Intraventricular Bleeding and Hematoma Size as Predictors of Infection Development in Intracerebral Hemorrhage: A Prospective Cohort Study

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Background: Acute intracerebral hemorrhage (ICH) is associated with increased susceptibility to bacterial infection. The physiopathology of this phenomenon is not very clear. We conducted a prospective observational study investigating the correlation and independent predictors of infections in patients with ICH. *Patients and methods:* Patients admitted between April 1997 and June 2013 with ICH diagnosis were evaluated for inclusion and exclusion criteria. *Results:* Two hundred twenty-two patients were included in this study. Ninety four patients (42.6%) presented with an infection during hospitalization being more common than pneumonia (30%) and urinary tract infections (14%). Intraventricular hemorrhage (IVH) (95% confidence interval [CI], 62.7% versus 39.3%; $P < .001$) and higher ICH score (95% CI, 2.31% versus 1.67%; $P = .0014$) were more common in patients who had infections. We found the following risk factors for having an infection in patients with ICH: IVH (odds ratio [OR] 2.3; 95% IC, 1.3-4.1), each point of ICH score (OR 1.3; 95% CI, 1.1-1.6), and having a hematoma volume larger than 30 cc (OR 2.0; 95% CI, 1.1-3.5). The localization of the hematoma was not found to be relevant. *Conclusions:* ICH score, size of the hematoma, and presence of IVH are independent risk factors for having an infection after ICH. **Key Words:** Intracerebral hemorrhage—ICH—hemorrhagic stroke—stroke inflammation—immune response—infections.

Introduction

Acute stroke is associated with increased susceptibility to bacterial infection,[1] pulmonary and urinary tract infections being the most frequent, with a prevalence of up to 33% during the acute phase of the stroke.[2] Pneumonia accounts for almost 20% of in-hospital deaths and poor outcomes at discharge.[3] Nearly all pneumonias occur within the first week after stroke.[4] The physiopathology of this phenomenon is not very clear. Impairment of consciousness and reduced bulbar reflex facilitate aspiration and are responsible for most pneumonias in stroke patients. However, there is increasing evidence that this is not the only mechanism; a transient immunodeficiency syndrome encompassing innate and adaptive immune cells has been observed in murine large ischemic stroke models and extensive damage in stroke patients.[5]

Experimental mice stroke models and large clinical series have shown an association with the development of infections within 24 hours after stroke, leading to high mortality.[6] Infections are preceded by a rapid suppression of peripheral cellular immune responses, which is mainly characterized by lymphocyte apoptosis and altered lymphocytic cytokine production.[5,7]

Intracerebral hemorrhage (ICH) accounts for 15%-25% of acute stroke. About 20% of patients suffering from a

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large intracerebral hematoma die within 30 days after ICH as a consequence of pneumonia or sepsis.[8] There are few studies characterizing the systemic immune response after ICH, all of them in animal experimental models.[9]

Although the characteristics of hematoma in ICH such as size, localization, and ventricular drainage are associated with global prognosis,[10] there are only a few studies investigating these variables and the risk of infection.[11] It is possible that the characteristics of the hematoma are determinant in both neurological impairment and immunosuppression syndrome, and could be related to the risk of infection after an ICH. We conducted a prospective observational study investigating the correlation and independent predictors of infections in patients with ICH.

Patients and Methods

Clínica Alemana is a teaching nonprofit private hospital of 350 beds in the Northeast of Santiago, Chile. Patients with suspected stroke are rapidly evaluated by a neurologist on call and a stroke fellow. Acute neurological assessment includes a neuroimaging protocol consisting of a noncontrast computed tomography (CT) scan and brain computed tomography angiography (CTA) or magnetic resonance angiography (MRA). CTA is offered to and performed in all patients without contraindications such as known allergies to iodized contrast mediums or renal failure. If CTA is contraindicated, patients undergo MRA.

After acute neurological assessment, patients are admitted in a stroke unit and followed up by a vascular neurologist. All patients are evaluated by a speech therapist before they receive oral feeding. Patients with trouble swallowing are fed by enteral route and are followed up by the speech therapy team until they can be fed by oral route or when the patient has had a gastrostomy in the more severe cases. Patients also receive physiotherapy within 24 hours of being admitted.

The data for this study were extracted from the Clínica Alemana Acute Stroke Registry (RECCA). RECCA is a prospectively database kept since 1997 in our institution for quality control of the Stroke Program and includes clinical assessment (National Institutes of Health Stroke Scale [NIHSS]), neuroimaging (brain CT, CTA or MRA, diffusion-weighted imaging–magnetic resonance imaging, and digital subtraction angiography), time from symptom onset, affected vascular territory, risk factors, treatments, complications, and outcome. All data were collected before the present study was planned.

