Teaching Course 13

New concepts in critical care of stroke patients - Level 3

Subarachnoid hemorrhage (SAH): how do we treat delayed ischemic neurological deficit (DIND)

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Introduction

SAH (bleeding into the subarachnoid space) is a neurologic emergency, with an overall mortality of up to 50% and 25% dying within the first 24 hours, often pre-admission. It often presents with maximal at onset and worst of life headache. Patients may demonstrate neck stiffness, nausea/vomiting, and impaired level of consciousness. Approximately 80% of nontraumatic SAH are due to aneurysmal rupture. Non-contrast head CT (at the best within 6 hours) is highly reliable for diagnosis. Management of SAH includes initial resuscitation with intubation if needed, continuous cardiopulmonary and neurologic monitoring, earliest possible analgesia and, if applicable, sedation, blood pressure management, coagulopathy correction, and seizure treatment. Complications are common, including seizure including status epilepticus, hydrocephalus, vasospasm, cardiopulmonary, endocrine and metabolic derangements, aspiration- and ventilator-associated pneumonia and other nosocomial infections, and, nowadays rarely, rebleeding, the latter only, if securing the aneurysm is delayed.

Admission to a neurocritical care unit is recommended and improves outcome.

Epidemiology

Headache accounts for approximately 2% of emergency department (ED) visits, with SAH occurring in 1% to 3% of these patients. The incidence of aneurysmatic SAH is approximately 7 to 10 per 100,000 per year.
Pathophysiology and Etiology of (SAH and) Vasospasm/DIND/DCI

Risk factors for aneurysm rupture, i.e. aSAH, include a family history of SAH or aneurysm (2 first degree relatives), smoking, hypertension, and alcohol abuse.

The so-called vasospasm of intracranial vessels is a delayed and frequently reversible vasculopathy or SAH complication that occurs within the first 2 weeks, most commonly not before day 3 and rarely after day 14 after the initial hemorrhage. The pathogenesis is still far from being fully understood. The upregulation of “spasmogenic” substances released during RBC lysis, like endothelin or endoglin is one of the pathophysiologic mechanisms for vasospasm and delayed ischemic complications (DIC) or delayed ischemic neurologic deficits (DIND), respectively. Recently, the scientific discussion on the pathophysiology of “vasospasm/DIND/DIC” has concentrated on the role of the vascular endothelium, e.g. cellular microparticles (derived from endothelial cells), angiopoietin 1 and inflammatory responses by endothelial cells etc., all of them contributing to an imbalance of endogenous vasodilating and vasoconstricting molecular mechanisms. The impaired capacity of autoregulation may add to reduction in cerebral blood flow (CBF) as does (unintentional) hypovolemia which may aggravate decrease in regional CPP. Very recently, the role of a locally activated coagulation cascade leading to intra-arterial micro-thrombus formation and arterio-arterial embolisation has been accepted as a major cause of DIND and DCI.

Initial Treatment / Management of SAH

SAH patients must be provided best cardiopulmonary and neurologic monitoring, adequate analgesia, antiemetics, and sedation, whenever
deemed necessary. Continuing cardiac monitoring is vital to evaluate for dysrhythmia, e.g. stress-associated (cave: catecholamine surge!) atrial or even, ventricular fibrillation, Takotsubo cardiomyopathy, or neurogenic lung-edema. Head of bed elevation to 30 can decrease elevated ICP. Continuous and regular reevaluation of neurologic status, incl pupillary size and reactivity and motor function is warranted. IV fluid administration targets euvoemia, normal glucose and electrolytes.

Blood pressure control may be required, though the optimal target is not yet clear. Permissive hypotension (systolic blood pressure (SBP) <100mmHg) may decrease the initial rebleeding rate but increases cerebral infarction rate. The American Stroke Association’s 2012 guidelines as well as the DGN guidelines recommend maintaining the initial SBP at less than 160 mm Hg. Cerebral perfusion pressure (CPP = MAP-ICP) should be maintained at > 60 mm Hg. Arterial catheter placement is to be done as soon as continuous blood pressure monitoring is considered necessary (e.g. during IV administration of vasoactive medications).

Antifibrinolytic agents, such as tranexamic acid and aminocaproic acid, may have potential in preventing rebleeding, they should not be administered indiscriminately as they enhance the risk of vasospasm associated cerebral infarction. The American Stroke Association recommends use of these agents for less than 72 hours only if definitive aneurysm treatment (i.e. securing the aneurysm) is delayed and there are no contraindications. Again, these agents may reduce rebleeding, though no benefit in mortality or neurologic outcome has been demonstrated. Therefore, the now widely employed option to secure the aneurysm as early as possible (at the best within <24 hours after the bleeding) has rendered these agents largely obsolet.
The two primary approaches for aneurysm repair include microvascular neurosurgical clipping or endovascular coiling, they must be employed in all (most) SAH patients at the earliest possible point of time (ideally < 6, max 24 hours). Endovascular coiling has demonstrated better outcomes when compared with clipping, though not all patients and/or aneurysms are suitable for coiling. The approach is determined by the aneurysm anatomy, clinician experience, timely availability, age and comorbidities.

Signs and Symptoms of Vasospasm/DIND/DCI and other complications of SAH

The incidence of vasospasm/DIND/DCI is related to the amount of blood in the CSF. Vasospasm may be present without any signs and symptoms (in 30% to 70%) but may lead to severe focal neurologic deficits, as hemiplegia or impaired level of consciousness. Whenever vasospasm leads to signs and symptoms, it is associated with significant morbidity. Hydrocephalus may occur in up to 30% of patients within the first 3 days, most commonly in those with severe bleeds, and may be asymptomatic. It should be considered if the SAH patient develops (sudden) neurologic worsening, including impairment of consciousness. Placement of an external ventricular drain, allowing for CSF drainage and precise monitoring of ICP is mandatory.

