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Imaging Predictors of Vasospasm and Delayed Cerebral Ischaemia After Subarachnoid Haemorrhage

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Abstract

Purpose of Review Acute spontaneous subarachnoid haemorrhage (SAH) is a severe disease, frequently complicated by vasospasm and delayed cerebral ischaemia (DCI), which have a negative impact on prognosis. Imaging studies are essential in the diagnosis of SAH. In this article, we review the available imaging techniques for prediction, monitoring and diagnosis of these complications of SAH.

Recent Findings Non-contrast computed tomography (CT) and transcranial Doppler (TCD) have been so far the mainly used techniques to evaluate SAH patients during the acute stage of disease and to screen for vasospasm and DCI. However, there have been new developments of brain imaging techniques, with the introduction of automated methods to quantify blood volume and cerebral flow velocities, and the use of perfusion studies that could contribute to predict or diagnose such complications. Magnetic resonance (MR) imaging studies are proving useful to evaluate early brain injury and to diagnose DCI. Newer angiography suites have sophisticated post-processing tools that quantify cerebral haemodynamics in SAH and may provide important clues for the diagnosis of vasospasm.

Summary Imaging studies are part of the standard management of patients with acute SAH. Blood quantification on CT and the evaluation of cerebral flow velocities on TCD are known to predict and monitor the occurrence of vasospasm. DCI has increasingly been recognized as the most clinically relevant complication of SAH but also the most difficult to predict. MR imaging is the most sensitive tool to diagnose DCI. Future developments in imaging are needed to predict this important complication and help to improve the prognosis of patients with SAH.

Introduction

Spontaneous (non-traumatic) subarachnoid haemorrhage (SAH) is responsible for approximately 5% of strokes, with an incidence of 7.2–10.5 per 100,000 person-years [1, 2]. It is most frequently caused by a ruptured intracranial aneurysm and carries high morbidity and mortality [3••]. Aneurysmal SAH is associated with significant pre-hospital mortality (reaching 50% in some series) and overall mortality of 18–67% [4, 5]. Complications of aneurysmal SAH such as vasospasm and delayed cerebral ischaemia (DCI) contribute for this elevated mortality and poor clinical outcome.

Vasospasm is defined as a narrowing of cerebral vessels, caused by contraction and hyperplasia of the muscular layer, not attributable to atherosclerosis or vessel hypoplasia, and can be diagnosed in angiographic imaging studies, such as digital subtraction angiography (DSA) [6, 7]. Angiographic vasospasm develops in up to 70% of patients after SAH, occurring most frequently at 6 to 8 days after aneurysm rupture and extending up to 14–21 days [8, 9]. The reduction of arterial diameter is thought to reduce cerebral perfusion and cause ischaemia. Microvascular spasm has also been described following aneurysmal SAH, and is not easily identified with current imaging techniques [10••].

DCI is defined as the development of a neurological deficit and/or the presence of ischaemic lesions on imaging studies, not immediately present after SAH, not related to treatment of the aneurysm, and not attributable to other causes [6, 7]. DCI occurs in about 30% of patients and is associated with worse clinical and cognitive prognosis [6]. The pathophysiology of DCI is multifactorial, and arterial vasospasm is only one of the contributors [10]. Angiographic vasospasm is not invariably associated with ischaemia, and cerebral infarction may originate in territories unaffected by vasospasm [11]. Therefore, monitoring the appearance of vasospasm exclusively would address only part of the problem. Nonetheless, prediction of both vasospasm and DCI is challenging and has been the focus of several studies, in an effort for improving the outcome of SAH patients.

Thanks to the development of new techniques and improvement of current imaging modalities, imaging studies play a growing role in prediction and diagnosis of these complications and in the management of SAH patients. This review focused on different imaging modalities and their role in predicting and assessing vasospasm and DCI.