Participants and Variables

All consecutive patients with acute nontraumatic ICH admitted to Clínica Alemana de Santiago between November 1997 and August 2013 were evaluated to determine whether they meet inclusion and exclusion criteria. Inclusion criteria for the present study were all consecutive patients with a clinical syndrome of stroke and brain CT compatible with ICH. Exclusion criteria were patients without complete data. ICH was diagnosed in patients with history, clinical examination results, and evolution typical of focal vascular brain damage with signs of brain hemorrhage on CT scan.

Prespecified variables included in the analysis were age, sex, hematoma characteristics such as size, localization, ventricular drainage, and ICH score.[12]

CTA scans were obtained with a multislice CT scanner Siemens Somatom Definition AS 128 (Erlangen, Germany) channels. Images where analyzed by a neuroradiologist. Volume was calculated from the first CT scan using the $A \times B \times C \times .5$ method.[13] Each patient was followed up by a second CT scan 24-36 hours after being admitted.

Infection was defined by the combination of the following 2 criteria during in-hospital stay: (1) presence of suggestive clinical and laboratory or radiological signs of infection (e.g., urinary tract symptoms, productive cough, pleuritic pain, dyspnea, tachypnea, fever, cultures positive for a pathogen, leukopenia [<4/L] or leukocytosis [>12/L], and chest X-ray infiltrate) and (2) serum C-reactive protein level of more than 40 mg/mL.

Standard Protocol Approval, Registrations, and Patient Consent

All aspects of the RECCA registry have been approved by the Ethics Committee of Universidad del Desarrollo—Clínica Alemana de Santiago prior to the initiation of the research. The Ethics Committee is the institutional review board of both institutions.

Analysis

The present study is reported according to the STROBE initiative. The cases were divided into 2 groups, depending on whether or not they had an infection during their hospitalization, and were compared for clinical, laboratory, and radiological variables in univariate analysis. Chi-square and Student *t*-test analyses were performed when appropriate and 95% confidence intervals (CIs) were obtained.[14] Multivariate logistic regression with 95% CIs was performed to investigate independent risk factors associated with an infection during the hospitalization in these patients.

Results

Between November 1997 and August 2013, 309 patients with a suspected ICH were admitted in our center of which 221 met the inclusion criteria. The general characteristics of the patient population are shown in Table 1. Ninety-four patients (42.6%) presented with an infection during hospitalization being more common than pneumonia (30%) and urinary tract infections (14%). As shown in Table 2 where we compared the 2 groups,

Table 1. *Characteristics of the ICH population*

Characteristics	
Age (years), mean (range)	66.3 (15-96)
Women, n (%)	106 (47.9)
Localization, n (%)	
1. Putamino-claustral	34 (15.3)
2. Thalamic	33 (14.9)
3. Cerebellar	18 (8.1)
4. Lobar	120 (54)
5. Pontine	8 (3.6)
6. Other	8 (3.6)
Volume (cc), mean (range)	43.8 (1-210)
IVH, n (%)	109 (49.3)
ICH score, mean	1.9

Abbreviations: ICH, intracerebral hemorrhage; IVH, Intraventricular hemorrhage.

Table 2. *Univariate analysis of variables associated with infections after ICH*

Variable	No infection N = 127	Infection N = 94	*P*
Women, n (%)	57 (44.80)	49 (52.13)	.29
Age (years), mean (range)	65.4 (15-94)	67.4 (15-96)	.42
Volume (cc), mean (range)	38.7 (1-210)	48.8 (1-204)	.11
IVH, n (%)	50 (39.3)	59 (59)	<.001
ICH score, mean	1.65	2.24	<.001
Supratentorial location, n (%)	106 (83.4)	81 (86.1)	.60

Abbreviations: ICH, intracerebral hemorrhage; IVH, Intraventricular hemorrhage.

intraventricular hemorrhage (IVH) (95% CI, 62.7% versus 39.3%; $P < .001$) and higher ICH score (95% CI, 2.31 versus 1.67; $P = .0014$) were more common in patients who had infections.

With multivariate logistic regression analysis (Table 3) we found the following risk factors for having an infection in patients with ICH: presence of a hemoventricle (odds ratio [OR] 2.3; 95% CI, 1.3-4.1), each point of the ICH score (OR 1.3; 95% CI, 1.1-1.6), and having a hematoma volume larger than 30 cc (OR 2.0; 95% CI, 1.1-3.5). The localization of the hematoma was not found to be relevant.

Discussion

The major finding of our study is the identification of the ICH score and the characteristics of hematoma, in particular size and presence of a hemoventricle, as independent risk factors for having an infection after an ICH. The results of the present study are similar to those of Diedler et al,[11] who described that infections were more common in patients with bigger hematoma size and presence of IVH.

