Subarachnoid Hemorrhage
Is It Time for a New Direction?

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Background and Purpose—Despite recent advances in the treatment of patients after subarachnoid hemorrhage, morbidity
and mortality rates have failed to improve significantly. Although this was often blamed on vasospasm, is it time to
consider alternative etiologies?

Summary of Review—Early brain injury (EBI) is a recently described term that describes the immediate injury to the brain
after subarachnoid hemorrhage. A number of pathways have been recognized as having a role in the etiology of EBI.
This review provides a brief synopsis of EBI and its implications for the future.

Conclusions—EBI may be responsible for the detrimental effects seen in patients after subarachnoid hemorrhage.
Additional studies are needed to determine the pathophysiology of EBI and to explore potential therapeutic
options. (Stroke. 2009;40[suppl 1]:S86-S87.)

Key Words: apoptosis ■ subarachnoid hemorrhage ■ vasospasm ■ early brain injury

Subarachnoid hemorrhage (SAH) has been managed by
surgical clipping for patients with aneurysmal SAH after
it was successfully performed by Dandy in 1937. More
recently, aneurysms are now treated with endovascular coil-
ing in the majority of cases. This of course avoids the need for
craniorrhaphy, which has been shown to improve outcome in
the short term. Surgical intervention, however, treats the
aneurysm but not the SAH itself. There are in fact limited
treatment options available for patients with SAH. Each year,
≈10 in 100,000 people experience an aneurysmal SAH.
SAH, therefore, is a devastating disease, carrying with it a
mortality of 12% before receiving medical attention. With an
additional 40% dying within a month of admission to hospital
and a 30% morbidity in the survivors, it seems clear that a
new approach with regard to the treatment of SAH is
warranted. There are 2 main issues that need to be addressed:
these are vasospasm and early brain injury (EBI).

Vasospasm
Vasospasm has been the focus of the majority of research
efforts during the past number of decades and there are a
copious number of articles on the topic, but unfortunately,
this has led to limited success with regard to improving
outcome. Calcium channel blockers are now the mainstay of
prophylaxis for vasospasm. The efficacy of this drug class is
certainly debatable, and the true impact it has had on outcome
after SAH is also controversial. The Cochrane Group found
that for oral nimodipine, the relative risk was 0.67 (95%
CI=0.55 to 0.81). However, they concluded that “the evi-
dence for nimodipine is not beyond all doubt, but given the
potential benefits and modest risks of this treatment, oral
nimodipine is currently indicated in patients with aneurysmal
SAH.” In 2005, a double-blind, randomized clinical trial
with clazosentan showed a significant dose-dependent 65%
reduction in the relative risk of angiographic vasospasm.
Surprisingly, however, the CONSCIOUS-1 trial failed to
demonstrate an improvement in outcome. This has led to
questions with regard to the clinical significance of angio-
graphic vasospasm. So much so that some authors have called
for a Kuhnian revolution in the field.

Early Brain Injury
EBI is a recent concept that looks at overall brain injury after
SAH. There have been a number of recent articles indicating
that the pathophysiologic consequences of an aneurysmal
SAH lead not only to vasospasm but also to a global ischemic
injury to the brain. This is a significant move away from the
previous theories of vasospasm as being the main conse-
quence of SAH, leading to neurologic deficits. Furthermore,
it should be pointed out that EBI may be the primary cause of
mortality in SAH patients. Therefore, it seems that EBI
should be considered a primary target for future research. EBI
occurs as a result of the impact of an aneurysmal SAH on the
brain. A number of key factors occur, including elevation
of intracranial pressure, reduction of cerebral blood flow, sup-
pression of cerebral perfusion pressure, fall in brain oxygena-
tion, blood-brain barrier breakdown, brain edema, and neu-
ronal cell death. For an in-depth review of the pathogenesis of

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EIBI in relation to SAH, see Cahill et al. The mechanisms behind many of these key events are poorly understood, and there are currently no treatment options available by which they can be prevented or treated. Although these factors have long been understood, their effects and consequences are not. Indeed, many of these factors are presumed to occur in the clinical setting but in fact have only ever been demonstrated in animal models.

There are currently a number of pathways that have been implicated in EIBI. These include the apoptotic pathways, inflammatory pathways, and ischemic pathways, to name but a few (see the Figure). In addition, all of these pathways have 1 common outcome, which is cell death. This can lead to blood-brain barrier breakdown and subsequent edema or directly to neuronal cell death. Apoptosis has been shown to be an important intracellular pathway leading to cell death, and inhibition of p53-modulated apoptosis has been shown to have favorable effects on mortality and outcome in animal models. Autopsy studies have demonstrated evidence of both apoptosis in the vasculature and cortical infarctions, which can occur in areas remote from the artery that bled. Dreier et al demonstrated cortical spreading depression in both animal models and patients with SAH. Furthermore, animal studies that included the use of hyperbaric oxygen to counteract the effects of cortical spreading depression have been favorable. Dumont et al proposed an inflammatory etiology for vasospasm, and this concept has been taken on by others.

Conclusions

EIBI is likely to be the result of a number of critical pathways that are probably interrelated with a similar end result, cell death. This leads to cortical ischemia, inflammation, neuronal cell death, brain edema, and possibly even vasospasm. What the key factors in this complex relationship are remain to be seen. However, one thing is clear: EIBI research is advancing and will continue to do so exponentially as more discoveries are made. Given the fact that the reversal of vasospasm does not appear to improve outcome, it could be argued that the treatment of EIBI may have more success. It may be that in the future, anti-EIBI treatments will finally provide a viable treatment option for patients with SAH.

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Disclosures

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References
