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Aneurysmal Subarachnoid Hemorrhage: Review of the Pathophysiology and Management Strategies

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Abstract

Purpose of Review Aneurysmal subarachnoid hemorrhage remains a devastating disease process despite medical advances made over the past 3 decades. Much of the focus was on prevention and treatment of vasospasm to reduce delayed cerebral ischemia and improve outcome. In recent years, there has been a shift of focus onto early brain injury as the precursor to delayed cerebral ischemia. This review will focus on the most recent data surrounding the pathophysiology of aneurysmal subarachnoid hemorrhage and current management strategies.

Recent Findings There is a paucity of successful trials in the management of subarachnoid hemorrhage likely related to the targeting of vasospasm. Pathophysiological changes occurring at the time of aneurysmal rupture lead to early brain injury including cerebral edema, inflammation, and spreading depolarization. These events result in microvascular collapse, vasospasm, and ultimately delayed cerebral ischemia.

Summary Management of aneurysmal subarachnoid hemorrhage has remained the same over the past few decades. No recent trials have resulted in new treatments. However, our understanding of the pathophysiology is rapidly expanding and will advise future therapeutic targets.

Keywords Subarachnoid hemorrhage · Early brain injury · Spreading depolarization · Delayed cerebral ischemia · Vasospasm

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating disease representing 5% of all strokes and occurring at an annual incidence, in the USA, of 6.9 to 9 in 100,000 cases [1, 2]. Over the past 3 decades, worldwide incidence has declined, mirrored by a reduction in smoking, uncontrolled hypertension along with higher rates of un-ruptured aneurysm repair [2]. Mortality has also declined and ascribed to rapid diagnosis and early treatment strategies [3]. Despite these advancements, mortality and morbidity remain high [2]. Fifteen percent of patients die at the time of aneurysmal rupture and 30-day mortality is up to 45% [2, 4]. Survivors often suffer substantial disability, half do not return to their baseline functional status and up to a quarter are reliant on others for their care [3]. These numbers fail to account for those with impaired cognitive function and mental health disorders which are underrecognized sequelae. As many as 35% of patients report decreased quality of life due to memory loss, depression, anxiety, and post-traumatic stress disorder [5–8•].

It is believed that the high mortality and morbidity following aSAH are related to the development of delayed cerebral ischemia (DCI). To date, much of the focus on aSAH research has been on treatment and prevention of vasospasm as a precursor to the development of DCI. Targeting vasospasm has not been fruitful and review of the literature has shown no new successful randomized controlled trials in management of aSAH in decades. Our understanding of the pathophysiology of secondary brain injury is rapidly evolving. While DCI remains an important factor in outcome, it is recognized that the development of DCI is multifactorial and not solely related to the development of vasospasm. Emerging evidence suggests that early brain injury (EBI), starting at the time of aneurysmal rupture, may play a substantial role in development of DCI.

Through this article, I propose reviewing aSAH as a disease process with 3 phases, each occurring on a continuum

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and contributing to outcome (Fig. 1). Epidemiology, pathophysiology, and management strategies can be evaluated in these three phases. The rupture of the aneurysm triggers a cascade of events that are all inter-related. The first phase is the acute phase and encompasses what happens in the first 24 h. The acute phase sets the stage for the later events. The second phase is the subacute phase which focuses on EBI and occurs in the first 72 h. The delayed or chronic phase occurs more than a week after the rupture and is hallmarked by vasospasm and DCI.

Acute Phase

Within seconds of an aneurysmal rupture, a patient experiences physiological changes leading to several complications within the first 24 h. The sudden release of blood into the subarachnoid space results in a sharp rise in intracranial pressure (ICP), a drop in cerebral perfusion pressure (CPP), and early ischemia. Prompt recognition and treatment are essential to prevent secondary brain injury. During this time, there are several devastating complications that may arise including rebleeding, hydrocephalus, seizures, and cardiopulmonary difficulties. The brain is very susceptible to these changes as they contribute to an oxygen supply and demand problem leading to activation of cell death pathways and EBI.