Early imaging predictors of vasospasm and DCI

Computed tomography

Computed tomography (CT) is the first imaging study used for the diagnosis of acute SAH. CT is a widely available technique, with short scanning times and possibility of sequential complementary angiographic evaluation with CT angiography (CTA), allowing for swift diagnosis and treatment decisions. In the first 6 h after SAH, the diagnostic sensitivity of non-contrast brain CT scan is approximately 100% [12]. CTA has shown a sensitivity of approximately 98% in identifying intracranial aneurysms, and when combined, CT and CTA can

diagnose aneurysmal SAH with greater than 99% sensitivity [13]. In addition to diagnosing SAH and screening the presence of aneurysm, initial imaging can provide some clues to predict the development of vasospasm and DCI (Table 1).

Quantification of cisternal blood is an important prognostic tool, and several scales have been developed for this purpose (Table 2). The widely used Fisher scale [18] and modified Fisher scale [14], as well as the more complex Hijdra scale [48], correlate the amount of blood and presence of intraventricular haemorrhage (IVH) to the risk of vasospasm, DCI and clinical outcome (Fig. 1) [14, 15, 18, 22, 23•, 48]. Of these rater-dependent scales, the Hijdra scale has proven to have the best inter-observer agreement [49]. The presence of IVH appears to be particularly relevant in predicting clinical vasospasm/DCI and outcome. Studies have shown that the combination of IVH and SAH is associated with worst outcome compared to IVH or SAH alone [19, 24, 50]. Semi-quantitative scores for IVH measurement exist, such as the Graeb score [51] and the modified Graeb score [52]. The latter has been shown to hold similar discrimination for DCI when compared to the modified Fisher scale, and, interestingly, combining these two scales in a dichotomized scale seems to improve prediction of DCI [25]. The presence of ICH is also an important predictor of DCI and unfavourable outcome [26, 53]. Acute hydrocephalus diagnosed in acute imaging has also been shown to associate to angiographic vasospasm and to negatively influence outcome [30, 54••].

The density of subarachnoid haemorrhage on initial imaging, as measured by the Hounsfield unit (HU) value of the haemorrhage, has been postulated to predict symptomatic vasospasm [27]. A recent study found that the HU value of blood in the inter-peduncular cistern in aneurysmal SAH patients significantly correlated with the incidence of symptomatic vasospasm [28]. New developments in quantification of cisternal blood include automatic volume quantification of total blood volume (TBV), calculated from admission CT. TBV automatic quantification has the advantage of being rater-independent and has been shown to predict DCI [16, 19].

Cerebral perfusion studies

Cerebral perfusion is reduced in the acute stage of SAH, especially in patients with poor clinical grade at admission [55–57], and a few studies have addressed the ability of admission CT perfusion to predict complications. Studies on the value of early CT perfusion (within 72 h from SAH) to predict vasospasm or DCI have shown inconsistent results, including large variability in perfusion thresholds. Etminan et al. [34] showed that an early mean transit time (MTT) > 4,2 s combined with SAH clot volume > 50 mL increased the risk for cerebral infarctions and poor outcome, but showed no association with vasospasm. Sanelli et al. [35] found threshold values of MTT 5,5 s and CBF 24 mL/100 g/min to predict vasospasm. In a study where CT perfusion was performed at < 48 h after SAH, significantly higher mean MTT values and lower mean cerebral blood flow (CBF) values were found in patients that later developed vasospasm [20]. Some authors found a significant association between lower CBF values and longer MTT with DCI [32, 35–37]. Lagares and colleagues [36] found an MTT value > 5,9 s to have a positive predictive value (PPV) of 100% for DCI and to be associated to a 20-fold risk increase of poor outcome. Dong

Table 1. Early (< 72 h) imaging predictors of vasospasm and/or delayed cerebral ischaemia

Imaging modality	Finding	Source of evidence type of studies	Advantages	Disadvantages
CT	Quantification of cisternal blood	Prospective [14–17] Retrospective [18–21] Meta-analysis [22, 23•]	Cost-effective; widely available; short scanning times; possibility of sequential angiographic evaluation	Ionizing radiation; lower sensitivity in parenchymal evaluation
	Presence of IVH	Prospective [24, 25] Retrospective [19]		
	Presence of ICH	Retrospective [26]		
	HU value of SAH	Prospective [27] Retrospective [28]		
	CSF volume	Retrospective [29]		
	Acute hydrocephalus	Retrospective [30]		
	Early brain edema (SEBES)	Prospective [31]		
Perfusion studies (CT or MRI)	Lower CBV and CBF and longer MTT, TTP (several different thresholds)	Prospective [32, 33] Retrospective [20, 34–37]	Short increase in scanning time; non-invasive	Conflicting data; lack of uniformization of post-processing parameters between different scanners and institutions; difficult interpretation; need for contrast (renal insufficiency, allergic reaction); exposure to ionizing radiation with CT perfusion
	TTD > 4,93 s TTS > 0,94 s	Prospective [32]		
	Tmax > 2,24 s	Prospective [33]		
DSA	Colour-coded DSA images, increased microvascular transit time	Prospective [38••] Retrospective [39]	Gold standard in detection and characterization of aneurysms and vasospasm; possibility for endovascular therapies	Invasive exam; exposure to ionizing radiation; complications (femoral hematoma, TIA/stroke)
	Ultra-early angiographic vasospasm	Prospective [40–42]		
MRI	Acute ischaemic lesions (DWI), changes in white matter integrity (DTI), global cerebral edema, vasogenic edema in normal-appearing white matter	Prospective [43••, 44, 45] Retrospective [46, 47]	Superior in evaluation of parenchymal lesions; greater sensitivity in detection of early ischaemic lesions	Less available in the emergency setting; longer imaging acquisition times; logistical challenge in severely ill patients; metallic implants contraindicated

CT computed tomography; *IVH* intraventricular haemorrhage; *ICH* intracerebral haemorrhage; *HU* Hounsfeld unit; *SAH* subarachnoid haemorrhage; *CSF* cerebrospinal fluid; *MRI* magnetic resonance imaging; *CBV* cerebral blood volume; *CBF* cerebral blood flow; *MTT* mean transit time; *TTP* time to peak; *TTD* time to drain; *Tmax* time to maximum residue; *DSA* digital subtraction angiography; *DWI* diffusion-weighted imaging; *DTI* diffusion tensor imaging; *TIA* transient ischaemic attack

Table 2. Scales for quantification of blood on admission CT after aneurysmal SAH

Fisher scale [18]	Modified Fisher scale [14]	Hijdra scale [48]
Grade 1: no SAH detected	Grade 0: no SAH or IVH	Cisternal Hijdra (range = 0–30)
Grade 2: diffuse thin (< 1 mm) SAH	Grade 1: focal/diffuse thin (< 1 mm) SAH, no IVH	No blood = 0 Small amount = 1
Grade 3: localized clot/thick (> 1 mm) SAH	Grade 2: focal/diffuse thin (< 1 mm) SAH, and IVH	Moderately filled = 2 Completely filled = 3
Grade 4: diffuse SAH and IVH and/or ICH	Grade 3: focal/diffuse thick (> 1 mm) SAH, no IVH	Ventricular Hijdra (range = 0–12)
	Grade 4: focal/diffuse thick (> 1 mm) SAH, and IVH	No blood = 0 Sedimentation = 1
		Partly filled = 2 Completely filled = 3

For Hijdra score calculation, ten basal cisterns (anterior interhemispheric fissure, lateral sylvian fissure, basal sylvian fissure, suprasellar cistern, ambient cistern and quadrigeminal cistern) and the four ventricles are considered
IVH intraventricular haemorrhage; *ICH* intracerebral haemorrhage

et al. in a large prospective study used whole-brain CT perfusion, and found early reduction of perfusion, in all parameters in patients that later developed DCI, specifically a time-to-maximum (Tmax) cut-off value of 2.24 s for early prediction of DCI at admission [33]. Recently, Malinova and colleagues [32] proposed CBF < 53,93 mL/100 g/min, CBV < 3,14 mL/100 mL, MTT > 4,25 s, time to peak (TTP) > 9,28 s and time to drain (TTD) > 4,93 s as threshold values for prediction of DCI. However, despite all available studies, data on the role of brain perfusion at early stage of SAH are conflicting [58–62], and the evaluation of perfusion is still not validated for the initial assessment of SAH patients, as a tool for prediction of vasospasm or DCI.

