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***Observational Study***

**Elevated soluble fas blood concentrations in patients dying from spontaneous intracerebral hemorrhage**

Lorente L *et al*. sFas concentrations in patients dying of intracerebral hemorrhage

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**Abstract**

BACKGROUND

Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation. However, there have been no data on the association between blood concentrations of soluble fas (sFas) (the main surface death receptor of the extrinsic apoptosis pathway) and the prognosis of spontaneous intracranial hypotension (SIH) patients.

AIM

To determine whether there is an association between blood sFas concentrations and SICH patient mortality.

METHODS

We included patients with **s**evere and supratentorial SIH. Severe was defined as having Glasgow Coma Scale < 9.We determined serum sFas concentrations at the time of severe SICH diagnosis.

RESULTS

We found that non-surviving patients (*n* = 36) compared to surviving patients (*n* = 39) had higher ICH score (*P* = 0.001), higher midline shift (*P* = 0.004), higher serum sFas concentrations (*P <* 0.001), and lower rate of early hematoma evacuation (*P* = 0.04). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95% confidence interval = 1.014-1.129; *P* = 0.01) controlling for ICH score, midline shift, and early hematoma evacuation.

CONCLUSION

The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

**Key Words:** Spontaneous intracerebral hemorrhage; Soluble fas; Apoptosis; Patients; Mortality

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**Core Tip:** Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation. However, there are no data on the association of blood concentrations of soluble fas (sFas) (the main surface death receptor of the extrinsic apoptosis pathway) with SICH patient prognosis. The objective of our study was to determine whether there is an association between blood sFas concentrations and SICH patient mortality. The association of blood sFas concentrations with SICH patient mortality is a novel finding of this study.

**INTRODUCTION**

Spontaneous intracerebral hemorrhage (SICH) leads to many disabilities and deaths annually worldwide[1]. Several studies of SICH patients undergoing surgical hematoma evacuation have shown apoptotic changes in brain samples from areas of hematoma compared with areas of the healthy brain[2-8]. Apoptosis can be activated by the release of mitochondrial cytochrome c into the cytoplasm (named the mitochondrial or intrinsic apoptosis pathway) or by the binding of a surface death receptor to its ligand (named extrinsic apoptosis pathway). The main surface death receptor is Fas, and its ligand is the FasL[2-8]. When binding between Fas and FasL occurs, a death signal appears and the the extrinsic pathway is activated. This death signal is responsible for the activation of caspase-8 (initiator caspase in the extrinsic apoptosis pathway), which leads to the activation of caspase-3 (the main effector caspase in extrinsic and intrinsic apoptosis pathways). Finally, caspase-3 is responsible for cell death[2-8]. Lower plasma Fas concentrations have been found in SICH patients than in healthy controls[9]. However, there are no data on the association between blood Fas concentrations and SICH patient prognosis.

Thus, the objective of this study was to determine whether there is an association between blood Fas concentrations and SICH patient mortality.

**MATERIALS AND METHODS**

***Design and subjects***

The following five Spanish Intensive Care Units recruited patients from 2016 to 2017 in this observational and prospective study: H General de La Palma, H Insular de Las Palmas de Gran Canaria, H Universitario de Canarias (San Cristóbal de La Laguna), H Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife), and H Universitario Dr. Negrín (Las Palmas de Gran Canaria). The study was performed with approval of the research ethic committee of each hospital, and written informed consent was provided by a family member of each patient.

We recruited 75 patients (29 females and 46 males) with severe and supratentorial SICH. Severe was defined as Glasgow coma scale (GCS) < 9[10]. We excluded patients aged < 18 years, pregnancy, malignant disease, or limited interventions order at hospital admission. In addition, we excluded patients with traumatic hemorrhage, hemorrhagic transformation of brain infarction, infratentorial hemorrhage or primary intraventricular hemorrhage (IVH). We also excluded patients in whom SICH was due to aneurysm, arteriovenous malformation, anticoagulant treatment, or fibrinolytic treatment.

We considered that SICH was due to hypertension if the patient was hypertensive and had no other cause of SICH. We considered that SICH was due to amyloid angiopathy if the patient was not hypertensive and any other cause of SICH was recorded. We considered that SICH was due to arteriovenous malformation or aneurysm if some of those findings were shown in computed tomography angiography. We considered that SICH was due to anticoagulant treatment or fibrinolytic treatment if some of those drugs were administered to the patient.

We registered the following data: age, sex, GCS, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, fibrinogen, international normalized ratio, platelets, activated partial thromboplastin time, lactic acid, glycemia and creatinine[11]. We also registered volume (calculated by the formula *AxBxCx*0.5); site and cause of SICH; ICH score; and the existence of transtentorial herniation, hydrocephalus, IVH, or midline shift. In addition, we registered the existence of early hematoma evacuation (within first 24 h of SICH diagnosis) and of mortality during the first 30 d[12,13].