Initial Evaluation

Patients most commonly present with acute onset "worst headache of life." This type of headache is severe, sudden, and maximal at onset. Other red flags include nausea and vomiting (77%), loss of consciousness (53%), Terson syndrome (40%) (vitreous hemorrhage), and meningismus (35%) [9•, 10]. Any patient with a suspicion of aSAH should undergo a noncontrast head computed tomography (CT) scan as soon as possible. The sensitivity approaches 100% in the first 24 h though declines over time and is only 60% sensitive at 1 week [11]. If CT is negative and the suspicion remains high, a lumbar puncture is recommended to evaluate for xanthochromia [3, 12, 13]. Xanthochromia can take up to 12 h to develop and may not be present on early samples. Though magnetic resonance imaging approaches the sensitivity of CT, it is often less readily available and not as rapid as CT scan [11]. At the author's institution, most patients undergo a CT angiogram to help identify the source of bleeding. CT angiogram is highly sensitive (90–97%) and specific (93–100%) for detection of aneurysms larger than 4 mm [14, 15]. Cerebral digital subtraction angiogram remains the gold standard imaging technique and is often performed for further evaluation of the aneurysm characteristics to facilitate securement planning.

Patients with aSAH should be assigned a disease severity score using the World Federation of Neurologic Surgeons (WFNS) or the Hunt and Hess scales (Table 1) [16, 17].

