Potential mechanisms and clinical significance of global cerebral edema following aneurysmal subarachnoid hemorrhage

J MOCCO, M.D., CARLTON S. PRICKETT, B.A., RICARDO J. KOMOTAR, M.D.,
E. SANDER CONNOLLY, M.D., AND STEPHAN A. MAYER, M.D.

Department of Neurosurgery, Columbia University, New York, New York

✓In an attempt to elucidate the pathophysiology and clinical significance of global cerebral edema (GCE) following aneurysmal subarachnoid hemorrhage (SAH), the authors explored potential mechanisms and reviewed findings associated with this phenomenon. Admission computed tomography (CT) scans show GCE in up to 20% of patients experiencing aneurysmal SAH. This edema is likely to have been initiated by transient global ischemia, as indicated by an association between ictal loss of consciousness and the development of edema. A further cascade of events, including a rise in intracranial pressure and compromise of the blood–brain barrier, are also likely contributors. Clinically, GCE on CT after aneurysmal SAH is predictive of a poor outcome. Further investigation is needed to gain a full understanding of edema development following SAH, with the hope that the knowledge can be used to influence treatment positively and improve outcome.

KEY WORDS • aneurysmal subarachnoid hemorrhage • global cerebral edema

ANEURYSMAL SAH is a frequently devastating event accounting for up to 7% of all strokes.⁶ Whereas modern diagnostic, medical, and surgical techniques have improved the associated mortality rate by 15% since the 1960s,⁹ the mean 28-day death rate after aneurysmal SAH remains as high as 40%.¹⁰ Moreover, a large percentage of survivors suffer lasting neurological deficits.¹⁷ Authors of previous studies have consistently identified predictors of death following aneurysmal SAH, including an advanced patient age,^{12,17,18} size of the causative aneurysm,²⁰ and a depressed neurological status 24 hours postictus.^{12,16,17} Additionally, recent evidence has indicated the presence of GCE as a significant predictor of poor outcome.⁴

Global cerebral edema infrequently has been identified in association with aneurysmal SAH, perhaps because of the difficulty in objectively identifying and quantifying edema on CT (Fig. 1). Claassen and colleagues⁴ addressed this issue in their study of 374 patients with aneurysmal SAH by comparing assessments made by two blinded

examiners of 36 CT scans from their database. The diagnosis of GCE required complete or near-complete effacement of the hemispheric sulci and basal cisterns as well as diffuse blurring or finger-like disruption of the normal gray–white matter junction at the level of the centrum semiovale. The interobserver reliability was excellent, with a κ value of 0.89.⁴ Magnetic resonance imaging and a newly proposed method called cerebral electrical impedance can also be used to assess cerebral edema.¹⁵ However, the usefulness of MR imaging in SAH is controversial,⁸ and cerebral electrical impedance is a nascent technology; hence, neither has been evaluated as an adjunct to CT in identifying GCE after aneurysmal SAH.

On admission CT, approximately 8% of the patients with aneurysmal SAH in the Claassen et al.⁴ study exhibited GCE, with a further 12% eventually suffering GCE within 5 days after admission. Similarly, authors of the International Cooperative Study on the Timing of Aneurysm Surgery reported the presence of GCE on admission CT scans in 6% of 3451 patients with aneurysmal SAH.¹² In a third study, Lagares et al.¹³ found that 7% of patients with aneurysmal SAH had global brain hypodensity on CT scanning, a finding that could also be equated with the presence of GCE. The consistent occurrence of GCE in a subset of patients with aneurysmal SAH has

Abbreviations used in this paper: BBB = blood–brain barrier; CI = confidence interval; CT = computed tomography; GCE = global cerebral edema; ICP = intracranial pressure; MR = magnetic resonance; OR = odds ratio; SAH = subarachnoid hemorrhage.

spurred further work directed at evaluating both the potential pathophysiological mechanisms and the clinical relevance of the process.