Digital subtraction angiography

DSA is routinely performed in acute SAH patients and is the gold standard technique for the detection of intracranial aneurysms. Since most patients perform DSA at admission, it would be tempting to identify predictors of vasospasm and DCI using this technique. A recently developed post-processing software, parametric colour coding, allows the evaluation of haemodynamic flow data from DSA acquisitions. Since then, some studies have analysed whether early haemodynamic changes detected on colour-coded DSA in the setting of aneurysmal SAH may be predictive of vasospasm or DCI. Burkhardt et al. found that patients developing vasospasm, either symptomatic or asymptomatic, had increased arterial flow velocities in the initial DSA [38••]. This increase in flow velocity may be due to vessel diameter reduction, increase in arterial blood pressure or both. Either way, these findings may represent early angiographic predictors of vasospasm and DCI and help identify patients at greater risk for these complications. An advantage of colour-coded DSA is the evaluation of microcirculatory changes, allowed by the higher temporal and spatial resolution of newer angiography suites. Gölitz et al. calculated cerebral circulation time, cortical relative time to peak and microvascular transit time (TT) in aneurysmal SAH patients [39]. The mean microvascular TT was significantly

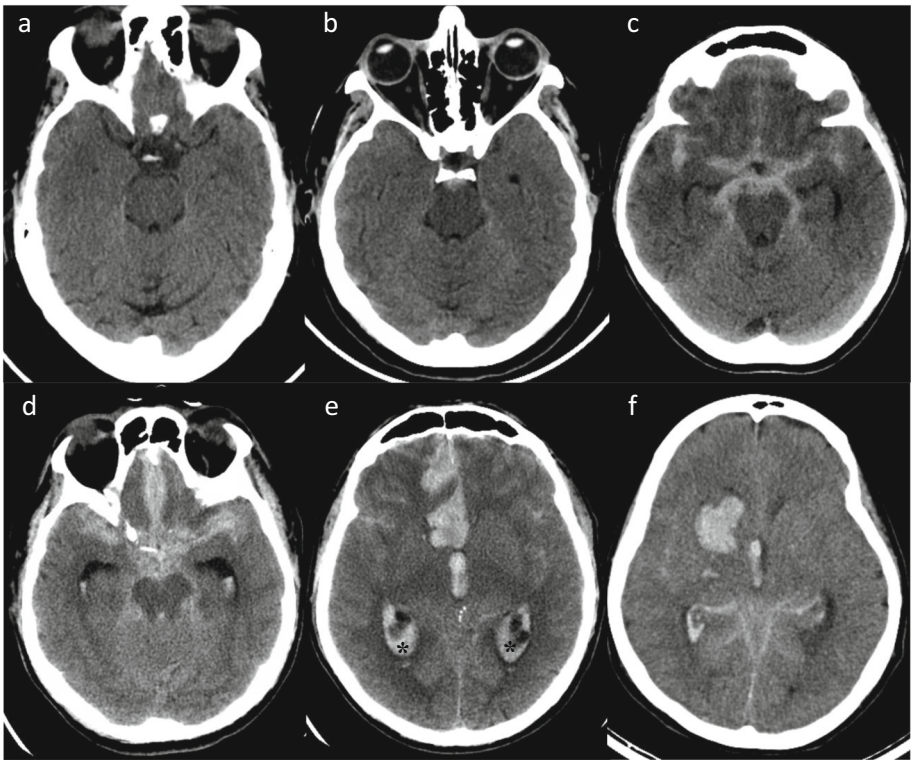

Fig. 1. Admission non-contrast CT scan of acute spontaneous SAH in five different patients, illustrating different grades of the Fisher scale: **a** Grade 1 in a patient with a ruptured P1 segment PCA aneurysm. **b** Grade 2 in a patient with a perimesencephalic haemorrhage. **c** Grade 3 in a patient with a ruptured right MCA aneurysm. **d** Grade 4 in a patient with ruptured anterior communicating aneurysm, with small amount of intraventricular blood. **e** Grade 4 in a patient with a ruptured anterior communicating artery aneurysm showing frontal hematoma and blood casts in both atria (*). **f** Grade 4 with IVH and ICH in a patient with a ruptured terminal segment right ICA aneurysm, showing a large intraparenchymal hematoma.