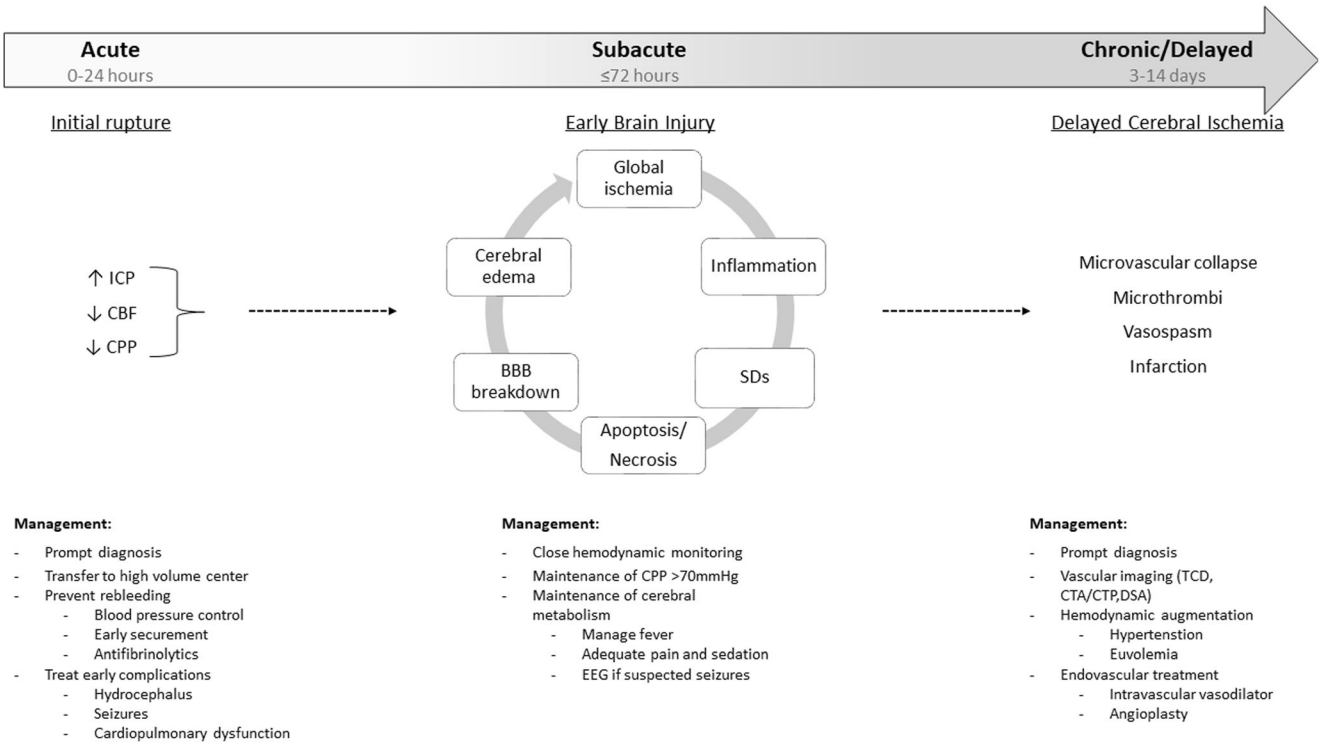

Fig. 1 aSAH as a disease process with 3 phases

Table 1 Subarachnoid Hemorrhage Grading Scales [16–18]

	Clinical Grading Scales			Radiologic Grading Scale	
	Hunt and Hess Scale	World Federation of Neurologic Surgeons Scale		Modified Fisher Scale	
Grade	Exam	Glascow Coma Scale	Exam	Subarachnoid hemorrhage	Intraventricular hemorrhage
0				Absent	Absent
1	Asymptomatic Mild headache Slight nuchal rigidity	15	-	Thin	Absent
2	Moderate/severe headache Nuchal rigidity Cranial nerve palsy	13–14	No motor deficit	Thin	Present
3	Confusion/lethargy Mild focal findings	13–14	With motor deficit	Thick	Absent
4	Stupor Severe focal findings	7–12	-	Thick	Present
5	Coma, posturing	3–6	-		

Higher scores on each of these are associated with worse clinical outcomes. The patient should also be assigned a radiologic scale, the modified Fisher scale (Table 1) which is based on CT appearance [18]. This scale has a near linear correlation to the development of vasospasm and DCI. Patients that have high scores on these scales also have a higher risk of both early and late complications.

Once aSAH is identified, it is critical to transfer the patient to a high-volume center (>35 cases/year) with access to neurocritical care, neurosurgery, and endovascular specialists [3, 13, 19–21]. Treatment in a high-volume center and access to neurocritical care are both associated with lower mortality, improved outcome, and a higher percentage of patients discharged home [19, 20, 22]. This improvement may in part be due to use of standardized management protocols and adherence to guidelines [23]. At the author's institution, we have created standard operating procedures based on the guidelines to direct care in a more efficient and evidence-based manner.

Early Complications

There are a multitude of early complications that can arise following an aSAH especially in the acute phase. This section will address the most common early complications and provide information on prevention and management strategies.

Rebleeding

Rebleeding is one of the most feared and dangerous early complications. It is associated with up to 60% mortality, significantly decreased odds of disability-free survival, and increased probability of cognitive impairment [24–26]. Rates of aneurysmal rebleeding have drastically improved since the 1980s when it was reported that more than 35% of patients experienced a rebleed prior to repair of their aneurysm [27–29]. Despite efforts to secure aneurysms more readily, recent data indicates that rebleeding continues to occur in 4–13% of patients within 24 h and that more than 50% of those occur within 6 h of onset [24–26]. The risk factors associated with rebleeding are higher grade, hypertension, lower Glasgow coma score, larger/irregular aneurysm, and delayed securement [24, 26].

Prevention of rebleeding is essential in the management of aSAH. The most definitive treatment is securement of the aneurysm. Historically early surgical treatment of aneurysms was considered very high risk due to unfavorable operating conditions, hyperemia, and high risk of laceration and infarction [30, 31]. Recognition of high risk of early rebleeding coupled with development of endovascular treatments led to a shift from late securement (after 10 days) to early securement (within 72 h) [3, 31]. However, controversy remains over the benefit of ultra-early securement within 24 h. Knowing the majority of rebleeding happens within the first 24 h, I believe the aneurysm should be secured as soon as possible within that time window. There is growing evidence that ultra-early securement is safe and not only reduces rebleeding but also improves outcome [30, 32, 33]. The method of securement can depend on many factors including the patient's age, aneurysm morphology and location, and presence of intraparenchymal hemorrhage. Following the international subarachnoid aneurysm trial (ISAT), coiling is the preferred method of securement, when feasible, and is associated with improved mortality and functional outcomes though does have a higher rate of aneurysm recurrence [33–38]. The choice of securement method should be made after a multidisciplinary discussion between the neurocritical care and endovascular and neurosurgical specialists.