Increased Intracranial Pressure (ICP) in SAH is usually due to hydrocephalus, diffuse brain edema and hyperemia after hemorrhage. For intubated patients with concern of elevated ICP, deepening of analgosedation might reduce ICP, however careful attention is required to maintain CPP. Hyperventilation should be used with utmost caution, since this reduces definitely cerebral perfusion. Decompressive craniectomy
may be needed for ICP control with cerebral edema, if other measures, including targeted temperature management or moderate therapeutic hypothermia, are not effective.

**Evaluation of Vasospasm/DIND/DCI**

In awake patients the diagnosis of a vasospasm/DIND/DCI is clinical: the patient complains of increasing headache and shows “neuro-worsening”, i.e. develops new focal neurological deficits and/or qualitative or quantitative impairment of consciousness.

Since in the majority of poor grade SAH patients, who are admitted to a Neurocritical Care Unit and - after securing the aneurysm - are deeply analgosedated, the neurological examination is virtually impossible, technical monitoring means and methods are indispensable.

The formerly recommended daily or twice daily **transcranial Doppler sonography** did not fulfill its promises in recognizing early and potentially cerebral-ischemia-relevant “vasospasm”. However, we still recommend its daily use, if the examiner is always the same neuro-intensivist and well familiar with this technique, the critical values being an increase in the mean flow velocity by > 50% and/or an MCA/ICA (Lindegaard)-Index > 3.

The golden standard technique in diagnosing the „vasospasm“ is the digital subtraction **angiography**; however less invasive techniques, as **CT**- or **MR**-angiography, including **perfusion techniques**, may be preferable.
In comatose, deeply analgosedated poor grade SAH patients the following invasive neuro-monitoring techniques are employed in high volume neurocritical care centers:

- brain oxygen monitoring,
- cerebral microdialysis for brain metabolic monitoring (brain tissue lactate, pyruvate, glucose, glycerol),
- cerebral blood flow,
- brain tissue temperature monitoring,
- continuous EEG for detection of suclinical seizures or status epilepticus,
- continuous invasive electrocorticography (COSBID) to detect the occurence of (clusters of) cortical spreading depolarisations which are assumed to herald very early the increased danger and risk of brain tissue ischemia.

**Management and Prevention of Vasospasm/DIND/DCI**

Nimodipine is an oral calcium channel blocker that may reduce vasospasm and reduces the risk of secondary cerebral ischemia. Multiple studies support its use; a Cochrane review demonstrated a risk ratio of 0.67 (95% CI 0.55-0.81) for reducing secondary ischemia, with a trend toward reducing mortality. The dose is 60 mg orally every 4 hours. Patients unable to take medications by mouth can be given nimodipine through a nasogastric tube. Nimodipine is available in its intravenous formulation, i.e. thereby allowing for most precise dosing and modulating its major side effect, arterial hypotension. It needs to be stressed that IV nimodipine requires invasive blood pressure monitoring, CPP monitoring.
and, thus, ICU management. Magnesium sulfate IV has not demonstrated efficacy in preventing vasospasm neither did statins, NMDA receptor antagonists, free radical scavengers, chelating agents and endothelin A receptor antagonists. Locally (intraventricularly) applied “prolonged-release” Nimodipine is currently subject of a phase 3 trial.

If symptoms of vasospasm occur, often with focal deficit or change in the level of qualitative and/or quantitative consciousness (3 to 14 days after the initial hemorrhage) or indicated by the above detailed invasive monitoring techniques, aggressive therapy is warranted. Immediate CTA is needed for definitive diagnosis, in particular for objectivizing the presence of vessel luminal narrowing and cerebral hypodensities and - in addition - differentiation from rebleeding or hydrocephalus. Formerly hemodynamic augmentation was recommended, aiming at MAP and cerebral perfusion, i.e. CPP. However, it has been shown that in the absence of the vital invasive cardiopulmonary and neuro-monitoring this hemodynamic augmentation worsens outcome.

Transluminal balloon angioplasty has been proposed to be the mainstay of treatment, however it is applicable only in large-diameter blood vessels with an unacceptably high rate of arterio-arterial embolism leading to exact what it was meant to prevent, namely cerebral ischemia. Therefore, this purely mechanical transluminal balloon angioplasty has been largely abandoned.

Intraarterial pharmacological vasodilator therapy can be used both for localized and diffuse vasospasm, papaverine, nimodipine, verapamil, milrinone and fasudil have been administered. One of the shortcomings of these intraarterial vasodilator therapy is its limited, i.e. transient time of
efficacy, case reports suggest a prolonged intraarterial application of, 
e.g., nimodipine achieving sustained effect. 

If invasive cardiopulmonary and neuromonitoring is available a cautious 
trial to improve / augment the cerebral hemodynamics is warranted and 
may even include invasive therapeutic hypothermia or targeted 
temperature management 

**Prognosis of SAH**

*Mortality/Morbidity:* 
Close to 15% of patients will die before they reach the hospital, with 25% 
dying within 24 hours and 45% of patients dying within 30 days. Morbidity 
is also severe, with only one-third of patients demonstrating full recovery 
after treatment. Prognosis is predicted by level of consciousness and 
neurologic examination on initial evaluation, amount of hemorrhage on 
initial imaging (increased hemorrhage associated with worse outcome), 
patient’s age (younger patients experience better outcome), timely 
aneurysm repair, quality/experience of the intervening neuro-radiologist 
or neurosurgeon, admission to a high volume center and post-
terventional care in a specialized neurocritical care unit.
Further Reading and References:


