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Research Submission

Headache in Cerebral Hemorrhage is Associated with Inflammatory Markers and Higher Residual Cavity

Rogelio Leira, MD, PhD; Mar Castellanos, MD, PhD; José Álvarez-Sabín, MD, PhD; Exuperio Diez-Tejedor, MD, PhD; Antonio Dávalos, MD, PhD; José Castillo, MD, PhD; On Behalf of the Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society

Background and Purpose.—The mechanisms responsible for headache in patients with intracerebral hemorrhage (ICH) are not completely understood. The present study was undertaken to analyze the headache-associated factors, the possible related biochemical mechanisms, and the headache potential predictors of outcome in spontaneous ICH.

Methods.—We prospectively studied 189 patients from a large cohort of 266 consecutive patients with supratentorial ICH admitted within the first 12 hours of symptoms onset. The presence of headache at stroke onset was evaluated in these patients. The volumes of the initial ICH, peripheral edema at 48 hours, and the residual cavity at 3 months were measured on CT scan. Glutamate, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α levels were measured in blood samples obtained on admission. The Canadian Stroke Scale (CSS) and the modified Rankin Scale were used to evaluate stroke severity and neurological outcome, respectively.

Results.—Headache at onset of stroke was observed in 65 patients (34.4%). Patients who experienced headache had a significantly higher frequency of history of infection ($P = .009$) or inflammation ($P = .045$), as well as higher body temperature ($P = .021$), leukocyte count ($P = .038$), ESR ($P = .011$), and mass effect ($P = .017$) on admission. Plasma concentrations of IL-6 and TNF-α were significantly higher in patients with headache than in those without. Headache was an independent predictor of the residual cavity volume in patients with spontaneous ICH (odds ratio 6.49; 95% CI 2.51 to 16.78; $P = .0001$).

Conclusions.—Headache at ICH onset is associated with clinical and biochemical markers of inflammation and is an independent predictor of higher residual cavity volume after spontaneous ICH.

Q1 **Key words: headache, intracerebral hemorrhage, inflammation, outcome**

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From the Department of Neurology, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain (Drs. Leira and Castillo); Department of Neurology, Hospital Universitari Doctor Josep Trueta, Girona, Spain (Dr. Castellanos); Department of Neurology, Hospital Universitari Vall d'Hebrón, Barcelona, Spain (Dr. Álvarez-Sabín); Department of Neurology, Hospital Universitario La Paz, Madrid, Spain (Dr. Diez-Tejedor); and Department of Neurology, Hospital Universitario Can Ruti, Barcelona, Spain (Dr. Dávalos).

Address all correspondence to Dr. José Castillo, Department of Neurology, Hospital Clínico Universitario, Santiago de Compostela, Spain.

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Headache is present in 30% to 60% of patients during the acute phase of intracerebral hemorrhage (ICH).[1-8] The mechanisms underlying headache in patients with ICH are not exactly known. It is commonly held that headache in ICH is related to the blood mass that causes local distention, distortion, deformation, or stretching of pain-sensitive intracranial structures.[8–10] The organization of the trigeminovascular system could explain the ipsilateral and sometimes the bilateral location of pain and the high frequency of headache in occipital and cerebellar hematomas.[8] However, other mechanisms are necessary to explain the headache observed in other ICH locations.

In this study, we analyzed the factors associated with headache, the possible related biochemical mechanisms, and the potential outcome predictor value of headache in patients with spontaneous supratentorial ICH.

PATIENTS AND METHODS

We studied 189 patients with a first-ever ICH. The patients were selected from a larger cohort of 266 patients with spontaneous supratentorial ICH admitted consecutively to 15 hospitals between May 1999 and April 2001 (Appendix I). For the purposes of this study, we excluded 77 patients in whom headache was not recorded due to communication difficulties. Inclusion criteria were time from the onset of symptoms to admission of <12 hours (in those with stroke present on awakening, time of onset was taken as the time when the patient was last seen normal); age <80 years; and absence of stupor or coma. The study was approved by the Institutional Review Board of all participating institutions and informed consent was obtained from the patients or their relatives.

Study Development.— On arrival in the emergency department, blood pressure and body temperature were recorded and blood samples were taken.

