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Clinical Study

Association between acute sympathetic response, early onset vasospasm, and delayed vasospasm following spontaneous subarachnoid hemorrhage

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ABSTRACT

Subarachnoid hemorrhage (SAH) is accompanied by a marked acute sympathetic response, and evidence exists for sympathetic participation in the development of cerebral vasospasm (VS). The purpose of this observational investigation was to assess the association between acute central catecholaminergic activity, early VS and delayed VS following SAH. SAH grade 3–5 patients who received ventriculostomy, and in whom bilateral temporal transcranial insonation was performed, were enrolled. Cerebrospinal fluid (CSF) was sampled (<48 hours) and assayed for catecholamines, which were correlated to measures of early and delayed sonographic anterior circulation VS. Clinical independent predictors of early VS included age (odds ratio .946 [95% confidence interval .902–.991]), CT scan score (4.27 [1.30–14.0]) and neurogenic cardiomyopathy (6.5 [1.24–34.1]). Age (.925 [.859–.996]) and CT scan score (8.30 [1.33–5.17]) also independently predicted delayed VS. Any early VS independently predicted conventionally defined delayed VS (10.9 [2.64–45.0]), and severe delayed VS was independently predicted by any early VS (9.87 [2.45–39.7]) and by conventionally defined early VS (12.3 [2.80–54.1]). The norepinephrine:3,4-dihydroxyphenylglycol ratio (NE/DHPG) independently predicted severe delayed VS (3.38 [1.01–11.35]), for which DHPG was a negative predictor (.356 [.151–.839]). Epinephrine was a negative predictor of any early VS (.574 [.357–.921]), any delayed VS (.372 [.158–.875]), and delayed conventional VS (.402 [.200–.807]). Early and delayed VS appear to be related processes that are generally unrelated to the acute central sympathetic response following SAH. The one exception may be severe delayed VS which may be associated with noradrenergic activation.

1. Introduction

Cerebral vasospasm (VS) occurs in approximately 70% of patients with subarachnoid hemorrhage (SAH),[1] causes symptoms in 25–33% of patients,[1] results in infarction in one-third of symptomatic patients,[2] and is a major determinant of outcome.[3] VS is typically considered a subacute or delayed complication that usually occurs 4–15 days following hemorrhage.[4] However, early or acute VS in the first few days after SAH has also been described, and may represent a similar related manifestation to delayed VS, or may be due to entirely different pathophysiologic processes.

Proposed vasoactive agents and processes implicated in the development of cerebral VS include oxyhemoglobin, free radicals, nitric oxide, endothelin molecules, arachidonic acid, inflammatory mediators, and endothelial alterations.[3] In addition, experimental and clinical studies provide convincing evidence for an autonomic component in the production of VS,[5–9] and various sympathomimetic compounds may induce cerebral vasoconstriction.[10] Anatomically, the intracranial arteries (and in particular the vessels of the anterior circulation)[11] possess extensive sympathetic innervation that participates in the modulation of cerebrovascular tone and autoregulation by inducing constriction.[12]

Acute SAH is accompanied by pronounced sympathetic activation[13] which has been linked to systemic cardiovascular manifestations[14] and clinical outcomes,[15] and which may theoretically contribute to the development of cerebral VS. The primary purpose of this investigation was to determine whether the acute central sympathetic response to SAH is associated with the development of early VS. Secondarily, the connection between early VS and delayed VS, and between the acute catecholaminergic response and delayed VS, was investigated.

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2. Methods

2.1. Study population

This investigation was an observational study of consecutive primary spontaneous non-recurrent SAH patients of Hunt–Hess (H/H) grades 3–5 who required ventriculostomy placement, and in whom endovascular aneurysmal obliteration was planned or performed. Patients requiring open craniotomy surgery for aneurysm obliteration were excluded. Demographic, clinical, radiologic, and laboratory data were obtained from family interviews or abstracted from the medical record. Sonographic data was abstracted from records maintained for all SAH patients undergoing transcranial ultrasound (TCUS) testing.

2.2. Cerebrospinal fluid acquisition, assay and analysis

During the first 48 hours following the ictus, all enrolled patients underwent cerebrospinal fluid (CSF) sampling for analysis. CSF samples were obtained by ventriculostomy drainage, following the disposal of a standard quantity (1 ml) of CSF present in the tubing. CSF samples (1 ml) collected in a glass red-top-tube were immediately placed and stored in a deep freeze at −80 °C. After defrosting and centrifugation, .3 ml aliquot samples of supernatant were assayed by alumina extraction and then analyzed by high performance liquid chromatography (HPLC), using a previously described technique.[16]

Every sample had 400 μl of TRIS–HCl buffer (121 g Tris and 20 g EDTA per liter) and 10 mg of alumina added. The contents were mixed on a shaker for 30 minutes, and centrifuged for 1 minute to pack down alumina. Effluent was aspirated and wasted, and residua were washed twice with milli-Q water. Elution was performed by vortex mixing of alumina in 100 μl of eluant acid (90% 0.2 N acetic acid + 10% 0.2 N H_3PO_4), followed by centrifuge and collection. Eluants 90 μl were injected into the HPLC system Model 717 Autosampler (Waters Corporation, MA, USA), and analyzed for catecholamines by reverse phase technique and electrochemical detection. Analytes included epinephrine (EPI), norepinephrine (NE), 3,4-dihydroxyphenylglycol (DHPG), 3,4-dihydroxyphenylalanine, dopamine, and 3,4-dihydroxyphenyl acetic acid (DOPAC).

