade fever on the next day which persisted later on. There is no diurnal variation in temperature i.e., temperature remains in plateau phase, not responded significantly to injection paracetamol and cold sponging . In the neurogenic fever there is absence of perspiration which is consistent with our findings in this study .

Patient with neurogenic fever are said to have relative bradycardia but in our study tachycardia is present in 12 Cases with pulse rate >120 /min at the time of admission and remained throughout raised. 4 patients had initially mild tachycardia i.e. pulse around 90/min. which later developed >110/min. The rest 2 patients had pulse in normal range at the time of admission which remained normal throughout the course. So presence of bradycardia in neurogenic fever is not consistent with our finding.

The treatment of neurogenic fever includes use of external cooling methods & injection paracetamol until the diagnosis is made and appropriate drug therapy may be started . The use of propranolol for control of centrally mediated fevers in patients with traumatic brain injuries has been suggested.[10] In a study conducted by Jay Merlin et al 3 patients admitted with severely traumatic injury with Glassgow coma score 3 to 4 who developed high grade fever were started on propranolol and their fever was reduced by at least 1.5 ®C within 48 hours. On weaning from propranolol the fever recurred and was again reduced after reinstitution of propranolol but as safety profile of propranolol is cause of concern in cardiac & COPD patients , it should be used cautiously in

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susceptible patients.[11] Dantrolene sodium which is used in malignant hyperthermiamay also be used in neurogenic fever but the side effects includes troublesome diarrhoea , hepatotoxicity , life threatening hyperkalemia and myocardial depression when used with calcium channel blockers .[12]

As each of these drugs has significant potential side effects, routine use without a firm diagnosis of neurogenic fever and their role in its treatment is not prudent . In our study we used only external cooling & injection paracetamol for management of neurogenic fever. However, large experimental studies are required with use of other drugs in treatment of neurogenic fever to prove their role in the management & to reduce the mortality due to neurogenic fever.

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