When securement is delayed, tranexamic acid may reduce rebleeding and improve overall mortality [39, 40]. Prolonged use of antifibrinolytics has been reported to increase deep vein thrombosis, stroke, and myocardial infarction and the current

guideline recommends use for no more than 72 h [3, 13]. Tranexamic acid at the author's institution is underutilized and given the high rates of ultra-early rebleeding should be considered more frequently.

Hypertension is a risk for rebleeding and the guidelines recommend close blood pressure monitoring and management to maintain systolic blood pressure less than 160 mmHg or mean arterial pressure less than 110 mmHg [3, 13]. Blood pressure should be controlled with short-acting intravenous medications or infusions to prevent wide fluctuations or hypotension which may result in a drop in CPP.

Hydrocephalus

Hydrocephalus is another early complication that can result from a change in cerebral spinal fluid (CSF) dynamics. It is reported to occur acutely in 50% of patients [9•]. Hydrocephalus can have a dramatic impact on neurologic examination and up to 30% of patients with poor-grade aSAH will become good grade with prompt CSF drainage [41]. Poor clinical grade should not be a reason to defer aSAH treatment. CSF diversion is essential and can be accomplished with placement of an external ventricular drain or in some cases a lumbar drain. There is a theoretical risk that CSF diversion will lead to increased transmural pressure and re-rupture of the aneurysm though this is not well elucidated in studies [42]. Aggressive drainage is often avoided until aneurysm securement.

Seizure

Seizure is also an early complication that occurs most frequently at the ictus of aneurysmal rupture in up to 26% of patients [43–45]. Clinical seizures after this time are rare occurring in about 2–8% [34, 43, 44, 46, 47]. The majority occur within the first 24 h and may be a hallmark of rebleeding [43]. Seizures are concerning because they not only contribute to elevated ICP but also to increasing brain metabolism and higher demand for oxygen potentially resulting in hypoperfusion [45, 48]. It is important to note that nonconvulsive status epilepticus can be present in up to 20% of patients, especially those in coma with high-grade hemorrhage [45, 48, 49]. Though antiepileptic drugs are widely used, multiple studies have found that antiepileptics are associated with poor cognitive outcome as well as increase hospital complications [29, 44, 47]. Given that seizures are uncommon after the ictus and antiepileptics carry substantial risk, the guidelines recommend against the routine use of seizure prophylaxis [3, 13]. If seizure prophylaxis is felt to be indicated, the guidelines recommend only a short course of less than 7 days which has been shown to be as effective as prolonged treatment [3, 13]. Patients with high-grade hemorrhage or a poor examination without clear explanation should have continuous electroencephalogram to look for presence of subclinical seizures and nonconvulsive status epilepticus [50–52].

