29 Vasospasm Following Aneurysmal Subarachnoid Hemorrhage

Eduardo Vieira and Hildo Azevedo-Filho

29.1 Introduction

Majority of morbidity and mortality due to aneurysmal subarachnoid hemorrhage (aSAH) is secondary to cerebral ischemia. Classically, the angiographic arterial narrowing following aSAH has been termed as angiographic vasospasm, which may or may not lead to clinical manifestations and cerebral ischemia, in which case it would be called symptomatic vasospasm. This concept has recently been questioned. Not always angiographic vasospasm leads to cerebral ischemia, which, in turn, may occur in a territory different from the one irrigated by the narrowed artery or even in the absence of any angiographic vasospasm, i.e., cerebral ischemia that occurs late (days after aSAH) cannot be attributed solely to the arterial narrowing seen on angiography [1]. Currently, the term "delayed cerebral ischemia" (DCI) has been proposed to replace the previously used "symptomatic vasospasm." The clinician should be able to recognize and differentiate the radiological vasospasm from the clinical worsening secondary to DCI, whose etiology is multifactorial and includes angiographic arterial narrowing (Fig. 29.1). Alternative mechanisms have been proposed and include microvascular spasm and failure of cerebral blood flow (CBF) autoregulation, microthrombosis and microembolism, cortical spreading depolarization and ischemia, and delayed neuronal apoptosis resulting from acute brain injury. A more extensive review of the pathophysiology of DCI is out of the scope of this review.

DCI is a diagnosis of exclusion. When there is neurological deterioration, the diagnosis of DCI can only be established when causes like hydrocephalus, hyponatremia, infection, and bleeding are ruled out, and the introduction of hypertensive therapy or endovascular treatment leads to clinical improvement. In the next sessions, we will discuss about the risk factors, prevention, monitoring, and treatment of DCI.

29.2 Risk Factors

The hemoglobin (Hb) in subarachnoid space is a very important factor that triggers vasospasm and DCI. Hb is extremely toxic in the subarachnoid space leading to the rapid activation of cellular adhesion molecules (CAMs) on luminal surface of endothelial cells, enabling macrophages and neutrophils to penetrate into subarachnoid space, where they will phagocytize RBCs and free Hb. After this process, however, macrophages and neutrophils are trapped in the subarachnoid space due to the lack of lymphatic drainage in CNS (central nervous system) and to the difficulty in CSF drainage resulting from aSAH. Between

E. Vieira (✉) · H. Azevedo-Filho
Department of Neurological Surgery, Hospital da Restauracao, Recife, Brazil

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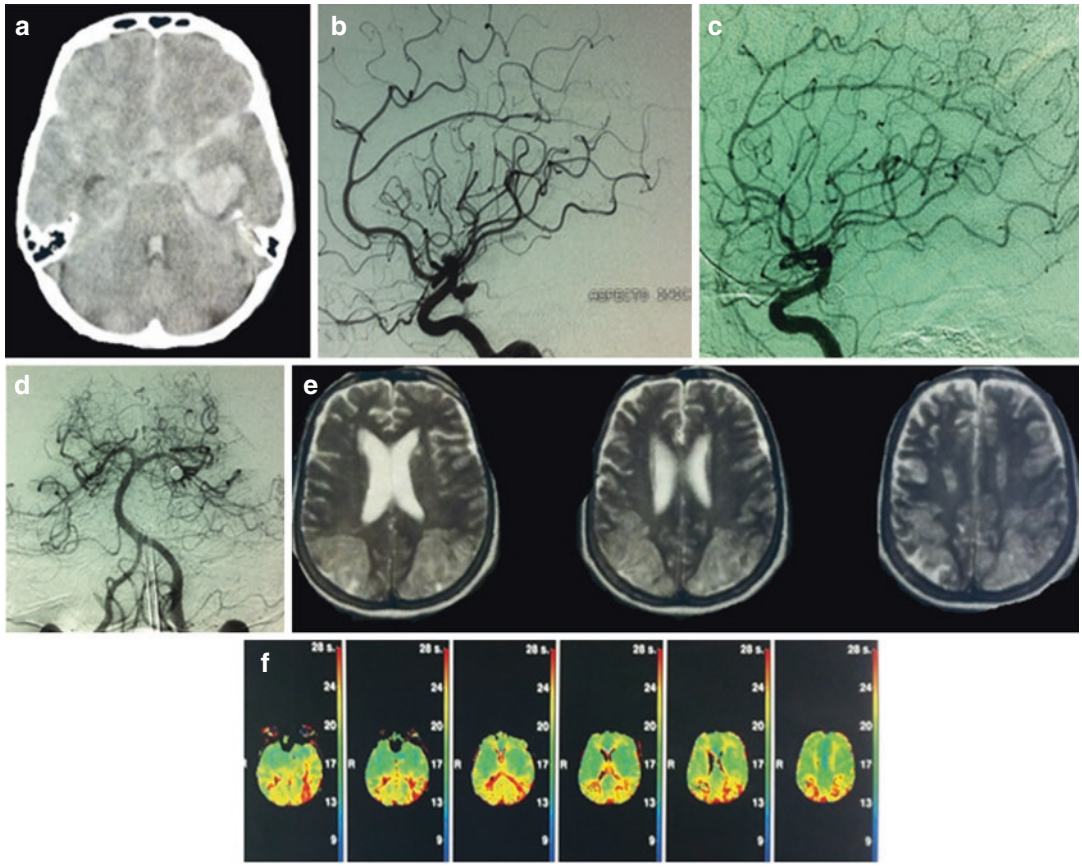

Fig. 29.1 This 72-year-old female patient with a typical history of sudden headache associated with disorientation (HH III) was admitted to hospital. (**a**) CT scan showed a Fisher III with medial temporal hematoma. (**b**) Angiography performed 24 h after admission confirmed an ICA-PCom aneurysm, which was coiled. The patient did well until the ninth day after bleeding, when she became drowsy and unresponsive. (**c**) and (**d**) Angiography performed on the tenth day after bleeding did not reveal vasospasm, and hypertensive therapy was maintained. (**e**) MRI showed ischemic areas predominantly in the territory of posterior cerebral arteries. (**f**) Perfusion study revealed a decreased CBF and CVF, consistent with irreversible ischemia. The cause of DCI is multifactorial, although it's associated with vasospasm, it can occur in the absence of angiographic vasospasm

2 and 4 days, these cells die and disintegrate, releasing intracellular endothelin and free oxygen radicals, leading to vasoconstriction and arteriopathy. That said, it is easy to realize that key factor for DCI is quantity of blood that stays in subarachnoid space.

Quantity of blood in subarachnoid space can be measured by cranial CT and based on this measurement; scales for predicting the possibility of vasospasm were developed. The most widespread and used is the one proposed by Fisher et al. (Table 29.1) [2]. Analyzing this scale, one can notice that patients at highest chance to have vasospasm and DCI are those classified as grade 3, and within this group, there is a wide possible range in quantity of blood present in subarachnoid space, creating a vital variation in probability of developing DCI and vasospasm in patients of the same group of the scale (Fig. 29.2), i.e., the Fisher scale fails to identify those patients at highest risk of developing DCI. Wilson et al. proposed a new scale (BNI scale) (Table 29.1) where the thickness of the clot present in the subarachnoid space was evaluated,

Table 29.1 Comparison between Fisher and BNI scales

Scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fisher	No blood	Clot less than 1 mm thick	Clot more than 1 mm thick	Grade 1 or 2 and associated intracerebral hematoma or hemoventricle	–
BNI	No blood	Clot less than 5 mm thick	Clot 5–10 mm thick	Clot 10–15 mm thick	Clot more than 15 mm thick

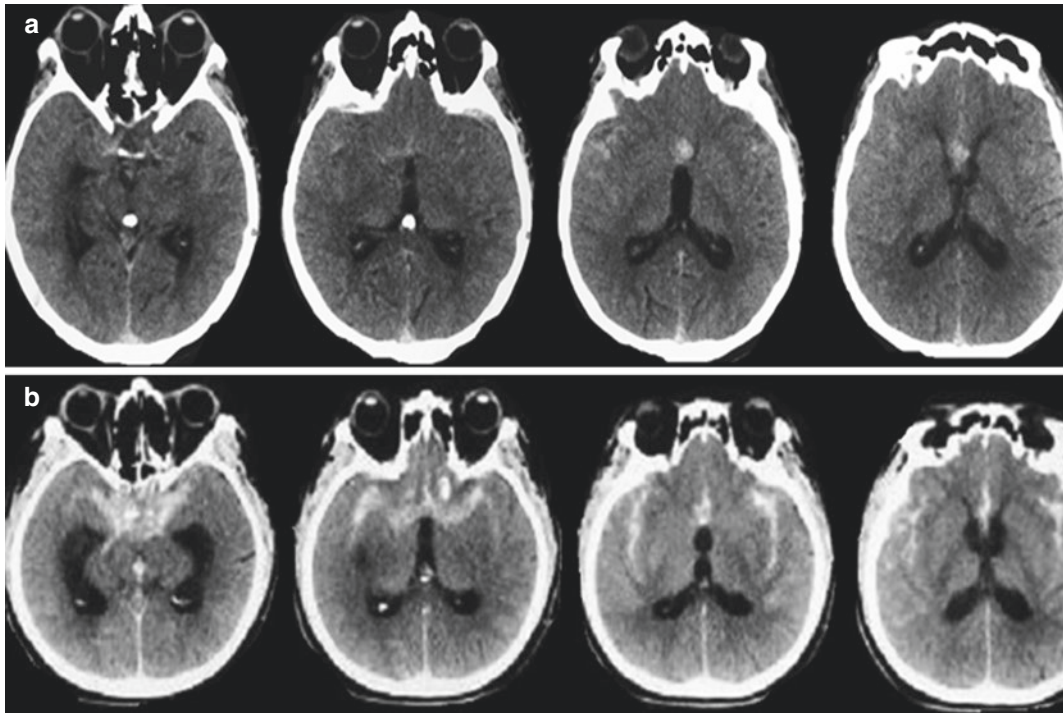

Fig. 29.2 Two patients (A and B) with a Fisher grade 3 aSAH. There is a significant difference between the volumes of blood present in the subarachnoid space between these two patients. Although classified within the same subgroup, patient B has a greater chance of developing vasospasm and DCI with a consequent poor outcome

stratifying those patients grouped as grade 3 in Fisher scale and showing that the size of the thickness of the clot in subarachnoid space is directly proportional to risk of vasospasm and DCI (Table 29.2) [3].

Other risk factors for having the vasospasm and DCI are Hunt-Hess grades 4 and 5, history of hypertension, smoking, early angiographic vasospasm, and young age (<35 years) [4–6]. Hypovolemia is an important and avoidable risk factor that can occur due to cerebral salt-wasting syndrome (CSWS) and should be avoided at all costs.

29.3 Prevention

One of the most important factors in the prevention of DCI is to maintain normovolemia. It is important to emphasize, however, that there is no space for prophylactic hypervolemic therapy, as it does not result in increased CBF nor in better clinical results [7].

The administration of nimodipine, a calcium channel blocker, for 21 days, starting from the moment of admission is probably the only class I recommendation on most recent guiding principle for the management of aSAH from AHA/

Table 29.2 Differences in the incidence of DCI between the BNI and Fisher scales in 218 patients

Fisher scale			BNI scale	
DCI (%)	Distribution (%)	Grade	Distribution (%)	DCI (%)
0	0	**1**	3.7	0
15	6	**2**	33	13
23	83.5	**3**	44.5	22
6	7.3	**4**	12.4	30
–	–	**5**	6.4	50

Using the classification of Fisher, 83.5% of patients are classified as grade 3, and within this subgroup, the greater the thickness of the clot on the CT scan, the greater the chance of DCI

ASA [8]. The drug should be administered orally with 60 mg that is given every 4 h, with a decrease in the relative risk (RR) for DCI of 18% (95% CI = 7–28%) and a number necessary to treat (NNT) of 13 [9, 10]. It is important to emphasize that there is no benefit if the drug is started more than 72 h after bleeding. Importantly, the medication does not prevent vasospasm. It is believed that nimodipine acts through neuroprotective mechanisms, stabilizing cell membranes, decreasing the risk of DCI, and improving patients' outcomes.

Endothelin is a potent vasoconstrictor peptide, mediator of cerebral vasospasm. It is formed through a wide diversity of cells, such as leukocytes and macrophages in the CSF as described above. The use of the inhibitor of endothelin clazosentan was evaluated in different studies.

The results showed that the drug reduces the incidence of angiographic vasospasm in a dose-dependent manner, with no influence, however, on the incidence of DCI and morbidity or mortality [11–14]. This clinical-radiological dissociation is one more data to support the theory that vasospasm cannot, solely, be responsible for DCI.

Statins and magnesium sulfate have been proposed for the prevention of vasospasm and DCI. Two randomized controlled trials (RCTs), the STASH study [15], for statins, and the MASH-2 study [16], for magnesium sulfate, showed that the use of these drugs is of no benefit on the prophylaxis of DCI. Although there is no indication of starting, patients who already use statins may continue the medication after aSAH.

29.4 Monitoring and Diagnosis

The best way to assess and monitor a patient at risk of vasospasm and DCI is through seriated clinical examinations. If there are a decrease level of consciousness and also an onset of new focal deficits, it should prompt investigation in order to exclude hydrocephalus, rebleeding, infection, and hyponatremia. If these entities are all excluded, the diagnosis of DCI is made, and treatment should be instituted as soon as possible.

