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Cerebral Hemodynamics By Transcranial Doppler And Protein S100β In Patients With Sepsis-Associated Encephalopathy

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Abstract:

Introduction: *Sepsis-associated encephalopathy (SAE) is a diffuse brain dysfunction secondary to a systemic response to infection. The diagnosis is currently by exclusion.*

Objectives*: to describe cerebral hemodynamic patterns, cerebral hemodynamic reserve (CHR) and the protein biomarker S100β in patients with SAE.*

Methods: *a prospective, longitudinal and descriptive study was carried out in the intensive care unit of the Centro de Investigaciones Médicos Quirúrgicas, from January 2014 to March 2016 in 20 patients with SAE in which the cerebral hemodynamic pattern and CHR were determined by transcranial Doppler (TCD) sonography and the protein biomarker S100β. The study variables are related.*

Results: *cerebral hemodynamic patterns most frequently found were: low flow and hyperemic, 35% respectively and cerebrovascular reserve capacity was variable (50% normal vs 50% decreased). The protein S100β was found to be elevated in 80% of the sample. The existence of hyperemic pattern, decreased cerebrovascular reserve capacity and high S100β protein was associated to mortality.*

Conclusions: *in patients with SAE there is not a typical cerebral hemodynamic pattern nor CHR. The protein S100 β can be used as a marker of brain damage in SAE. The existence of the triad: hyperemic pattern, diminished cerebrovascular reserve capacity and high S100β protein is indicative of poor prognosis.*

Keywords: *sepsis-associated encephalopathy, transcranial Doppler, S100 β protein.*

Sepsis-associated encephalopathy (SAE) is defined as a diffuse brain dysfunction secondary to a systemic response to infection[1,2]. In 1990 Young et al[3] proposed the term. It occurs in up to 70% of septic patients and has been reported as the most common form of encephalopathy among critical patients although, due to the use of sedation in these patients, the entity may go undetected, resulting in under-recording of the disease[4-6].

The physiopathology of SAE is complex. The end result of the different mechanisms involved is cell damage to the brain with mitochondrial, endothelial and neurotransmission dysfunction. The inflammatory response that accompanies sepsis is responsible for cerebral hemodynamic disorders mainly at the microcirculatory level; microglial activation and subsequent release of nitric oxide (NO), cytokines and reactive oxygen species (ROS) in the brain that are accompanied by blood-brain barrier (BBB) dysfunction[7].

The clinical picture of this entity is typically one of confusion, disorientation, agitation and fluctuations in the level of alertness that can lead to coma. On neurological physical examination, osteotendinous hyperreflexia and signs of frontal release such as the palmar grasp and snout reflex may be present; myoclonus, tremor or asterixis may also appear[1].

Diagnosis is often difficult due to the multiple possible causes of neurological dysfunction in critical patients, and therefore requires exclusion of structural, metabolic and toxic causes[1].

Successful treatment of the underlying critical illness almost always achieves complete resolution of the encephalopathy, and profound long-term cognitive impairment is rare[1]. The complexity of the diagnosis of this entity has kept its study as an unresolved research problem.

In patients diagnosed with SAE, there is little research on the use of TCD for the evaluation of cerebral hemodynamics, one of the physiopathological pillars of this entity. The few studies carried out show heterogeneous results[8].

On the other hand, the introduction of biomarkers into present-day medicine is an issue of cardinal importance due to the early nature of diagnosis and evolutionary assessment, among other benefits[9-11].

The protein S100β is a calcium-binding peptide used as a parameter of glial activation and/or death in many CNS disorders. It is found in high concentrations in astrocyte glial cells and Schwann cells and indicates brain damage[12-14]. Similarly, few studies have assessed its usefulness as a biomarker in patients with SAE[15-19].

OBJECTIVES

To describe cerebral haemodynamic patterns, cerebral haemodynamic reserve and protein biomarker S100β in patients with a diagnosis of sepsis-associated encephalopathy.

METHOD

A descriptive, prospective and longitudinal study was conducted on 20 patients diagnosed with SAE and admitted to the ICU of the Centro de Investigaciones Médicos Quirúrgicas between January 2014 and March 2016.

For the differential diagnosis of other encephalopathies not associated with sepsis, all patients were tested for: glycemia, bilirubin, coagulogram, liver profile, urea, creatinine and gasometry.

The patients included in the study underwent a baseline study of transcranial Doppler sonography (DWL (Elektronische Systeme GmbH, Germany) Multidop T), determination of cerebral haemodynamic reserve by acetazolamide test and protein dosage S100β.