Cardiopulmonary

Cardiopulmonary dysfunction is common after aSAH and is related to catecholamine release and sympathetic overstimulation [53–55]. Higher grade aSAH have an increased risk of cardiopulmonary dysfunction. The cardiac dysfunction can manifest as changes in the electrocardiogram, for example, T-wave inversion, ST depressions, or even ST elevations among others [55, 56]. While these changes are a result of ischemia, they occur in the absence of coronary artery disease [57]. Cardiac enzymes, troponin, and creatinine kinase-MB can also be elevated [55, 58]. Echocardiography may show wall motion abnormality and one of the most typical findings is apical ballooning and takotsubo cardiomyopathy [57, 59, 60]. Cardiac evaluation with electrocardiogram, cardiac enzymes, and echocardiogram is essential in the evaluation of aSAH as acute heart failure and development of hypotension are associated with increased mortality and poor functional outcome [54, 55, 58]. Pulmonary edema can result from the acute heart failure though patients may also develop neurogenic pulmonary edema independent of cardiac function. Acute lung injury and acute respiratory distress syndrome have also been described in patients with aSAH [55]. Prompt recognition and management of the cardiopulmonary complications is paramount. Hypoxia and hypotension have deleterious effects on the already vulnerable brain and work to increase secondary brain injury. Clinicians must maintain brain perfusion and oxygenation. Fortunately, the cardiopulmonary effects tend to be transient and aggressive support can prevent accumulation of further brain injury. Treating stress cardiomyopathy with inotropes, milrinone and dobutamine, improves cardiac output and may improve brain perfusion [55]. No study points to one being more effective. I have favored the use of milrinone given that some studies suggest milrinone may prevent vasospasm and improve outcome [61]. Patients with cardiopulmonary dysfunction should have early volume correction and prevention of hypervolemia. Ventilation with lung preservation strategy and low volume ventilation may also improve oxygenation and outcome.

Subacute Phase

The subacute phase encompasses a cascade of events occurring within the brain during the first 72 h following aSAH. Through recent research, it has become obvious that the pathophysiological changes occurring after aSAH are more extensive than previously appreciated. EBI is an emerging concept and focus of research. The changes occurring during this phase set the stage for the development of vasospasm and DCI.

Early Brain Injury

EBI refers to the complex pathophysiological mechanisms occurring immediately following the hemorrhage. EBI occurs within the first 72 h though has long-lasting chronic sequelae and impacts the development of DCI [62••, 63]. EBI is increasingly recognized as an important cause of secondary brain injury, mortality, and disability [62••, 63, 64]. Those at the highest risk include patients with high-grade hemorrhage, larger blood volume, prolonged loss of consciousness, early brain edema, and ischemia [62••].

The pathophysiological mechanisms are under investigation and much of our current knowledge comes from animal data. EBI begins immediately upon blood entering the subarachnoid space. It is proposed that a sudden rise in ICP results in a drop in cerebral blood flow (CBF) and CPP [63]. Multimodality monitoring data suggests that brain tissue oxygen is reduced, and lactate-pyruvate ratio is increased further supporting the hypothesis that early brain hypoperfusion plays a role in EBI [62••, 64]. These immediate changes result in cerebral ischemia and activation of the intracellular apoptosis and necrosis pathways [63]. There has been extensive animal research revealing apoptosis and necrosis primarily occurs in the vasculature, hippocampus, and periventricular tissue and can lead to microvascular failure, microthrombi, and oxidative stress [63], ultimately resulting in cell death, blood brain barrier disruption, and cerebral edema [63]. Brain edema plays a major role in EBI and is an independent predictor of mortality [65]. Edema further promotes brain hypoperfusion and creates a repetitive cycle of cell death and secondary brain injury [64].

Neuroinflammation is a characteristic response to brain damage and likely another key component of EBI [66•, 67]. It can result from blood degradation products, apoptosis, necrosis, and ischemia [62••]. Pro-inflammatory cytokines particularly interleukin 6 (IL-6) and matrix metalloproteinase 9 (MMP-9) have been implicated in development of brain edema and secondary brain injury including vaspospasm and DCI [62••, 64, 67, 68•, 69]. IL-6 and MMP-9 are upregulated shortly after aSAH onset and high levels of each are associated with poor-grade hemorrhage, hypoperfusion (particularly CPP <70 mmHg), and cerebral edema [62••, 64]. Expression of pro-inflammatory cytokines has been shown to potentiate EBI in rat models [64]. These inflammatory cytokines may act to further the brain damage mentioned above by contributing to endothelial damage, apoptosis, blood brain barrier breakdown, and cerebral edema. Inflammation further adds to the cycle of EBI and secondary brain damage [62••, 67].