***Blood samples and determination of serum Fas concentrations***

We collected serum samples at the time of severe SICH diagnosis and froze the samples at -80 °C. We determined all soluble fas (sFas) concentrations at the same time with a Human Fas enzyme-linked immunoassay (ELISA) Kit (Elabscience, Houston, TX, United States), which had 19 pg/mL as the detection limit and < 6% as the intra- and inter-assay variation coefficients. This kit uses sandwich ELISA as the method. The micro ELISA plate provided in this kit was pre-coated with an antibody specific to human Fas. The optical density (OD) was measured with spectrophotometry at a wavelength of 450 ± 2 nm. The OD value was proportional to the concentration of human Fas. The concentration of human Fas in samples was calculated by comparing the OD of the samples with the standard curve. Some of those patients were included in our previous publication determining serum sFasL concentrations, and serum sFas concentrations were determined in the current work[14].

***Statistical analyses***

We described continuous variables as medians (interquartile ranges) and categorical variables as frequencies (percentages). We compared continuous variables by the Wilcoxon-Mann-Whitney test and categorical variables by the chi-square test. The estimation of 30-d mortality prediction for serum sFas concentrations was performed using receiver operating characteristic analysis. We constructed Kaplan-Meier curves of 30-d mortality in patients with serum sFas concentrations higher and lower than 63 ng/mL (which was the Youden J index). We analyzed the possible association of serum Fas concentrations and SICH patient mortality controlling for ICH score, midline shift, and early hematoma evacuation. Statistical analyses were performed using LogXact 4.1 (Cytel Co., Cambridge, MA, United States) and SPSS 17.0 (SPSS Inc., Chicago, IL, United States), and *P* < 0.05 was considered statistically significant.

**RESULTS**

We found that non-surviving patients (*n* = 36) with respect to surviving patients (*n* = 39) had higher age (*P* = 0.001), APACHE-II score (*P <* 0.001), ICH score (*P* = 0.001), ICH volume (*P* = 0.04), midline shift (*P* = 0.004), and serum sFas concentrations (*P <* 0.001). In addition, non-surviving patients with respect to surviving patients had lower GCS (*P <* 0.001) and lower rate of early hematoma evacuation (*P* = 0.04) (Table 1).

We found that serum sFas concentrations had an area under the curve for mortality prediction of 83% (95% confidence interval [CI] = 72%-90%; *P <* 0.001) (Figure 1). The mortality prediction for serum sFas concentrations cutoff point of 63 ng/mL had sensitivity of 72% (55%-86%), specificity of 77% (61%-89%), negative likelihood ratio of 0.4 (0.2-0.6), positive likelihood ratio of 3.1 (1.7-5.7), negative predictive value of 75% (63%-84%), and positive predictive value of 74% (61%-84%). We found in the Kaplan-Meier analysis that patients with serum sFas concentrations > 63 ng/mL showed higher death risk (hazard ratio = 4.7; 95%CI = 2.3-97; *P <* 0.001) (Figure 2). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95%CI = 1.014-1.129; *P* = 0.01) controlling for ICH score, midline shift, and early hematoma evacuation (Table 2).

**DISCUSSION**

Several studies of SICH patients have shown apoptotic changes in brain samples after hematoma evacuation[2-8]. However, there are no data on the association of blood concentrations of sFas with SICH patient prognosis. Our study reports the novel findings of the existence of higher serum sFas concentrations in non-survivor than survivor SICH patients and the existence of an association between serum sFas concentrations and 30-d mortality controlling SICH severity and early hematoma evacuation.

Fas is the main surface death receptor of the apoptosis extrinsic pathway. After binding to its specific receptor (FasL), a death signal appears that is responsible for the activation of caspase-8 activation[2-8]. Afterwards, when this initiator caspase of the apoptosis extrinsic pathway (caspase-8) is activated, the activation of executor caspase (caspase-3) occurs. Finally, activation of this executor caspase is responsible for apoptotic cellular death[2-8]. Thus, it is possible that the findings of our study showing higher serum sFas concentrations in non-survivor with respect to survivor patients may reflect a lower apoptosis degree due to lower activation of the apoptosis extrinsic pathway in survivor patients. However, a limitation of our study was the fact that apoptotic brain damage was not assessed. In addition, the absence of serum sFas concentrations during patient evolution and in healthy subjects were other limitations. A promising finding is that the administration of Fas/FasL system inhibitors is associated with a reduction of neuronal cell death in rat models of brain ischemia[15-17]. Therefore, we believe that the findings from our study showing higher serum sFas concentrations in non-survivor with respect to survivor SICH patients and those findings from brain ischemia animal models showing the reduction of neuronal cell death using Fas/FasL system inhibitors could motivate research on the Fas/FasL system and its modulation in SICH patients.

**CONCLUSION**

The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

**ARTICLE HIGHLIGHTS**

***Research background***

Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation.

***Research motivation***

There are no data on the association of blood concentrations of soluble fas (sFas) (the main surface death receptor of extrinsic apoptosis pathway) with SICH patient prognosis.

***Research objectives***

To determine whether there is an association between blood sFas concentrations and SICH patient mortality.

***Research methods***

We included patients with **s**evere and supratentorial SICH. Severe was defined as having Glasgow coma scale < 9.We determined **s**erum sFas concentrations at the time of severe SICH diagnosis.

***Research results***

We found that non-surviving patients (*n* = 36) compared to surviving patients (*n* = 39) had higher ICH score (*P* = 0.001), higher midline shift (*P* = 0.004), higher serum sFas concentrations (*P <* 0.001), and lower rate of early hematoma evacuation (*P* = 0.04). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95% confidence interval = 1.014-1.129; *P* = 0.01) controlling for ICH score, midline shift, and early hematoma evacuation.

***Research conclusions***

The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

***Research perspectives***

The beneficial results of blockade of the Fas system in animal models could motivate its investigation in these patients.

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**Footnotes**

**Institutional review board statement:** The Institutional Board of each hospital approved the study protocol: H. General de La Palma, H. Insular de Las Palmas de Gran Canaria, H. Universitario de Canarias (San Cristóbal de La Laguna), H. Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife), and H. Universitario Dr. Negrín (Las Palmas de Gran Canaria).

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** All authors have no conflicts of interest to declare.

**Data sharing statement:** The datasets generated during the current study are available from the corresponding author on reasonable request.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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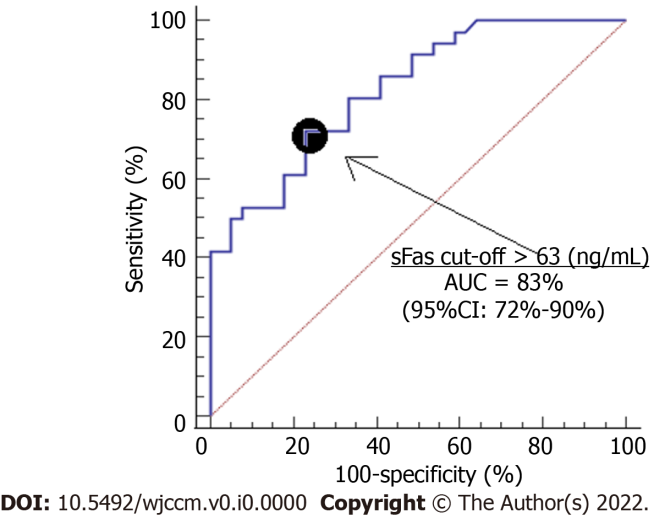
Grade C (Good): C

Grade D (Fair): 0

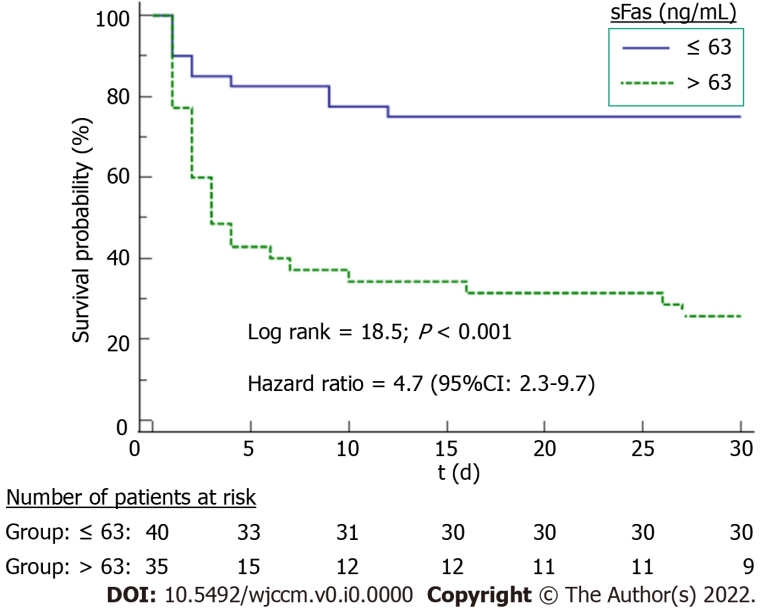
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**Figure Legends**

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**Figure 1 Receiver operating characteristic analysis using serum soluble fas levels as a predictor of mortality at 30 d.** AUC: Area under curve; CI: Confidence interval.

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**Figure 2 Survival curves at 30 d using serum soluble fas levels of 63 ng/mL as the cutoff.** CI: Confidence interval.

**Table 1 Clinical and biochemical characteristics of 30 d surviving and non-surviving patients with spontaneous intracerebral hemorrhage**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Surviving, *n* = 39** | **Non-surviving, *n* = 36** | ***P* value** |
| Sex, *n* (%) |  |  | 0.35 |
| Female | 13 (33.3) | 16 (44.4) |  |
| Male | 26 (66.6) | 20 (55.6) |  |
| Age in yr, *n* (median *P* 25-75) | 57 (51-63) | 68 (57-75) | 0.001 |
| Cause of SIH, *n* (%) |  |  | 0.99 |
| Hypertension | 35 (89.7) | 33 (91.7) |  |
| Amyloid angiopathy | 4 (10.3) | 3 (8.3) |  |
| Volume of SIH in cc, *n* (median *P* 25-75) | 41 (23-66) | 72 (29-98) | 0.04 |
| Transtentorial herniation, *n* (%) | 2 (5.1) | 2 (5.6) | 0.99 |
| Hydrocephalus, *n* (%) | 17 (43.6) | 23 (63.9) | 0.11 |
| Intraventricular hemorrhage, *n* (%) | 13 (33.3) | 20 (56.6) | 0.07 |
| Site of SIH, *n* (%) |  |  | 0.91 |
| Lobar | 24 (61.5) | 23 (63.9) |  |
| Basal ganglia | 7 (17.9) | 7 (19.4) |  |
| Thalamus | 8 (20.5) | 6 (16.7) |  |
| Midline shift in mm, *n* (median *P* 25-75) | 5 (0-8) | 10 (5-15) | 0.004 |
| GCS, *n* (median *P* 25-75) | 8 (6-8) | 4 (3-7) | < 0.001 |
| APACHE-II score, *n* (median *P* 25-75) | 19 (15-21) | 25 (23-28) | < 0.001 |
| ICH score, *n* (median *P* 25-75) | 2 (1-3) | 3 (2-4) | < 0.001 |
| aPTT in s, *n* (median p 25-75) | 29 (26-30) | 29 (24-33) | 0.28 |
| Platelets as × 103/mm3, *n* (median *P* 25-75) | 208 (161-262) | 200 (143-259) | 0.83 |
| Fibrinogen in mg/dL, *n* (median *P* 25-75) | 402 (311-626) | 487 (366-542) | 0.42 |
| INR, *n* (median *P* 25-75) | 1.07 (0.94-1.21) | 1.09 (0.90-1.21) | 0.76 |
| Lactic acid in mmol/L, *n* (median *P* 25-75) | 1.60 (0.90-2.10) | 1.75 (1.20-2.70) | 0.07 |
| Glycemia in g/dL, *n* (median *P* 25-75) | 140 (120-194) | 166 (133-211) | 0.06 |
| Sodium in mEq/L, *n* (median *P* 25-75) | 140 (137-143) | 139 (136-145) | 0.79 |
| Creatinine in mg/dL, *n* (median *P* 25-75) | 0.80 (0.60-0.91) | 0.80 (0.60-1.10) | 0.90 |
| PaO2/FIO2 ratio, *n* (median *P* 25-75) | 296 (194-375) | 270 (214-387) | 0.83 |
| Early hematoma evacuation, *n* (%) | 15 (38.5) | 6 (16.7) | 0.04 |
| sFas in ng/mL, *n* (median p 25-75) | 22 (17-63) | 141 (49-286) | < 0.001 |

APACHE II: Acute Physiology and Chronic Health Evaluation; aPTT: Activated partial thromboplastin time; FIO2: Fraction inspired of oxygen; GCS: Glasgow Coma Scale; ICH: Intracerebral hemorrhage; INR: International normalized ratio; PaO2: Pressure arterial of oxygen; SICH: Spontaneous intracerebral hemorrhage; SIH: Spontaneous intracranial hypotension.

**Table 2 Multiple logistic regression analysis to predict 30 d mortality**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Odds ratio** | **95%CI** | ***P* value** |
| Serum sFas in ng/mL | 1.070 | 1.014-1.129 | 0.01 |
| ICH score as points | 47.71 | 2.24-1012.34 | 0.01 |
| Midline shift in mm | 1.758 | 1.133-2.727 | 0.01 |
| Early hematoma evacuation as yes *vs* no | 0.002 | 0.001-0.210 | 0.01 |

CI:Confidence interval; ICH: Intracerebral hemorrhage.