Table 3. *Multivariate logistic regression model predicting infections after ICH*

Variable	OR	Low	High
Sex	.79	.46	1.36
Age	1.0	.98	1.02
IVH	2.38	1.38	4.1
Big hematoma	2.22	1.28	3.82
ICH score	1.35	1.12	1.63
Supratentorial location	1.23	.58	2.61
Infratentorial location	.82	.35	1.91

Abbreviations: ICH, intracerebral hemorrhage; IVH, Intraventricular hemorrhage; OR, odds ratio.

The strength of the present study is the large number of patients, 221, all of whom were treated and followed up in a stroke unit. The weakness of the present study is that 88 patients had missing data that could not be analyzed, which could affect the precision of the results.

It is also important to consider that we included all patients with acute nontraumatic ICH. The most common cause of ICH is hypertension, but this cohort could also include less common causes such as arteriovenous malformations, and ruptured aneurysms.

We were surprised to find that the localization of the hematoma was not a risk factor. We have expected that patients with infratentorial hematomas, which more commonly produce impairment of consciousness, reduced bulbar reflex, and higher risk of aspiration, would have a higher risk of infections. These results support the idea that there must be an important role for the immune modulating response in the risk of infection after an ICH, an immune response that could be modified by the characteristics of the hematoma as seen in experimental animal models.[9]

Previous reports from other groups have shown an immunomodulating effect of the anti-inflammatory cytokines after central nervous system lesions.[15] It is probable that this immunomodulating response could result to a higher risk of having an infection prior to ICH.

As previously mentioned, infections are an important risk factor for bad prognosis in patients with stroke. Prophylactic antibiotic therapy has being studied to prevent infections and improve outcome; a meta-analysis by the Cochrane collaboration (2012) investigating the efficacy of preventive antibiotic therapy in the acute phase of stroke showed that antibiotic prophylaxis reduced infections but not mortality, with the caveat that the studies found were small and heterogeneous.[16] We found no studies of antibiotic prophylaxis specifically for ICH.

Proposing antibiotic prophylaxis in these patients raises the issue of the potential promotion of antibiotic resistance in common bacteria. So it is very important in any future trial to carefully select the population that could benefit from such an intervention. We think that our results could help to select the high-risk population in future trials testing antibiotics or other interventions to reduce infections after ICH.

In conclusion, our study showed a number of factors that work as independent predictors of infections in patients with ICH.

References

1. Sykora M, Diedler J, Poli S, et al. Autonomic shift and increased susceptibility to infections after acute intracerebral hemorrhage. Stroke 2011;42:1218-1223.
2. Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. Lancet Neurol 2008;7:341-353.
3. Koennecke HC, Belz W, Berfelde D, et al. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. Neurology 2011;77:965-972.
4. Katzan IL, Cebul RD, Husak SH, et al. The effect of pneumonia on mortality among patients hospitalized for acute stroke. Neurology 2003;60:620-625.
5. Chamorro Á, Meisel A, Planas AM, et al. The immunology of acute stroke. Nat Rev Neurol 2012;8:401-410.
6. Prass K, Meisel C, Höflich C, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. J Exp Med 2003;198:725-736.
7. Meisel MD, Andreas Meisel MD. Suppressing immunosuppression after stroke. N Engl J Med 2011; 365:22.
8. Naidech AM, Bendok BR, Tamul P, et al. Medical complications drive length of stay after brain hemorrhage: a cohort study. Neurocrit Care 2009;10:11-19.
9. Illanes S, Liesz A, Sun L, et al. Hematoma size as major modulator of the cellular immune system after experimental intracerebral hemorrhage. Neurosci Lett 2011;490:170-174.
10. Bart Brouwers H, Greenberg SM. Hematoma expansion following acute intracerebral hemorrhage. Cerebrovasc Dis 2013;35:195-201.
11. Diedler J, Sykora M, Hahn P, et al. C-reactive-protein levels associated with infection predict short- and long-term outcome after supratentorial intracerebral hemorrhage. Cerebrovasc Dis 2009;27:272-279. doi:10.1159/000199465; [Epub 2009 Feb 6].
12. Hemphill JC, Farrant M, Neill TA Jr. Prospective validation of the ICH Score for 12-month functional outcome. Neurology 2009;73:1088-1094.
13. Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996;27:1304-1305.
14. Hemphill JC 3rd, Bonovich DC, Besmertis L, et al. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke 2001;32:891-897.
15. Liesz A, Suri-Payer E, Veltkamp C, et al. Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. Nat Med 2009;15:192-199.
16. Westendorp WF, Vermeij JD, Vermeij F, et al. Antibiotic therapy for preventing infections in patients with acute stroke. Cochrane Database Syst Rev 2012;(1):CD008530.