The presence of headache at onset was particularly evaluated in the patients. Neurological examination was performed by a neurologist experienced in using the Canadian Stroke Scale (CSS),[10] and stroke severity was assessed on admission, at 48 hours, 7 days, and 3 months. The CSS measures the level of consciousness (alert = 3 and drowsy = 1.5); speech (normal = 1, expressive deficit = 0.5, and receptive deficit = 0); orientation (oriented = 1 and disoriented or not applicable = 0); facial paresis (none = 0.5 and present = 0); weakness in arm, hand, and leg (none = 1.5, mild = 1, significant = 0.5, and total = 0 scored individually for each item), with a total score ranging from 1.5 (maximum deficit) to 10 (absence of deficit).

Stroke outcome was evaluated by using the modified Rankin Scale (mRS) at 90 days. Patients with a mRS $\leq$2 were considered to have a good outcome, while those with a mRS >2 were in the poor outcome category. This scale also included mortality because patients who died were scored with the worst possible score (value of 6) in this scale.

Three head CT studies were performed on all patients: at entry into the study, at 48 hours, and at 3 months $\pm$ 1 week from ICH onset. CT scans were performed with a matrix of 512 $\times$ 512 and the slice thickness was 8 to 10 mm. Lesion volumes were calculated on the radiographic plate by one evaluator who was blinded to the clinical and biochemical data; the formula 0.5 $\times$ a $\times$ b $\times$ c was used (where a is the maximal longitudinal diameter, b is the maximal transverse diameter perpendicular to a, and c is the number of slices containing hemorrhage). The ICH topography was classified as *lobar* when it affected predominantly the subcortical white matter of the cerebral lobes or as *deep* when it was limited to the basal ganglia, the thalamus, or both. The presence of intraventricular extension of the hematoma was recorded, but its volume was not measured. Neither the presence nor the quantity of associated subarachnoid hemorrhage was evaluated in this study. In the second CT study, the volume of the ICH plus that of the zone of peripheral hypodensity was determined using the same volumetric method described above; the volume of the hypodensity was calculated by subtracting the volume of the ICH from that of the total lesion (ICH + peripheral hypodensity). The volume of the residual cavity (hypodensity) was determined on the CT scan at 3 months by using the same formula.

Patients were admitted to a neurological ward or an acute stroke unit and were managed by a specialized

stroke team and nursing staff. Antihypertensive treatment with IV labetalol or captopril was administered in case of systolic blood pressure >185 mmHg or diastolic blood pressure >105 mmHg. Subcutaneous heparin was used for the prevention of deep-vein thrombosis and pulmonary embolism. Glucose-containing IV solutions or corticosteroids were not used, but patients with severe intracranial hypertension were treated with IV mannitol. Hyperthermia was controlled by the administration of metamizol or acetaminophen. None of the patient was part of a therapeutic clinical trial. We recorded 72 clinical, biochemical, and neuroimaging variables on admission (Appendix II).

Laboratory Tests.— Blood samples were drawn on admission during the painful period in those patients with headache and in all patients without headache. Blood was obtained by venipuncture and collected in crystal tubes with potassium edetate, centrifuged at 3000*g* for 5 minutes, and immediately frozen and stored at −80°C. Glutamate concentrations were analyzed by high-perfomance liquid chromatography following the method described elsewhere.[11] Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured with commercially available quantitative sandwich ELISA (Quantikine) kits obtained from R&D Systems (Minneapolis, MN, USA), as previously described.[12] Biochemical determinations were performed by researchers blinded to clinical and radiological data.

Statistical Analyses.— Categorical variables are shown as percentages. Continuous variables are presented as mean ± SD, and those with no normal distribution are presented as median (quartiles). Test performed were the χ^2 or two-sided Fisher's exact test for the categorical variables and the Student's *t*-test or the Mann-Whitney test for the continuous variables as appropriate (SSPS 10 software, Chicago, IL, USA). Factors associated to headache in the univariate analyses ($P < .05$) were tabulated and were analyzed in two different logistic regression models: model 1 (clinical and neuroimagen variables) and model 2 (biochemical variables). Regression estimates are indicated as odds ratio, confidence interval of odds ratio (95%), and *P* values for covariates that reached significance are listed.