Potential Mechanisms

Global cerebral edema following aneurysmal SAH has recently been postulated to develop in the classic biphasic manner commonly described in ischemic stroke (Fig. 2).³ The triggering event is intracranial circulatory arrest as ICP reaches levels approaching mean arterial pressure, which can result in cytotoxic edema when early global ischemic injury causes failure of cell membrane regulatory channels, resulting in cellular swelling. This phenomenon can be visualized in a mouse model as early as 2 minutes after aneurysmal SAH by using apparent diffusion gradients on MR imaging.² The notion that brief global ischemia can be the genesis of the cytotoxic phase is supported by the association found between a loss of consciousness during ictus and the formation of early edema;⁷ that is, the global ischemia that causes a loss of consciousness is also responsible for the initiation of edema formation. Moreover, the early edema has been observed along with vasomotor paralysis and a rise in cerebral blood volume as a “reflex triad” response to severe intracranial insult, including aneurysmal SAH and traumatic brain injury.⁷

It has been demonstrated in both experimental and clinical scenarios that an acute rise in ICP occurs after aneurysmal SAH.²¹ Postulations regarding the mechanism for this rise have ranged from a volume increase resulting from the bleed itself, to impeded cerebrospinal fluid drainage, to the aforementioned vasomotor paralysis associated with vascular engorgement and an increase in cerebral blood volume.³ Almost certainly, the resulting tissue expansion from cytotoxic edema should be included as a contributor to increased ICP, which in turn leads to a reduction in cerebral blood flow and therefore further ischemia. This progression of ischemia exacerbates the cytotoxic effect, but also sets off an apoptotic cascade that can lead to the vasogenic phase of edema formation by disruption of the BBB.³ This reasoning has recently been validated in an animal model in which the intraperitoneal administration of caspase 3 and p53 inhibitors before and after the induction of aneurysmal SAH reduced apoptosis sufficiently to significantly preserve the BBB and reduce edema formation.¹⁹

The biphasic nature of edema formation discussed previously and the early versus delayed formation of edema identified in the study by Claassen et al.⁴ should not be confused as synonymous. A biphasic mechanism has been proposed to describe the pathophysiological process, whereas early edema as seen on admission CT and delayed edema seen on follow-up CT are merely temporal distinctions describing how long after ictus the edema was identifiable on neuroimaging. It is likely that GCE, whenever it develops, follows the biphasic pattern and that delayed GCE is, at least partly, a progression of events stemming from ictal ischemia. In the study by Claassen and colleagues, ictal loss of consciousness correlated with both admission and delayed edema, indicating that the biphasic formation likely persisted through the periictal period, resulting in later GCE. Notably, many patients in

FIG. 1. A: Admission CT scan (SAH Day 0) obtained in a 55-year-old man with a Hunt and Hess Grade V SAH, revealing global edema. The SAH was caused by a left anterior communicating artery aneurysm, which was clipped. A follow-up CT scan (SAH Day 18) showed complete normalization of the previous imaging findings. The patient had moderate cognitive disability at 3 months post-SAH. B: Admission CT scans (SAH Day 0) obtained in a 61-year-old woman with a Hunt and Hess Grade II SAH, demonstrating no evidence of edema. The SAH was caused by a right anterior communicating artery aneurysm. On Day 4 she exhibited lethargy with elevated transcranial Doppler ultrasonography velocities (224 cm/sec in the left middle cerebral artery) and was treated with hypertension-hypervolemia therapy. On Day 5 her level of consciousness deteriorated further, and a repeated CT scan showed global edema. She improved clinically after discontinuing the vasopressors. Follow-up CT scans showed gradual resolution of global edema. From reference 4, with permission.

FIG. 2. Schematic showing the hypothesized mechanism for the development of GCE following aneurysmal SAH (aSAH). The hemorrhagic ictus causes global ischemia, leading to loss of consciousness (LOC), apoptosis, and membrane dysfunction, which in turn results in cellular swelling. A rise in ICP due to this and other processes decreases cerebral blood flow (CBF), thereby exacerbating the ischemia and thus the edema while also contributing to an apoptotic cascade leading to compromise of the BBB. A second phase of edema development follows as fluid crosses the BBB. CSF = cerebrospinal fluid.

the study with confirmed delayed GCE showed subtle abnormalities at the gray–white matter junction, which, although not significant enough to qualify as frank edema, may have represented evidence that the process had already begun.