longer in patients that later had DCI, possibly indicating an early onset of microcirculatory injury in these patients. A threshold value of 2.69 s was suggested to predict development of DCI, with a sensitivity of 71%, but a specificity of only 54%. Angiographic vasospasm occurring within 48 h of aneurysmal rupture, known as ultra-early angiographic vasospasm, occurs in 4.6–13% of patients and is associated with increased risk of DCI and worse clinical outcome [40–42].

Early brain injury: a new marker?

Increasing attention has been drawn to early brain injury (EBI), defined as parenchymal insult occurring in the first 72 h after SAH [10••, 63, 64], thought to contribute to the later occurrence of DCI. Pathophysiological mechanisms of EBI are complex and still not fully understood. A recently developed score, the "Subarachnoid Haemorrhage Early Brain Edema Score" (SEBES) [31], includes early CT changes such as sulci effacement and disruption of the grey-white matter junction on admission CT, as markers of early brain injury, that predict DCI and unfavourable outcome and associate with the occurrence of vasospasm. In line with its superiority in evaluating brain lesions, MRI is the preferred imaging

technique to detect early parenchymal changes. Early acute ischaemic lesions on diffusion-weighted imaging (DWI), changes in white matter integrity measured with diffusion tensor imaging, global cerebral edema or vasogenic edema in normal-appearing white matter [43••, 44, 46, 65, 66] can be associated with the development of DCI in the course of SAH [43••, 45–47, 66].

Combined predictors

Imaging parameters can be used as independent predictors of vasospasm and DCI, or they can be combined with clinical parameters to increase specificity and sensitivity. The VASOGRADE scale is a simple 3-category grading scale that can predict the risk of DCI, based on combining the modified Fisher scale and the World Federation of Neurosurgical Societies (WFNS) scale [67]. The HAIR score allows risk stratification for in-hospital mortality and is based on the four variables that name it: Hunt and Hess score, age, IVH and re-bleed [68]. One other recent study proposed an early score for DCI prediction that included 4 variables: WFNS scale, modified Fisher scale, SEBES and intraventricular haemorrhage [69]. Although VASOGRADE scale and HAIR score did not show to be superior to clinical evaluation in prediction of cerebral infarction and unfavourable outcome [70], they are superior to radiological scales alone [71].

In summary, the initial imaging evaluation of SAH patients provides potential predictors of vasospasm and DCI. The amount of subarachnoid blood on non-enhanced CT has the most robust evidence as a predictor of vasospasm and DCI. However, newer approaches, such as automatic measurement of subarachnoid blood volume, and colour-coding post-processing of DSA images might help identify patients that will develop vasospasm and DCI. Early perfusion imaging has shown to predict vasospasm and DCI, but is not reproducible across studies. MRI is still not routinely performed upon admission in SAH patients; however, it is the most sensitive imaging technique for diagnosis of early brain injury and could be an early tool for predicting DCI. Combined use of clinical and imaging parameters might increase sensitivity and specificity in the prediction of these complications.

Diagnosis and monitoring of vasospasm

Delayed vasospasm is a well-established complication of aneurysmal SAH occurring in about 70% of patients, most often 6 to 8 days after aneurysm rupture [8, 9]. About a third of patients will develop symptoms from vasospasm and eventually ischaemic lesions. Screening of vasospasm is a standard current practice in SAH, essential for correct management, especially in patients in poor neurological grade that cannot be evaluated clinically. Vasospasm is potentially reversible, both pharmacologically and by endovascular techniques. Several techniques for diagnosis and monitoring of vasospasm have been studied, and their main advantages and disadvantages are summarized in Table 3.