Cortical spreading depolarizations (SDs) are slow moving, self-propagating waves of neuronal and glial depolarization detected using electrocorticographic monitoring through subdural electrodes [70]. In healthy patients, SDs are associated with vasodilation and hyperemia; however, following brain injury, there is inverse neurovascular coupling resulting in vasoconstriction, reduced CBF, and hypoperfusion [70, 71]. SDs may be triggered by ischemia and likely contribute to EBI. It has been reported that up to 80% of poor-grade aSAH patients experience SDs [72••]. Eriksen described that 33 of 37 high-grade aSAH patients with early focal brain injury on initial CT had SDs compared to 7 of 17 patients without early focal brain injury [73••]. Following aSAH, SDs can lead to loss of spontaneous brain activity, called cortical spreading depression. Over time, SDs may lead to profound disruptions that result in expansion of existing damage [74•, 75]. SDs are thought to confer injury through energy depletion, excitotoxicity, and spreading ischemia [74•]. aSAH patients with poor outcome had significantly higher number of SDs with evidence of depressions [73••]. Imaging and histological studies also show a correlation between SDs and development of cytotoxic edema [72••]. Prolonged SD duration has also been associated with DCI and worse outcome after aSAH [76, 77].

To summarize, EBI encompasses all pathophysiological processes occurring in the first 72 h including elevated ICP, brain hypoperfusion, neuroinflammation, and SDs resulting in secondary brain injury as evident by brain ischemia, edema, and microvascular collapse. EBI sets the stage for the development of DCI and leads to poor neurologic outcome following aSAH. There is currently no therapeutic intervention to target prevention or treatment of EBI. However, further elucidation of the pathophysiologic mechanisms will help to devise a therapeutic strategy in the future.

Early management should be aimed at preventing secondary brain injury through providing adequate oxygen delivery and meeting the brain's metabolic demands. Rapid recognition and treatment of the early complications mentioned previously (rebleeding, hydrocephalus, seizures, cardiopulmonary failure) will help to mitigate brain damage related to EBI. Optimizing CPP is essential as recent data suggests that CPP maintenance above 70 mmHg early on may improve brain tissue hypoxia and overall brain perfusion leading to less metabolic stress and improved outcomes [64]. CPP optimization is often recommended after development of vasospasm and DCI though may be beneficial from the onset of bleeding. Though evidence is sparse, I feel strongly that this early maintenance of CPP is likely to have an impact on later development of brain injury. Treatment of anemia is also suggested to maintain adequate oxygen delivery [3, 13]. Aggressive control of fever is necessary to reduce metabolic demand on the brain [3, 13]. Multimodality monitoring may assist in individualizing treatment strategies and is done at some institutions [78].

Neuroinflammation has proven a difficult target as many studies have failed to show effect. Several agents including nonsteroidal anti-inflammatories, thromboxane synthase inhibitors, steroids, nitric oxide, and various immunosuppressants have failed to show benefit and cannot be recommended [79••, 80, 81].

Targeting SDs in the prevention of secondary brain injury is currently under investigation. The physiological understanding

of SDs is rapidly increasing though the pharmacological targeting is in its early stages. There is limited evidence that treating or limiting SDs has an impact on brain damage or outcome. Current targets are to block initiation of SD, modulate the propagation, reduce the amplitude, decelerate progression, and improve hemodynamic response [82•, 83•]. Some evidence suggests N-Methyl-D-Aspartate (NMDA) and α-Amino-3-Hydroxy-S-Methyl-4-Isoxazolepropionic acid (AMPA) receptors should be targeted. Using ketamine to block NMDA receptor activity seems to decrease ischemia though no clinical trials have shown benefit [82•, 84•]. Though there is limited data on the use of ketamine to treat SDs in SAH, small retrospective data suggests that the dose of ketamine needed far exceeds the typical ketamine dosing (in the range of 2–7 mg/kg) and even at that the effect was minimal [84•]. Further evaluation is required before any recommendation for its use can be made [83•].

Chronic/Delayed Phase

The delayed phase is marked by the development of vasospasm and DCI which most commonly occur 3–14 days post aSAH. DCI with cerebral infarction is the leading cause of morbidity in survivors. DCI has historically been attributed to the development of vasospasm though recent evidence implicates a more complex pathophysiology.