Brain hemodynamic patterns were defined as follows: **Normal**: that which presented a cerebral blood flow (CBF) with mean velocity (mV) and pulsatility index (PI) within the normal range defined in the reference values[20]. **Low flow:** that which presented an CBF with mV less than the reference values, independently of PI. **High resistance:** that which presented an CBF with a higher PI than the reference values, with mV within the normal range. **Vasospasm:** the CBF

with mV greater than the reference values, with Lindegaard index > 3, regardless of the PI. **Hyperemia:** those that presented an CBF with a mV greater than the reference values, with a Lindegaard index < 3, independently of the PI. The Lindegaard Index is the ratio of mV middle cerebral artery (mVMCA) to mV extracranial internal carotid artery (vMEICA). **Cerebral circulatory arrest:** that which presented isolated systolic spike findings, reverberant flow or absence of cerebral blood flow.

Acetazolamide test**:** Acetazolamide was administered at a dose of 15 mg/kg without exceeding a dose of 1 gram, intravenously, dissolved in 50 ml of physiological serum at 0.9% in bolus of three minutes of infusion. Flow rates and pulsation rates were recorded at 5, 10, 15 and 20 minutes after administration of Acetazolamide.

Cerebrovascular reserve (CVR) was defined as the percentage increase in the flow velocity of the middle cerebral artery after administration of acetazolamide. CHR was calculated as the percentage increase over basal mVMCA. Values < 10 % increase indicated exhausted CHR, between 10-40 % were considered decreased and > 40 % increase was considered normal or adequate. The protein S100β was quantified in Elecsys equipment (HITACHI) and the range of normality is < 0.105 µg/L.

STATISTICAL ANALYSIS

The statistical evaluation was carried out with the software SPSS 20 for Windows. For the descriptive analysis, the mean and standard deviation were used for the processing of the quantitative variables and the percentage for the qualitative ones.

The contingency table method was used through the chi-square statistician to establish the relationship between variables.

The comparison of means was made by means of the test ¨t of Students¨. Statistical significance was declared when $p < 0.05$.

RESULTS

The sample consisted of 14 (70%) male and 6 (30%) female patients.

The average age of the patients was 58.55 years (limits: 38-90 years).

The mean APACHE II was 21.17 (±6.09) with a mean risk of death of 41.37 % (±17.58).

Fifty percent of the sample presented as primary focus of infection, the intra-abdominal (10 patients), see Table 1.

Table 1. Location of the primary focus of infection in the patients of the study sample.

Location	n	%
Intra-abdominal	10	50
Respiratory	6	30
Urinary	2	10
Non-localized septic syndrome	2	10

(n=20).

In the study sample the most frequent cerebral hemodynamic patterns by TCD were: hyperemic pattern and low flow in similar proportion, see Table 2.

Table 2. Brain hemodynamic patterns at the time of diagnosis

Pattern	n	%
Hyperemic	7	35
Low flow	7	35
Highly resistant	2	10
Normal	4	20

(n=20).

In the group of deceased patients the cerebral haemodynamic pattern that predominated was hyperemic, see Table 3.

Table 3. Relationship of cerebral hemodynamic patterns at the time of diagnosis and the result at discharge from the intensive care unit.

Pattern	Result at discharge from ICU		Total
	Alive	Deceased	
Hyperemic	1	6	7
Low flow	3	4	7
Highly resistant	1	1	2
Normal	2	2	4
Total	**7**	**13**	**20**

(n= 20), X^2=0,551, ICU - intensive care unit.

When the acetazolamide test was performed to evaluate the cerebrovascular reserve capacity (CVRC), higher average velocity in the middle cerebral artery (MCA) were found in the group of patients who died. Differences of statistical significance occurred at zero and 20 minutes, see Table 4.

Table 4. Relationship mean velocity in the right middle cerebral artery according to evaluation time in the acetazolamide test and condition at discharge from the intensive care unit.

Variable	mV t0	mV t5	mV t10	mV t15	mV t20
Alive	44,42	60,42	66,10	68,57	58,14
Deceased	65,30	73,84	76,92	76,07	75,76
X^2	0,049	0,941	0,392	0,307	0,036

(n=20), mV: mean Velocity MCA, t: time.

In the study sample there was a predominance of patients with high values of the protein biomarker S100 β, see Table 5.

Table 5. Qualitative results of the determination of protein S100β in the study sample.

Result	N	%
High	16	80
Normal	4	20
Total	**20**	**100**

(n=20).

In the group of deceased patients the mean protein values S100β were higher than in the group of living patients, see Table 6.

Table 6. Relationship between average protein values of S100β and the state at discharge from the intensive care unit.

Variable	Result at discharge from ICU		X^2
	Alive	**Deceased**	
Protein S100β (µg/L)	0,188	0,614	0,165

(n=20), ICU: intensive care unit

The total number of patients with decreased CVRC was characterized by high protein values S100β, see Table 7.

Table 7. Relationship between cerebrovascular reserve capacity and qualitative S100β protein.

Cerebral vascular reserve capacity	**Protein S100ß**		**Total**
	Normal	**High**	
Normal	4	6	10
Decreased	0	10	10
Total	**4**	**16**	**20**

(n=20), X^2=0,025.

In the group of deceased patients the association CVRC decreased and protein S100β high predominated, see Table 8.

Table 8. Relationship between cerebrovascular reserve capacity patterns and protein S100β with intensive care unit discharge status.

Patterns	**Result at discharge from ICU**		**Total**
	Alive	**Deceased**	
CVRC Normal - S100β Normal	1	3	4
CVRC Normal - S100β High	3	3	6
CVRC Decreased - S100β Normal	0	0	0
CVRC Decreased - S100β High	3	7	10
Total	**7**	**13**	**20**

(n=20), X2=0.644, CVRC: cerebrovascular reserve capacity, ICU: intensive care unit

In the group of deceased patients the association of diminished CVRC and hyperemic pattern of cerebral hemodynamics predominated, see Table 9.

Table 9. Relationship between cerebral vascular reserve capacity patterns and cerebral hemodynamic patterns with the state at discharge from the intensive care unit.

Patrones	**Result at discharge from ICU**		**Total**
	Alive	**Deceased**	
CVRC Normal - chP Normal	0	2	2
CVRC Normal – chP Low flow*	3	4	7
CVRC Normal – chP Hyperemic	1	0	1
CVRC Decreased - chP Normal	2	0	2
CVRC Decreased – chP Low flow*	1	1	2
CVRC Decreased – chP Hyperemic	0	6	6
Total	**7**	**13**	**20**

(n= 20), X2=0.068, CVRC: cerebral vascular reserve capacity, chP: cerebral hemodynamic pattern, * includes high resistance pattern, ICU: intensive care unit

DISCUSSION

The present research evidences a heterogeneous pattern of cerebral hemodynamics evaluated by TCD in severe patients with a diagnosis of SAE. The review on the subject carried out by Azevedo and collaborators[21] finds similar results; there are authors who state as a main characteristic, a decrease in the mean velocity of the middle cerebral artery and others report an increase in this variable. One hypothesis put forward by the researchers who participated in the review, was the existence of stages related to time since the diagnosis of sepsis; an early stage (in the first 24 hours) characterized by an increase in mean and systolic velocity in the middle cerebral artery, accompanied by an increase in pulsatility index and a late stage that they conceptualize after 48 hours of evolution, where the decrease in mean velocity and pulsatility index predominates. The authors of the present study consider that sepsis is a complex process and the division by time of the stages into hours is too simple for its physiopathology. The use of biomarkers could in the near future help in its stratification.

The literature includes other diseases with more defined sonographic patterns. In 62% of the patients studied by Murillo et al[22,23] a pattern of cerebral hypoperfusion is described in the initial stages of severe cranial encephalic trauma and a publication by Abdo et al[24] shows that a low flow pattern was obtained in 57% of patients with acute liver failure.

The heterogeneous pattern of cerebral hemodynamics, with the same proportion of low flow pattern as hyperemic, justifies the sonographic study by TCD for its characterization and optimization of performance behavior according to the pattern.

In the separate analysis of the variables and patterns of cerebral hemodynamics, the findings that relate the higher systolic and mean velocities and the hyperemic pattern to mortality are of interest.

The literature reviewed presents situations of increased cerebral blood flow velocities in patients diagnosed with bacterial meningoencephalitis. One of the hypotheses is the presence of microorganisms in the meninges, with the consequent inflammation, leukocyte reaction and presence in blood and cerebrospinal fluid of proinflammatory mediators with vasoactive capacity that could be the cause of the increased blood flow velocity in the brain vessels.

Fassbender and colleagues[25] found a correlation between elevated values of proinflammatory cytokines, IL-1beta, IL-6, prostacyclin and elevated flow velocities. Significant presence of end products of NO metabolism in the CSF has also been observed at high concentrations without correlation with leukocyte count, proteins or TNF- α[26,27]. These vasodilator substances have not been found in significant amounts in aseptic meningitis[28]. Radiological and necroscopic studies reveal that several other factors may influence or cause the changes in flow velocity in brain vessels during meningitis. In addition to the vasodilation phenomena described, it is possible to find areas of inflammatory-type stenosis in cerebral arterial vessels that may even evolve into organic stenosis after the repair phase.