Digital subtraction angiography

At the present time, DSA still remains the gold standard for diagnosis of radiographic vasospasm, additionally allowing for endovascular treatment. Nonetheless, as an invasive technique which brings additional risks, requiring

Table 3. Imaging modalities in diagnosis and monitoring of vasospasm

Imaging modality	Finding	Source of evidence type of studies	Advantages	Disadvantages
DSA	Reduced vessel diameter, delay in transit time in colour-coded DSA images	Prospective [38••] Retrospective [39, 72]	Gold standard in diagnosis of vasospasm; possibility for endovascular treatment	Invasive technique; radiation exposure; contrast administration; costly, less available; requiring an angiography suite and experienced operators
TCD	Mean flow velocity Lindegaard ratio, Sviri ratio, intracranial arteriovenous index Image-guided TCD TCD automated analysis	Meta-analysis [73] Prospective [74, 75] Retrospective [76] Prospective [77] Retrospective [78]	Non-invasive; widely available; inexpensive; portable/bedside technique; repeatable; no ionizing radiation	Operator-dependent; time-consuming; suboptimal insonation windows; only proximal segments of large intracranial arteries are studied
CTA	Reduced vessel diameter Vessel volumetric analyses	Meta-analysis [79] Retrospective [80, 81]	Fast, inexpensive; widely available; non-invasive; can be performed immediately following non-contrast CT	Ionizing radiation; contrast injection; beam hardening artefacts from vascular clips or endovascular coils; requires transportation to CT scan; moderate inter-rater reliability
MRI	TOF MRA Black-blood MRA Vessel wall imaging	Prospective [82, 83] Retrospective [84] Retrospective [85] Prospective [86]	Assessment of tissue viability; no radiation exposure; possibility of no contrast administration	Less accurate compared to DSA; less available; longer scanning times; difficult in severely ill patients
CT perfusion	Lower CBF, increased MTT Parameters with low-dose CT Perfusion	Prospective [55, 87–90] Retrospective [91–94] Meta-analysis [79] Retrospective [95]	Qualitative and quantitative analyses of cerebral haemodynamics; rapid, widely available; non-invasive	Operator-dependent; post-processing required; not externally validated; ionizing radiation exposure; contrast administration
MR perfusion	DWI-PWI mismatch	Prospective [96] Retrospective [97, 98]	Assessment of tissue viability; no radiation exposure; possibility of no contrast administration	Less available; longer scanning times; logistic challenge in severely ill patients

DSA digital subtraction angiography; *TCD* transcranial Doppler; *CTA* computed tomography angiography; *MRI* magnetic resonance imaging; *TOF* time-of-flight; *MRA* magnetic resonance angiography; *CBF* cerebral blood flow; *MTT* mean transit time; *DWI* diffusion-weighted imaging; *PWI* perfusion-weighted imaging

radiation exposure and contrast, DSA is not used as a monitoring technique but is rather performed following clinical or TCD suspicion of vasospasm [72]. Newer developments, such as colour-coded DSA, described in the previous

