

# Headache in the presentation of noncephalic acute illness

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## ABSTRACT

**Background:** Headache is a frequent symptom of many systemic diseases that do not involve cranial structures. In this observational study, we assessed factors associated with headache in the acute presentation of systemic conditions in a nonsurgical emergency department (ED). **Methods:** Consecutive patients, admitted to Soroka University Medical Center ED due to noncephalic illness, were prospectively surveyed using a structured questionnaire focused on the prevalence and characteristics of headache symptoms. Medical data were extracted from the patient's charts. **Results:** Between 1 and 6/2012, 194 patients aged  $64.69 \pm 19.52$  years, were evaluated. Headache was reported by 83 (42.7%) patients and was more common among patients with febrile illness (77.5% vs. 22.5%,  $P < 0.001$ ). Respiratory illness and level of O<sub>2</sub> saturation were not associated with headache. Headache in the presentation of a noncephalic illness was associated with younger age (58 vs. 69,  $P < 0.001$ ) and with suffering from a primary headache disorder (48.2% vs. 10.8%,  $P < 0.001$ ). Headache was also associated with higher body temperature and lower platelets count. **Conclusions:** Headache is a common symptom in acute noncephalic conditions and was found to be associated with younger age and febrile disease on presentation. Patients who present with primary headache disorders are more prone to have headache during acute illness. Acute obstructive respiratory disease, hypercarbia or hypoxemia were not associated with headache.

**Key words:** Emergency department, fever, headache, migraine

## Introduction

Headache is a common symptom of many diseases; it directly involve intracranial or cephalic pathologies such as sinusitis or otitis media.<sup>[1]</sup> Headache may present as the hallmark of the disease in other systemic conditions such as hypertensive crisis,<sup>[2]</sup> preeclampsia,<sup>[3]</sup> or Rickettsia infections.<sup>[4]</sup>

However, headache is a common symptom in many common acute noncephalic conditions as well. Previous studies showed an association between acute headache and various febrile conditions such as

pneumonia, upper respiratory tract infection (URTI),<sup>[5-7]</sup> systemic viral infections (especially caused by human metapneumovirus respiratory tract infection),<sup>[8]</sup> and even urinary tract infections (UTI).<sup>[9]</sup> Other noninfectious conditions such as: Acute exacerbations of chronic obstructive pulmonary disease (COPD) or asthma, anemia, congestive heart failure (CHF),<sup>[10,11]</sup> fasting,<sup>[12]</sup> and elevated blood pressure (without hypertensive crisis) were all associated with headache as well.<sup>[13]</sup>

Many clinical factors were found to be associated with acute headache during illness. Fever is usually considered to be the most important determinant,<sup>[8]</sup> but other factors such as hypoxia and hypercapnia not only due to pulmonary disease<sup>[14]</sup> but also due to obstructive sleep apnea and high altitude,<sup>[15]</sup> hypoglycemia,<sup>[16]</sup> hypothyroidism,<sup>[17]</sup> and

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dehydration<sup>[18]</sup> were all found to be independently associated with acute headache.

In this study, we sought to evaluate the characteristics associated with an acute headache among patients with noncephalic acute medical condition.

## Methods

### Setting

Emergency department (ED) of Soroka University Medical Center (SUMC), a tertiary referral, 1000 beds medical center, and serving over 700,000 residents of Southern Israel. The 60 beds ED treats over 500 adult patients a day on average. This prospective observational study took place at the medical ED. The study was approved by the SUMC internal review board.

### Patients

The acutely adult ill medical patients were screened between January and June 2012. Patients presenting with chief complaint of headache, acute cephalic illness (stroke, seizures, cranial lesions, sinusitis, or central nervous system infections), treated with vasodilators for hypertensive crisis or chest discomfort, or those with chronic headache (>14 days of headache per month for longer than 3 months) were excluded. Patients younger than 18 and who could not give an adequate headache history due to either the severity of their medical condition, language barrier, or cognitive impairment were excluded as well.

### Data collection

Patients were interviewed using a structured questionnaire by a surveyor who was not involved in the patients' medical care. The questionnaire was designed to capture headache symptoms, headache history, as well as demographic data. The following clinical data were extracted from the patients' ED chart: Vital signs, O<sub>2</sub> saturation, primary diagnosis, diagnostic procedures, and blood test results.

Patients were asked to report if they had to deal with headache attacks that are not related to acute medical illness during the last year (active episodic headache) and whether they used to have headache during similar medical events in the past (at least once).