Critical patients, especially those who already present in coma, are harder to monitor and to evaluate. Because of its noninvasiveness and wide availability, transcranial Doppler ultrasonography (TCD) is the most commonly employed auxiliary method. Although it has high specificity, it lacks sensibility for the development of DCI, especially for territories other than the middle cerebral artery (MCA) [17]. One should never rely solely on TCD to rule out vasospasm and DCI.

In these cases, other auxiliary methods that can be employed are the CT angiography (CTA) and CT perfusion. The CTA has excellent accuracy (98–100%) for severe vasospasm (narrowing>50%) when compared to digital subtraction angiography (DSA) but loses sensitivity in mild to moderate vasospasm (57–85%). CT perfusion complements CT angiography demonstrating perfusion abnormalities, even in the absence of proximal vasospasm. Three parameters are calculated, which, if considered together, can guide the treatment of vasospasm and DCI in critically ill patients:

- Mean transit time (MTT) is the average length of transit time for blood that is located in particular area of the brain. It is defined in seconds.
- Cerebral blood volume (CBV) is the whole blood volume that stays in a certain volume of the brain, which is usually measured in ml/100 g.
- Cerebral blood flow (CBF) is the volume of blood that flows in a certain volume of the brain, which is usually measured in ml/100 g/min.

Table 29.3 Variables to be observed on CT perfusion and treatment to be adopted

MTT	CBV	CBF	Meaning	Treatment
↑	↔ or ↑	↔	Perfusion abnormality adequately compensated by cerebral autoregulation	Close observation
↑	↔ or ↑	↓	Perfusion abnormality with reversible cerebral ischemia (penumbra)	Hypertensive and/or endovascular
↑	↓	↓	Perfusion abnormality with irreversible cerebral ischemia	Not indicated

The MTT is the most sensitive parameter for DCI and vasospasm and should be the first to be evaluated when analyzing the CT perfusion. Increase in MTT demands strict observation of CBV and CBF (Table 29.3) [18]. MRI with diffusion and perfusion sequences is also a good alternative but more expensive, time-consuming, and less available. Although DSA is still defined as a gold standard auxiliary method for diagnosis of vasospasm, its use must be reserved when endovascular treatment of DCI is considered.

29.5 Treatment

Once the diagnosis of DCI is confirmed, appropriate therapy should be started promptly. Classically, the first-line treatment has been the triple-H treatment which includes hypertension, hemodilution, and hypervolemia. Initial goal should be to raise the mean arterial pressure (MAP) by 20% from baseline. If this measure fails, sequential increases of 10% are induced until clinical response is achieved (with a limit of 220 mmHg and 120 mmHg for systolic and diastolic blood pressure, respectively). During this hypertensive therapy, close monitoring of cardiac function is necessary, especially in elderly or high Hunt-Hess grade patients, because they are at greater risk of cardiomyopathy related to aSAH. If, after 6–12 h of triple-H therapy, there is no clinical improvement, then endovascular therapy is indicated.

Recently, the utility of each component from triple-H treatment has been evaluated. Of the three components, the more beneficial one is hypertension, which acts in increasing oxygenation and CBF. Hypervolemia and hemodilution may increase the CBF but have been associated with decreased cerebral tissue oxygenation (PtiO2) [19, 20]. This effect seems to be associated with a decrease in Hb levels caused by hemodilution. During triple-H therapy, hemoglobin concentration should be monitored and should not fall below 9–10 g/dl. In critically ill patients, ideally PtiO2 should be monitored.

Once indicated, endovascular therapy should be performed as soon as possible. Balloon angioplasty is the preferred method and should be used whenever feasible. Usually it is reserved for proximal vasospasm, including supraclinoid ICA, proximal ACA (mainly A1), proximal MCA (M1, M2), vertebral artery (VA), basilar artery (BA), and proximal PCA (P1, P2). Early angiographic studies (baseline) must be assessed before proceeding with angioplasty in order to avoid dilatation of a hypoplastic vessel. Angioplasty at the location of recent clipping of a ruptured aneurysm is not safe and carries high risk of vessel rupture [21]. Intra-arterial infusion of vasodilators (papaverine, milrinone, or, preferably, nimodipine which is a calcium channel blockers) has a modest and ephemeral benefit and should be used in conjunction with balloon angioplasty or in the case of distal vasospasm, in which case angioplasty is not feasible.

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