RESULTS

Of the 189 patients studied, 65 (34.4%) complained of headache at onset of ICH. Table 1 shows the clinical characteristics, CT findings, and biochemical marker levels on admission and their association with headache. Patients who experienced headache had significantly higher frequency of history of infection ($P = .009$) or inflammation ($P = .045$) within the 15 days preceding ICH onset, and they were also showed higher body temperature ($P = .021$), leukocyte count ($P = .038$), and ESR ($P = .011$) on admission. Plasma concentrations of IL-6 (26.7 ± 12.7 vs. 15.1 ± 4 pg/mL; $P < .0001$) and TNF-α (18.2 ± 12.4 vs. 10.5 ± 7.7 pg/mL; $P < .0001$) were significantly higher in patients with headache than in those without headache. Among radiological variables, only mass effect was associated with the presence of headache (65.3% vs. 50.1%; $P = .017$). No other finding in the initial CT scan (ICH volume, intraventricular bleeding, or peripheral hypodensity) was significantly associated with headache at ICH onset. The frequency of ICH location (lobar or deep) was similar between the two groups.

In the logistic regression analysis with clinical variables (model 1, Table 2), the antecedent of infection (odds ratio 5.00; 95% CI 1.05 to 23.78; $P = .042$), and mass effect (odds ratio 2.08; 95% CI 1.03 to 3.87; $P = .003$) were independent factors associated with the presence of headache at ICH onset. In the logistic regression analysis with biochemical variables (model 2, Table 2), the plasma level of IL-6 (odds ratio 1.26; 95% CI 1.15 to 1.39; $P < .0001$) was an independent factor associated with headache in ICH.

Patients with headache had no statistically significant difference in mortality or functional disability at 3 months. The residual cavity volume at 3 months was significantly higher (29.5 ± 35.9 vs. 10.6 ± 15.7 cc; $P < .0001$) in the group of ICH patients with headache on admission (Table 3).

COMMENTS

This study shows that headache at ICH onset is associated with clinical and biochemical markers of inflammation and is an independent predictor of higher residual cavity volume after spontaneous ICH.

The incidence of headache at onset of spontaneous ICH registered in our study (34.4%) was

similar to previous reports.[1–8] The frequency of ICH location was similar between the groups with and without headache. In contrast, other studies showed that the frequency was higher in cerebellar and occipital lobar hemorrhages.[4,8] The frequency of ICH location (lobar or deep) was similar between the two groups in our study. In contrast, headache was reported to be more frequent in lobar hematomas than in basal ganglia hematomas.[16]

The cause of headache in ICH is not completely understood. A simple explanation could be a direct effect of the blood mass that causes local distention, or distortion, of pain-sensitive intracranial structures.[8–10] According to this, in our study, mass effect was associated with the presence of headache at ICH onset. The organization of the trigeminovascular system explains the ipsilateral and sometimes the bilateral location of pain and the high frequency of headache in occipital and cerebellar hematomas.[8] However, other mechanisms are necessary to explain the headache in other lobar ICH.

No other finding on the initial CT scan (ICH volume, intraventricular bleeding, or peripheral hypodensity) was significantly associated with headache at ICH onset, although the incidence of intraventricular bleeding was higher in the group of ICH without headache (35.5% vs. 26.2%).

ICH patients with headache showed higher body temperature on admission. Increased body temperature shortly after ischemic stroke independently predicts poorer outcome,[14-16] but the significance of hyperthermia after ICH has not been established. It may be the result of the acute phase reaction and inflammatory response or may be by itself deleterious, as occurs shortly after ischemic stroke. Increased body temperature has been associated with greater mortality and poor stroke outcome in some studies,[17] but these findings were not replicated by others.[18,19]

Table 1.—Univariate Analysis: Clinical Characteristics, CT, and Biochemical Markers in Patients with and Without Headache at ICH Onset

	ICH with Headache n = 65	ICH Without Headache n = 124	*P* Value
Age (year)	69.4 ± 10.5	71.3 ± 10.6	.322
Sex, male (%)	49.2	61.3	.046
Arterial hypertension (%)	73.8	65.3	.151
Infection (15 days before) (%)	13.8	3.2	.009
Inflammation (15 days before) (%)	9.2	2.4	.045
Fever (15 days before) (%)	7.7	4.0	.230
SBP (mmHg)	178.7 ± 30.6	175.9 ± 27.2	.485
DBP (mmHg)	100.2 ± 19.7	96.9 ± 18.1	.284
Body temperature (°C)	36.8 ± 0.8	36.6 ± 0.6	.021
CSS	5 (3.2 to 6.5)	4.5 (3 to 6.5)	.782
ICH volume 48 hours (cc)	41.3 ± 33.3	38.9 ± 46.6	.237
Peripheral hypodensity volume 48 hours (cc)	11.8 ± 14.8	12.5 ± 16.9	.956
Lobar location (%)	30.8	22.6	.146
Ventricular bleeding (%)	26.2	35.5	.127
Mass effect (%)	65.3	50.1	.017
Serum glucose levels (mg/dL)	147.3 ± 48.1	145.9 ± 45.7	.933
Leukocyte count ($\times 10^3$/mmc)	11.2 ± 8.4	8.9 ± 3.1	.038
Fibrinogen level (mg/dL)	437.2 ± 129.8	415.4 ± 114.3	.292
C-reactive protein	11.8 ± 11.6	8.4 ± 10.6	.265
ESR 1Â h, mm	27.9 ± 16.6	22.7 ± 18.2	.011
Glutamate (μM/mL)	184.1 ± 88.1	166.7 ± 86.1	.201
IL-6 (pg/mL)	26.7 ± 12.7	15.1 ± 6.4	<.0001
TNF-α (pg/mL)	18.2 ± 12.4	10.5 ± 7.7	<.0001

Table 2.—Logistic Regression: Models 1 and 2.—Adjusted Odds Ratio of Headache for Baseline Characteristics Variables Q4

Independent Variable	Odds Ratio	95% Confidence Interval	*P* Value
Model 1			
Sex	1.08	0.81 to 2.15	.179
Infection (15 days before)	5.13	1.16 to 20.13	.012
Inflammation (15 days before)	2.86	0.72 to 6.14	.318
Body temperature	2.17	0.84 to 3.08	.083
Leukocytes	1.05	0.93 to 1.11	.446
ESR	1.56	0.78 to 2.24	.504
Mass effect	2.08	1.03 to 3.87	.003
Model 2			
IL-6	1.19	1.11 to 1.28	<.0001
TNF-α	0.99	0.95 to 1.03	.755

Two laboratory markers of the stress reaction on admission (high neutrophil count and high ESR) are associated with headache in ICH. Biochemical changes have also been related to the pathogenesis of headache in ischemic stroke but are still poorly understood in ICH. Glutamate concentration in plasma and CSF of patients with headache at the onset of cerebral infarction are significantly higher than those of patients without headache, suggesting glutamate participation in the genesis of pain.[11,20] However, the release of excitatory amino acids might not be the cause rather an epiphenomenon of pain. Although symptomatic spreading depression, and consequently glutamate release may be related to the cortical lesion, glutamate increase is more likely associated with the hypoperfusion that develops in the core of infarction and in the surrounding ischemic penumbral area.[21] In the current study, we found no differences between plasma glutamate levels and between the group of patients with and without headache. These results suggest that excitotoxic mechanism does not play an important role in the pathophysiology of headache that accompany ICH.

Table 3.—Univariate Analyses: Outcome Variables at 3 Months

	With Headache (n = 65)	Without Headache (n = 124)	*P* Value
CSS	5.5 (0 to 8.5)	6.5 (3.5 to 9.5)	.094
Rankin	3 (2 to 6)	3 (1 to 5)	.100
Mortality	27.7	16.9	.062
Residual cavity volume (cc)	29.5 ± 35.9	10.6 ± 15.7	<.0001

Plasma concentrations of IL-6 and TNF-α were significantly higher in patients with headache than in those without headache. Serum cytokine studies in headache patients have yielded conflicting results. Previous studies have described increased plasma levels of IL-5 and IL-4 in patients with migraine,[22] and higher CSF levels of IL-6 in acute stroke patients with headache compared to those without headache.[20] In fact, headache at onset of the ischemic stroke was demonstrated to be an independent predictor of neurological worsening, and we hypothesized that headache might be a surrogate marker of the molecular mechanisms involved in neurological worsening after acute ischemic stroke. High levels of proinflammatory molecules within 24 hours of ICH onset were correlated with the magnitude of the subsequent perihematoma brain edema.[23] The correlation of high levels of IL-6 and TNF-α with the hypodensity surrounding the hematoma is in agreement with the notion of edema that is an indicator of the inflammation response induced by the hematoma. The increase in plasma levels of molecular markers of inflammation in our patients with headache in ICH might reflect changes in the permeability of the blood-brain barrier because in situations in which the barrier remains undamaged, cytokines increase in CSF but not in plasma.[24] Our results suggest that headache in ICH

may also be related with inflammatory mechanisms and cerebral edema (as an indicator of the inflammatory response induced by the hematoma), although it could also be an epiphenomenon because ICH volume, mass effect, and peripheral hypodensity were not significantly associated with headache at ICH onset.