### Statistical analysis

The preferred method of analyses for continuous variables was parametric. Nonparametric procedures were used only if parametric assumptions could not

be satisfied, even after data transformation attempts. Parametric model assumptions were assessed using normal plot or Shapiro–Wilk's statistic for verification of normality and Levene's test for verification of homogeneity of variances. Categorical variables were tested using Pearson's Chi-square test for contingency tables or Fisher exact test, as appropriate. Multivariate analysis was performed by Poisson regression with robust error variance.<sup>[19]</sup> Modified Poisson approach was used to estimate the relative risk (RR) adjusted for potential confounders. Variables were included into the model based on the statistical and clinical significance. We reported the final parsimonious model.

To evaluate the possible nonlinear association between the body temperature and probability of the headache, we have used headache predicted probabilities by local regression (LOESS) curves adjusted for: Gender age, platelet count, saturation level, and similar problem before.

Results are presented as RRs with confidence intervals, mean ( $\pm$ standard deviation), and median (interquartile range).

Two-sided  $P < 0.05$  was considered statistically significant. IBM SPSS statistics 20.0 software (IBM) was used for the statistical analysis results.

## Results

During the study, 199 patients were recruited. Five patients were not included in the final analysis due to incompleteness of the clinical data. The distribution of the primary diagnosis was as following: CHF (37, 19.0%), COPD exacerbation (34, 17.5%), pneumonia (15, 7.7%), URTI (23, 11.9%), exacerbations of asthma (21, 10.8%), UTI (18, 9.3%), hypertension (15, 7.7%), and fever of undetermined cause (31, 16.0%). Out of the 194 evaluated patients, 52 (26.8%) patients had unprovoked episodes of headache.

Headache was reported during the current acute illness by 83 (42.8%) of the patients. The headache was of moderate (35, 42.0%) to severe (30, 36.0%) intensity, bilateral (68, 76.0%) or localized to the frontal regions of the head (45, 54.2%), and generalized in 20 patients (24.1%). Table 1 summarizes the baseline characteristics of patients with and without headache. Patients with headache were younger (median age  $69.88 \pm 15.38$  vs.  $58 \pm 22.18$ ,  $P < 0.001$ ) and had higher proportion of active primary headache: 40 (48.2%) versus

12 (10.8%),  $P < 0.001$ . Patients with febrile illness had significantly higher rate of headache: (48, 57.8%) versus 39 (35.1%),  $P < 0.001$ .

**Table 1: Patient population - baseline characteristics**

Variable	No headache (n=111)	Headache (n=83)	P
Gender - Male n (%)	61 (55.0)	39 (47.0)	0.27
Age (years, mean±SD)	69.88±15.38	58±22.18	<0.001
Marital status* - Married n (%)	66 (60.6)	47 (57.3)	0.65
Ethnicity - Jewish	84 (77.1)	63 (76.8)	0.67
Active episodic headache, n (%)	12 (10.8)	40 (48.2)	<0.001
Duration of headache symptoms (years) median (IQR)	7.5 (1.75-24)	6 (2-10)	0.7
History of headache on similar events n (%)	11 (9.9)	59 (72.0)	<0.001
Smoking n (%)	34 (30.6)	27 (32.9)	0.73
Febrile disease* n (%)	39 (35.1)	48 (57.8)	0.002
Respiratory disease* n (%)	65 (58.6)	27 (32.5)	<0.001
HTN n (%)	7 (46.6)	8 (53.3)	0.39
Pneumonia n (%)	5 (35.7)	9 (64.2)	0.09
URTI n (%)	14 (63.6)	8 (36.3)	0.51
UTI n (%)	13 (72.2)	5 (27.8)	0.17
Fever of unspecified etiology n (%)	7 (22.5)	24 (77.5)	<0.001
Exacerbations of asthma n (%)	15 (71.4)	6 (28.6)	0.16
COPD n (%)	23 (67.6)	11 (32.4)	0.17
CHF n (%)	26 (72.2)	10 (27.8)	0.04

\*Marital status: Married, single, \*Febrile disease: Pneumonia, URTI, UTI or fever of unspecified etiology, \*Respiratory disease: Exacerbations of asthma, COPD or CHF. CHF: Congestive heart failure, COPD: Chronic obstructive lung disease, UTI: Urinary tract infection, URTI: Upper respiratory tract infection, HTN: Hypertension, IQR: Interquartile range, SD: Standard deviation