Delayed Cerebral Ischemia

DCI is any neurological deterioration (focal deficit or decline in Glasgow coma scale by 2 or more points), lasting greater than 1 h and not attributable to another cause [85]. It is reported to occur in 30% of aSAH patients and is a major contributor to death and disability [3, 85]. Historically, the development of DCI was thought to be secondary to vasospasm which is seen radiographically in 70% of patients. However, over the years, it has become increasingly clear that vasospasm alone cannot account for the development of DCI. Effective treatment of vasospasm does not necessarily correlate with decreased incidence of DCI or improved outcomes as seen in the Clazosentan trials [86–88]. Also, the only Food and Drug Administration–approved medication, nimodipine, had no effect on vasospasm yet improved DCI and patient outcomes [89, 90]. Multiple other treatments aimed at vasospasm including magnesium, statins, and methylprednisolone have made it to clinical trials and failed to show outcome benefit [91–95]. These negative trials further support the idea that the pathophysiology of DCI is complex and multifactorial. It is proposed that both DCI and vasospasm result from physiological changes occurring during EBI including cerebral vascular dysfunction, microthrombosis, SDs, and neuroinflammation [85]. The risk factors for the development of DCI are similar to those for EBI and include high-grade hemorrhage and modified fisher score, as well as prolonged loss of consciousness [10]. Also playing a role is accumulation of early complications including rebleeding, hydrocephalus, seizures, and cerebral edema [3].

Predicting who will develop DCI is problematic and while we are moving away from vasospasm as the sole contributor to DCI it does remain an important factor and clinical indicator that DCI and infarction are impending. During the delayed/chronic phase, prompt recognition of neurologic decline is essential. Patients should have frequent neurologic evaluations and prompt management if decline is noted.

Management

Monitoring for vasospasm is essential in the management of aSAH patients. Development of vasospasm likely gives insight into those at higher risk of developing DCI. Transcranial Doppler (TCD) is the most widely used tool to screen for presence of vasospasm [96, 97]. It is noninvasive, low risk, and readily available [85]. TCD is most sensitive for middle cerebral artery spasm [98]. Velocities over 120 cm/s in the middle cerebral artery have a high negative predictive value for the presence of spasm while velocities over 180 cm/s have a high positive predictive value [85]. Serial examinations and the trend in velocity are often more important than any singular value. Elevation in TCDs will prompt closer evaluation for symptomatic vasospasm. If symptomatic vasospasm is suspected, adjunctive imaging with CT angiogram and CT perfusion may be indicated. In recent years, CT angiogram has become more widely used as it is highly sensitive and specific [99, 100]. It may overestimate the degree of spasm though can be used in conjunction with CT perfusion imaging. CT perfusion is emerging as a potential test to evaluate for hypoperfusion in the presence or absence of large vessel vasospasm. aSAH patients with perfusion deficit were 23 times more likely to have DCI than those without perfusion deficit [101]. CT perfusion may be able to detect DCI early when it is still reversible [102, 103]. Digital subtraction angiogram remains the gold standard for vasospasm evaluation and should be performed if clinical vasospasm is suspected. This allows both diagnosis and potential treatment. Multimodality monitoring may provide further information about potential hypoperfusion and risk of DCI. Brain tissue oxygen monitoring measures the partial pressure of oxygen in a small area of the cortex and levels less than 20 mmHg are associated with risk of ischemia [9•, 78]. Microdialysis measures interstitial levels of glucose, lactate, pyruvate, and glutamate. The lactate-pyruvate ratio is a marker of anaerobic metabolism and has been associated with the development of DCI [9•].