2.3. TCUS

All SAH patients routinely underwent twice daily TCUS evaluation for the detection of VS. The initial ultrasound typically included insonation of anterior and posterior circulations, whereas subsequent evaluations only insonated the anterior circulation unless clinical suspicion existed for vertebro-basilar compromise. Via bilateral temporal bone windows (transtemporal), the middle cerebral arteries (MCA) were generally insonated from a distance of 50–60 mm, and the anterior cerebral arteries (ACA) were insonated at a distance of 65–70 mm.[17] The cervical extracranial internal carotid arteries (ICA) were insonated at a distance of 40–50 mm (submandibular) bilaterally. Insonation distances varied depending on cranial size and on vessel location and anatomy. Precise arteries were identified based on waveform location, direction and characteristics, and insonation intervals ranged from 2–4 mm. For every individual vessel insonated, the maximum mean velocity (Vm) obtained was used for interpretation. All ultrasound procedures were performed using the Nicolet Pioneer System (Viasys, Conshohocken, PA, USA).

2.4. Definition of VS

For the MCA, minimal VS criteria required a Vm of $\geqslant$120 cm/s, plus a velocity ratio $\geqslant$3 in comparison to the ipsilateral extracranial ICA. Severe MCA VS was defined as a Vm $\geqslant$200 cm/s plus a MCA/ICA $\geqslant$6. Due to the absence of a universally accepted or standardized definition for VS of the ACA, various criteria for VS were considered including that proposed by Alexandrov et al. for "definite" spasm = 120 cm/s.[18] In addition, correlation analyses were performed between MCA and ACA maximum Vm, so as to derive analogous criteria for any and severe ACA VS. Correlations performed for acute and subacute periods complementarily indicated that a MCA maximum Vm of 120 cm/s (minor MCA spasm) corresponded to an ACA maximum Vm of 100 cm/s, and that a MCA maximum Vm of 200 cm/s (severe MCA spasm) corresponded to an ACA maximum Vm of 140 cm/s (Fig. 1). Thus, any ACA VS was defined as Vm $\geqslant$ 100 cm/s, "conventional" VS was defined as Vm $\geqslant$ 120 cm/s, and severe VS as Vm $\geqslant$ 140 cm/s.

2.5. Outcomes and endpoints

Early VS was defined as spasm of the MCA or ACA vessels during days 1–3, and delayed VS defined as spasm during days 4–15, following the onset of hemorrhage (day 0).[4] Patients were excluded if no or only unilateral temporal insonation was achieved. Patients were omitted from early VS analyses if TCUS was not performed up to day 3, and omitted from delayed VS analyses if TCUS was not performed up to day 10. For analysis of early VS and delayed VS, outcome measures included any MCA/ACA spasm (minimum criteria), MCA/ACA spasm (conventional ACA criteria), and severe MCA or ACA spasm. Early and delayed Vm for the MCA and ACA vessels were entered into correlation analyses along with individual CSF catecholamine parameters so as to identify any potential linear or positive associations.

2.6. Variable categorization

Clinical severity was measured according to the standard H/H scale. Due to the relatively low number of H/H grade 5 patients, grades 4 and 5 were grouped and the variable was dichotomized between grade 3 and grades 4 and 5 for all calculations. Admission CT scans were scored for hemorrhage quantity using the technique by Frontera et al., which provides the optimal correlation between radiographic severity and risk for complications and adverse outcomes.[19] Due to a disproportion in the distribution of CT scores, scores 1 and 2 (S1/2) and scores 3 and 4 (S3/4) were combined, and the variable was dichotomized between S1/2 and S3/4 for all calculations.

2.7. Statistical analyses

For comparisons of categorical variables Fisher's exact or chi-squared tests were used, and for comparisons of continuous variables the nonparametric rank sum or two-tailed *t*-test were used. For correlations between continuous variables, Pearson's ρ was calculated. Due to the non-normal distribution of catecholamine parameters, levels and ratios were log-transformed for all analyses. Any variables demonstrating an association in univariate analyses ($p < .1$) were cumulatively entered into multivariate logistic regression models along with variables of interest and individual catecholamine variables, using backward stepwise elimination technique. For all analyses, a p value < .05 was considered statistically meaningful. Statistical computations were performed using the Statistical Package for the Social Sciences version 12 (SPSS Inc., Chicago, IL, USA).

2.8. Approval, consent, conduct, venue

The research was approved by the Institutional Review Board of the Office of Human Research at Thomas Jefferson Medical Center.