Besides through progression of the initial injury, delayed GCE can also result from any of a number of other processes, including autoregulatory breakthrough in the setting of hypertension, microvascular compromise resulting in ischemia, cytotoxic effects of blood products, and water dysregulation due to aquaporin dysfunction.⁴ Evidence for autoregulatory breakthrough can be seen in Claassen and colleagues⁴ finding that the use of vasopressors to maintain hypertension in the face of vasospasm is associated with the development of delayed GCE. Impairment of autoregulation after aneurysmal SAH is well documented,^{5,22,24} so it is reasonable to suppose that maintaining a high mean arterial pressure can result in intracerebral fluid extravasation. This theory is supported by data in two patients treated with hypertension-hypervolemia therapy after aneurysmal SAH, whose deterioration was attributed to hypertensive encephalopathy.¹ This danger highlights the need for careful attention to a delicate balance when using hypertension therapy after aneurysmal SAH: perfusion pressure must be high enough to prevent ischemia due to vasospasm but low

enough to minimize edema formation by extravasation through dysregulated vasculature.

Although some research data suggest that a progressive cycle of edema formation leading to microvascular compression can lead to further ischemia and therefore to GCE,¹¹ Claassen and colleagues⁴ did not show an association between vasospasm and edema. Note, however, that their angiographic, radiographic, and clinical measurements of vasospasm were designed to evaluate large vessels only. Hence, their study cannot exclude a microvascular component of GCE. Meanwhile, the inflammatory potential of blood components has been noted experimentally in intracranial hemorrhage and shown to produce vasogenic edema;^{14,23} however, this process has yet to be evaluated in aneurysmal SAH. Hypoosmolality and hyponatremia also have the potential to contribute to edema via the shift of water intracellularly; to date, however, no strong evidence has been put forth in support of such an association.⁴

Clinical Significance

Whatever the pathophysiological mechanisms involved, the presence of GCE following aneurysmal SAH has been shown to be strongly associated with a poor out-

come. In a prospective observational cohort study of 374 patients with aneurysmal SAH, more than 40% of patients with GCE on admission or follow-up were deceased 3 months after ictus, compared with only 18% of those without GCE.⁴ Results of a multivariate logistic regression identified GCE as an independent predictor of death at 3 months (OR 2.5, 95% CI 1.1–5.6). In fact, it was the only independent radiographic predictor of poor outcome. Interestingly, results of the multivariate model identified GCE as a predictor of death or disability in patients younger than 58 years (OR 3.1, 95% CI 1.2–7.9) but not in older patients (OR 1.1, 95% CI 0.4–3.1). Perhaps the susceptibility to neurological damage from GCE is reduced in the elderly population as a result of cerebral atrophy, which leaves room for some edema before the damage occurs, whereas a brain not marked by deterioration is acutely vulnerable to even small rises in ICP. These results were consistent with the finding by Lagares et al.¹³ that brain CT hypodensity following SAH confers a marked risk of poor outcome compared with no hypodensity (relative risk 20.4, 95% CI 2.7–154.7). Further investigation into the reasons for this finding is warranted.

Conclusions

In summary, GCE is seen in a distinct subset of patients experiencing aneurysmal SAH. Although its exact pathophysiology is unclear, this edema appears to be initiated by a transient global ischemia at ictus and perpetuated by a cascade of events, including a rise in ICP and a breakdown of the BBB. This hypothesis is supported by the association between ictal loss of consciousness, which is also the result of transient global ischemia, and the development of GCE. Additionally, radiographically identified GCE itself is a predictor of poor outcome when noted after aneurysmal SAH, especially in the younger population. Future research should be focused on clarifying the mechanisms by which GCE develops after aneurysmal SAH, its influence on outcome, and optimal management paradigms. A better understanding of the pathophysiology of this condition can one day lead to effective medical resuscitation strategies for the diffuse brain injury that occurs with poor-grade SAH.

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Address reprint requests to: J Mocco, 710 West 168th Street, Room 431, New York, New York 10032. email: jdm32@columbia.edu.