The residual cavity volume at 3 months was significantly higher in the group of ICH patients with headache on admission. In the logistic regression analysis, headache was an independent factor associated with the volume of residual cavity in patients with spontaneous ICH. The effect of headache remained significant after further adjustment for biochemical markers but was markedly reduced by the glutamate and IL-6 effect (data not shown). These findings suggest that inflammation and excitotoxicity may be involved in causing secondary damage after ICH.[23]

Certain limitations of our prospective study must be emphasized. Because this is a multicenter study, enrolled patients were admitted into different hospitals with different neurological wards and/or stroke units. Since specialized medical and nursing personnel were taking care of the patients and the same treatment protocols were followed in the different institutions, it is not likely that the CSS scores of the patients might have been different depending on the facility. Seventy-seven patients were excluded due to communication difficulties (speech or language difficulties, or patients with reduced level of consciousness). This could bias the study in favor of mild ICHs, and nondominant hemispheric hemorrhages.

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APPENDIX I

Participating Centers, Investigators, and the Number of Patients Studied: Hospital Clínico Universitario, Santiago de Compostela (62): José Castillo, Rogelio Leira; Hospital Universitari Doctor Josep Trueta, Girona (47): Antonio Dávalos, Yolanda Silvia; Hospital Virgen del Rocío, Sevilla (21): Alberto Gil Peralta, Enrique Montes; Hospital Virgen Blanca, León (21): Javier Tejada; Hospital Clinic, Barcelona (20): Ángel Chamorro, Nicolás Vila; Hospital Arquitecto Marcide, Ferrol (19): Francisco López, José Aldrey; Hospital Clínico, Valencia (17): José Miguel Láinez, Raquel Chamarro; Hospital Provincial, Pontevedra (16): Manuel Seijo Martínez; Hospital de La Princesa, Madrid (13): José Vivancos, Raquel González; Hospital Clínico, Madrid (9): José Egido; Hospital Vall d'Hebrón, Barcelona (8): José Álvarez-Sabín, Joan Montaner; Hospital Gregorio Marañón, Madrid (5): Antonio Gil, Fernando Díaz; Hospital Virgen de la Concha, Zamora (3): José Carlos Gómez; Hospital La Paz, Madrid (3): Exuperio Diez-Tejedor; Hospital Clínico, Zaragoza (2): Enrique Mostacero.

APPENDIX II

List of Clinical, Laboratory, and Neuroimaging Variables Analyzed on Admission Variables on admission:

- Age
- Sex
- Time of onset
- Time delay to study inclusion
- Arterial hypertension
- Alcohol use
- Liver disease
- Renal failure
- Tobacco use
- Diabetes mellitus
- Antiplatelet drug use
- Sympathicomimetic drug use
- Cytostatic drug use
- Illicit drug use
- Hematologic disease
- TIA/cerebral infarction
- Cognitive deterioration
- Infection (15 days before)
- Inflammation (15 days before)
- Fever (15 days before)
- Coma
- Vomiting
- Seizures
- Body temperature
- Systolic blood pressure
- Diastolic blood pressure
- Headache
- Headache location
- Headache characteristics
- CSS
- ICH location
- Ventricular bleeding

Q6

- Mass effect
- Perihematoma hypodensity
- ICH volume
- Total volume
- Edema volume
- Leukoaraiosis
- Cerebral atrophy
- Lacunar infarction
- Old lesion on CT scan
- Hematocrit
- Hemoglobin level
- Leukocyte count
- Neutrophil count
- Platelet count
- Fibrinogen level
- Protrombin time
- Coagulation time
- C-reactive protein
- ESR
- Serum glucose levels
- HDL cholesterol
- LDL cholesterol
- SGOT
- SGPT
- GGTP
- Alkaline phosphatase level
- CPK level
- Intracranial pressure
- Intracranial hypertension
- Interleukin-6 levels
- Tumor necrosis factor-α levels

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Queries

Q1 Author: Please provide “the list of Abbreviations”

Q2 Author: Please note that the reference citations are not in sequence. Also note that the reference citation 13 is not cited in text.

Q3 Author: Please check whether we can change the representation of “1ª h, mm” to “mm/1st h” in ESR (Table 1).

Q4 Author: Please check the edits to the Table 2 caption.

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