**Table 2: Headache and clinical parameters**

Variable	No headache (n=111)	Headache (n=83)	P
Pulse (bpm) (mean±SD)	88.47±18.43	96.36±21.19	0.007
O <sub>2</sub> saturation (without oxygen supplementation) (mg/L) median (IQR)	94 (90-96)	95 (92.25-98)	0.02
O <sub>2</sub> saturation (with oxygen supplementation) (mg/L) median (IQR)	98 (95-99)	96 (91-97)	0.07
Systolic blood pressure (mmHg) (mean±SD)	142.80±29.68	136.04±29.06	0.12
Diastolic blood pressure (mmHg) (mean±SD)	70.87±15.92	70.10±15.94	0.74
Body temperature (°C) (mean±SD)	37.04±0.96	37.39±1.08	0.04
Glucose (mg/dL) (mean±SD)	135.29±58.95	132.55±66.99	0.76
Creatinine (mg/dL) (mean±SD)	1.03±0.53	0.86±0.27	0.005
Urea (mg/dL) (mean±SD)	51.14±31.64	38.86±21.78	0.003
Sodium (mmol/L) (mean±SD)	137.24±4.66	137.45±4.63	0.76
Potassium (mmol/L) (mean±SD)	4.35±0.46	4.20±0.45	0.03
pH blood (mol/L) (mean±SD)	7.38±0.05	7.38±0.04	0.80
pCO <sub>2</sub> (mmHg) (mean±SD)	44.95±14.23	41.79±10.75	0.20
HCO <sub>3</sub> <sup>-</sup> (mEq/L) (mean±SD)	26.57±6.08	24.86±4.36	0.10
White blood cell count (×10 <sup>9</sup> /L) (mean±SD)	11.24±9.38	11.08±7.69	0.90
Hemoglobin (mmol/L) (mean±SD)	12.29±1.77	13.08±2.09	0.006
Platelet count (fL) (mean±SD)	255.30±93.40	221.76±67.96	0.005

SD: Standard deviation, IQR: Interquartile range

Table 2 depicts the clinical parameters of the acute illness. The presence of headache was positively associated with body temperature, pulse rate, hemoglobin, and O<sub>2</sub> saturation and negatively associated with concentrations of creatinine, urea and potassium, and platelet count. Hospitalization duration did not differ between those with and without headache: 5 (3–8) days versus 4.5 (2.75–6),  $P = 0.21$ .

Multivariate analysis [Table 3] found that younger age ( $P = 0.007$ , RR = 0.98), higher body temperature ( $P = 0.017$ , RR = 1.21), experiencing headache on similar conditions ( $P < 0.001$ , RR = 3.89), and lower platelet count ( $P < 0.001$ , RR = 0.96) were independently associated with headache. Gender, oxygen saturation, urea to creatinine ratio, and blood urea levels were not associated with headache. Figure 1 (LOESS analysis) confirms the independent association between headache and body temperature. After adjustment for gender, age, platelet count, saturation level, and similar previous headache, we have found that higher the fever is, higher the chances to have a headache.

## Discussion

We found that headache is an extremely common symptom experienced by more than 40.0% of the patients evaluated in the medical ED due to acute noncephalic illness, most of them experiencing moderate to severe pain, adding to the discomfort from the acute illness. Our results demonstrate that the likelihood of headache is associated with younger patient's age, a history of headache on similar circumstances, elevated body temperature, and lower platelet count.

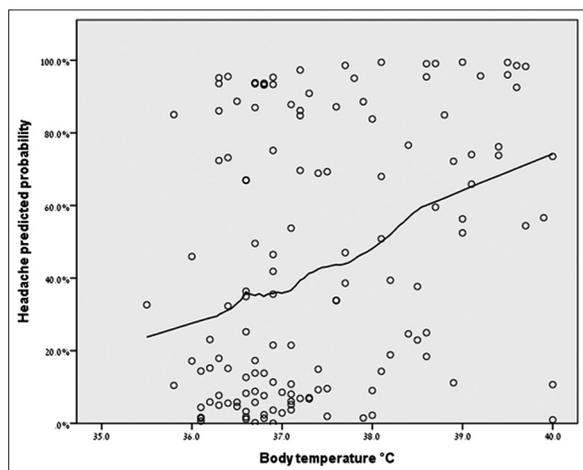
Other patient characteristics (such as gender, ethnicity, and smoking) were not associated with headache during acute illness. Several clinical parameters in univariate analysis were found to be significantly associated with headache: Higher levels of hemoglobin, creatinine, urea and potassium as well as lower O<sub>2</sub> saturation. Nevertheless, the association lacked clinical relevance and did not reach statistical significance in multivariate analysis.