It is essential to treat neurologic decline quickly and aggressively to prevent permanent brain injury. Centers should create a standardized protocol for management that is based on best evidence. Development and use of protocols can help

improve outcome [23]. To date, nimodipine is the only pharmacological treatment to reduce development of DCI and improve outcome [90]. Nimodipine should be given to all aSAH patients for the duration of hospital stay, up to 21 days [3, 13]. The recommended therapies for DCI include induced hypertension and endovascular treatment. "Triple H" therapy (hypertension, hemodilution, hypervolemia) has fallen out of favor [104]. Hypertension remains the only component of "Triple H" therapy that effectively increases perfusion and brain oxygenation [105–107]. Both hypervolemia and hemodilution lead to more deleterious effects [107–110]. Blood pressure should be titrated in a stepwise manner until clinical symptoms improve [9•]. When neurologic deficit persists, endovascular therapy is recommended [3, 13]. The use of intravascular vasodilators (milrinone, verapamil, nicardipine) is associated with substantial improvement in angiographic spasm and clinical examination [111]. Angioplasty can be considered if spasm is refractory to intravascular dilation.

Prognosis following aSAH can be difficult. Many studies evaluated patients within 3 months of onset though recent evidence suggests this time frame does not accurately reflect prognosis. Patients evaluated a year later continued to improve [112••]. At 3 months, 53.8% experienced good outcome, whereas at 1 year, 66.3% had good outcome [112••]. This suggests that our understanding of brain recovery following aSAH is lacking and care must be taken when having discussions of prognosis during hospitalization.

Conclusion

aSAH is a multifaceted and complex disease that carries a high mortality and morbidity. Though we have been studying this disease for decades, treatment options remain limited. Recently, our understanding of the pathophysiology has undergone a paradigm shift away from vasospasm and toward a multifactorial process that begins at the onset of hemorrhage. Rupture of an intracranial aneurysm triggers a cascade of events that can be split into 3 phases occurring on a continuum. Each phase is predicated by the prior and affects the latter. Blood in the subarachnoid space triggers the development of EBI which results in microvascular collapse, blood brain barrier breakdown, cerebral edema, vasospasm, microthrombi, neuroinflammation, and SDs all of which ultimately lead to DCI and infarction. Further elucidation of the pathways involved in EBI will help to design appropriate therapeutic targets in the future.

Abbreviations AMPA, A-Amino-3-Hydroxy-S-Methyl-4-Isoxazoleproprionic acid; aSAH, Aneurysmal subarachnoid hemorrhage; CBF, Cerebral blood flow; CPP, Cerebral perfusion pressure; CSF, Cerebrospinal fluid; CT, Computed tomography; DCI, Delayed cerebral ischemia; EBI, Early brain injury; IL-6, Interleukin 6; ISAT, International subarachnoid aneurysm trial; ICP, Intracranial pressure; MMP-9, Matrix metalloproteinase 9; NMDA, N-methyl-D-aspartate; SDs, Spreading depolarizations; TCD, Transcranial Doppler; WFNS, World Federation of Neurologic Surgeons; aSAH, Aneurysmal subarachnoid hemorrhage; DCI, Delayed cerebral ischemia; EBI, Early brain injury; ICP, Intracranial pressure; CPP, Cerebral perfusion pressure; CT, Computed tomography; WFNS, World Federation of Neurologic Surgeons; ISAT, International subarachnoid aneurysm trial; CSF, Cerebrospinal fluid; CBF, Cerebral blood flow; IL-6, Interleukin 6; MMP-9, Matrix metalloproteinase 9; SDs, Spreading depolarizations; NMDA, N-methyl-D-aspartate; AMPA, A-amino-3-hydroxy-S-methyl-4-isoxazoleproprionic acid; TCD, Transcranial Doppler

Declarations

Conflict of Interest Marcey L. Osgood declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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112.•• Cinotti R, Putegnat JB, Lakhal K, Desal H, Chenet A, Buffenoir K, et al. Evolution of neurological recovery during the first year after subarachnoid haemorrhage in a French university centre. Anaesth Crit Care Pain Med. 2019;38(3):251–7. https://doi.org/10.1016/j.accpm.2018.10.002 **This paper is extremely important for those treating subarachnoid hemorrhage patients and highlights the fact that prognosis is difficult. Patients may have greater potential for recovery than anticipated.**

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