These vasculitic phenomena are usually local and reversible, true vasospasm phenomena with a pathogenesis similar to that described in the acute phase of subarachnoid haemorrhage, attributed to a periarterial irritative phenomenon (purulent material in this case) that would affect the entire arterial wall and cause a narrowing of the vessel and, secondarily, very significant elevations in flow velocity in the affected artery. It is not uncommon for a hypodense radiological area to appear later in the territory irrigated by this artery[29].

The research subject of this work is patients diagnosed with SAE, in which the presence of microorganisms in the CNS is ruled out as the cause of the symptoms and signs, unlike patients diagnosed with bacterial meningoencephalitis. As far as we know, this is the first time that the association of mean velocities and high systolic and a hyperemic pattern with a higher probability of death in patients with SAE has been reported. In this case the explanation may correspond with that stated by Azevedo et al[21] : endothelial cells of the brain vessels that are activated prematurely by pro-inflammatory cytokines and endotoxins may reduce the vasoactive response of the endothelium through NO, promoting vasoconstriction mediated by prostanoids and endothelins.

Endothelial activation of iNOS is responsible for the overproduction of NO, which can lead to cerebral vascular dilatation and counteract early vasoconstrictive response. The findings described above give TCD in patients diagnosed with SAE an outstanding prognostic utility, as well as the importance for therapeutic suitability.

The study of CVRC measured by TCD and acetazolamide test did not provide any diagnostic or prognostic significance as an isolated test. Azevedo and colleagues[21] decided not to incorporate this study in their meta-analysis because of the dissimilarity of the few studies published[30,31]. However, in the present study, the higher cerebral blood flow velocities in all the time intervals measured in the group of deceased patients again appear as data of prognostic significance. One question that arose during the investigation was whether patients with a hyperemic chP and diminished CVRC were really diminished or were at their maximum capacity for regulation.

There are few works in the literature evaluating the usefulness of the protein biomarker S100β in septic patients. The results provided by this research are favorable for its use as a diagnostic and prognostic marker of brain damage in patients with SAE.

Similar findings to ours were found by Yao and collaborators[19].The biomarker S100β as an isolated study showed good sensitivity for SAE, but low specificity; in that work the diagnostic and prognostic superiority of S100β in sepsis, over specific neuronal enolase, was demonstrated.

When performing an analysis of the main findings of the interrelations between variables (chP - CVRC - S100β protein), the association is striking: hyperemic pattern - CVRC decreased - S100β protein elevated, being the coexistence of these three situations in a higher probability of death for septic patients diagnosed with SAE. At the beginning of this section, the authors of the present research comment, with the support of the literature, on the physiopathological principles of the increase in cerebral blood flow velocity in patients with SAE.

A scientific question at this point is: what can explain the worse prognosis of patients with hyperemic pattern of cerebral hemodynamics compared to the low-flow group? Perhaps the explanation can be found in joint research on metabolism and cerebral hemodynamics in patients with head trauma.

The classic work of Obrist and colleagues[32] shows how patients with low flow pattern achieve near-normal values of arteriovenous oxygen difference ($DavO_2$), however, patients with hyperemic pattern show $DavO_2$ below the limits of normality. The article by Obrist et al[32] and more recently that of Cruz et al[33] , have shown that the worst result is given by the decoupling between cerebral blood flow (CBF) and cerebral metabolic rate of O_2 (flow - metabolism), with unfavourable results associated with hyperemic patterns.

In summary, transcranial Doppler sonography is presented as a study of value for diagnosis, therapeutic actions and prognosis in patients with SAE. The protein biomarker S100β has diagnostic and prognostic utility. The association of hyperemic pattern - diminished CVRC - high protein S100β, predicts high probability of death.

Limitations detected in the present research allow the authors to recommend for future studies, to take into account the time of diagnosis of sepsis and SAE, as well as to carry out studies of brain metabolism together with the studies of cerebral hemodynamics.

CONCLUSIONS

There is not a typical pattern of cerebral hemodynamics and the cerebrovascular reserve capacity is variable in sepsis-associated Encephalopathy. Therefore, the performance of transcranial Doppler in these patients is useful in order to optimize the therapeutic behavior.

The protein biomarker S100β is a good indicator of brain damage in patients diagnosed with sepsis-associated Encephalopathy.

The triad: hyperemic cerebral hemodynamic pattern, diminished cerebrovascular reserve capacity and high S100β protein is indicative of Sepsis-associated encephalopathy with high probability of death.

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Author contribution to the research

AAC, GLA and JSL were the principal investigators of the study. AAC, GLA and JSL were included in preparing the concept and design. AAC, GLA and JSL revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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