Headache disorders are chronic disorders with episodic manifestations. Active headache disorders are characterized by the occurrence of headache episodes within the previous year.<sup>[20]</sup> Active headaches are reported by 53.0% of adult population and active migraine by 14.7% of the population.<sup>[21]</sup> In our cohort, the prevalence of active headache was relatively low (26.8%) possibly due to the relatively old age of the study population.

**Table 3: Multivariate Poisson regression model with a robust error variance for evaluating headache**

	P	RR	95% CI	
			Lower	Upper
Age, per year	0.007	0.98	0.98	0.99
Fever groups	0.017	1.21	1.03	1.42
Platelets, per thousand	<0.001	0.96	0.93	0.98
Similar headache before	<0.001	3.98	2.79	1.42

Fever groups divided by mean±SD. A <36.24, 36.24 ≤ B <37.35, 37.35 ≤ C <38.45, D ≥38.45. CI: Confidence interval, RR: Relative risk, SD: Standard deviation



**Figure 1:** Association between headache and body temperature. Local regression (LOESS) curves, based on the probabilities of headaches, adjusted for: Body temperature, gender, age, platelet count, saturation level and similar headache before

An active headache disorder probably represents personal vulnerability to headache, possibly triggered by the acute illness. Most of the patients experiencing headache in our cohort, reported experiencing headache in similar occasions in the past.

As was suggested previously, fever is part of a systemic presentation considered to be a trigger for headache.<sup>[8]</sup> A cross-sectional epidemiologic survey of a representative 25–64-year-old general population demonstrated that lifetime prevalence of fever-induced headaches was 63.0%.<sup>[22]</sup> Furthermore, among children aged 0–14, suspected infections and fever accounted for 56.8% of the headache and migraine episodes.<sup>[23]</sup> Our study confirms the close independent association between headaches and fever.

Several pathophysiological mechanisms involved in the pathogenesis of primary headaches may be affected by fever. Pyrogenic cytokines (interleukin-1 [IL-1], IL6) and prostaglandins cause rise in temperature.<sup>[24]</sup> Body temperature is largely regulated by the hypothalamus and the induction of fever is believed to be caused by inflammatory modulation of its activity.<sup>[25]</sup> The hypothalamus is also involved in the pathophysiology

of migraine mediated by calcitonin gene-related peptide (CGRP).<sup>[26-28]</sup>

Recently, the role of CGRP in migraine pathophysiology was extensively studied. CGRP seems to be involved in the evolution of bacteria-induced hyperpyrexia. It has been suggested that bacteria activate CGRP through lipopolysaccharide and endotoxins. This activation leads to secretion of IL1 and IL6, which in turn, activate the hypothalamus and cause fever.<sup>[29]</sup> Inflammatory mediators themselves are contributors to the pathophysiology of both tension-type and migraine headache, and anti-inflammatory drugs are commonly used as acute treatments for headache attacks.<sup>[30]</sup>

Activation of the serotonergic system, especially through 5HT1 receptors is considered as a major part of migraine pathophysiology.<sup>[31]</sup> Serotonergic system activation is involved in hyperpyretic states as demonstrated by hyperthermia during episodes of serotonergic syndrome,<sup>[32]</sup> and by the temperature lowering effect of 5HT1A agonist on patients infected by *Plasmodium falciparum*.<sup>[33]</sup> It has been speculated that migraine attacks are caused by dysregulation of brain temperature, possibly as a defense mechanism.<sup>[34]</sup>

The association between lower platelet count and headache during acute medical illness is small, yet significant and independent. Several lines of evidence suggest that increased platelet activity is associated with migraine attacks.<sup>[35]</sup> Furthermore, as explained before increased levels of 5HT during migraine causes reversible platelets aggregation.<sup>[36]</sup> Thus, the suggested mechanism explains that increased platelet aggregation, slightly decreasing the platelet count, possibly lead to the association between lower platelet count and headache in an acute illness. It was also suggested that sub-clinical platelet aggregation may induce headache attacks.

Our study has several limitations. It is a single-center study, with a relatively small sample size, limited to patients referred to the ED, therefore its generalizability to other clinical settings is limited. By excluding cephalic illnesses, we could not evaluate the diagnostic contribution of headache in differentiating cephalic from noncephalic disorders. Patients who were actively complaining about headache where not all diagnosed as suffering from migraine or tension-type headache.

Nevertheless, it seems that headache is a common distressing contributor in acute ED patients. It seems that alleviation of headaches in those settings should be directed to temperature lowering. Larger studies are needed to evaluate the significance of the association

between headache and lower platelet count in acute medical illness conditions.

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### Conflicts of interest

There are no conflicts of interest.

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