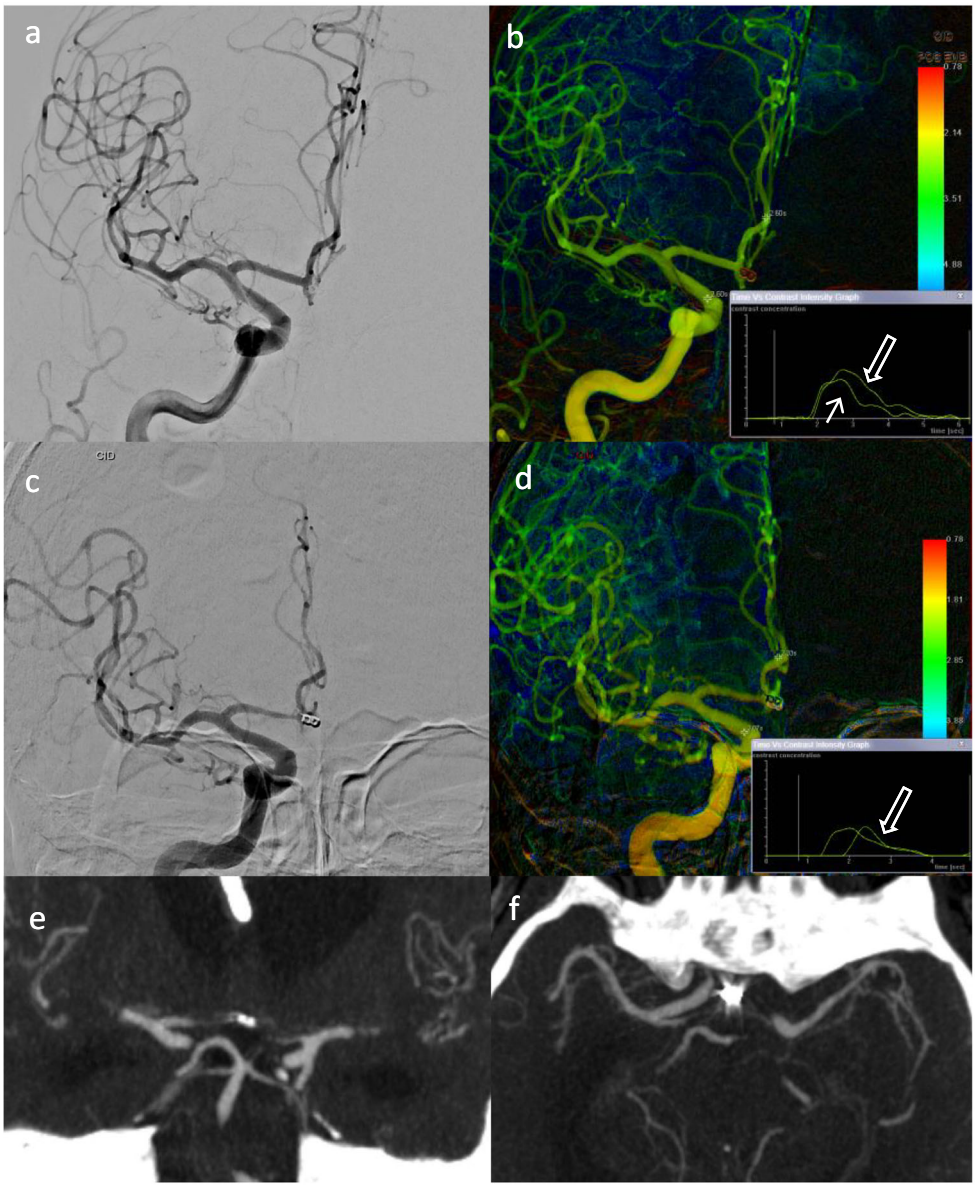

Fig. 2. Thirty-six-year-old patient with a ruptured anterior communicating artery aneurysm. Admission DSA showed normal diameter of the arteries (**a,** right internal carotid artery injection, AP view). Colour-coded DSA images (**b**) show no delay in transit time between ICA and A1 at post-embolization period, as demonstrated by the time-contrast concentration curves with similar times measured in the internal carotid artery (white arrow) and in the A2 segment of the anterior cerebral artery (open arrow). At 15 days, moderate vasospasm of the A1 and A2 segments of the anterior cerebral artery are noted on DSA (**c**), with corresponding delay of contrast arrival at the A2 segment on the colour coded DSA images (open arrow) (**d**). A CTA performed on the same day (**e**, coronal; **f**, axial MIP reconstructions) showed similar vasospasm in the A1 segments bilaterally. Note how the presence of metallic artefacts originated from the aneurysmal coils impairs correct assessment of adjacent arteries (f)

section, allow the evaluation of microcirculatory changes secondary to vasospasm (Fig. 2).

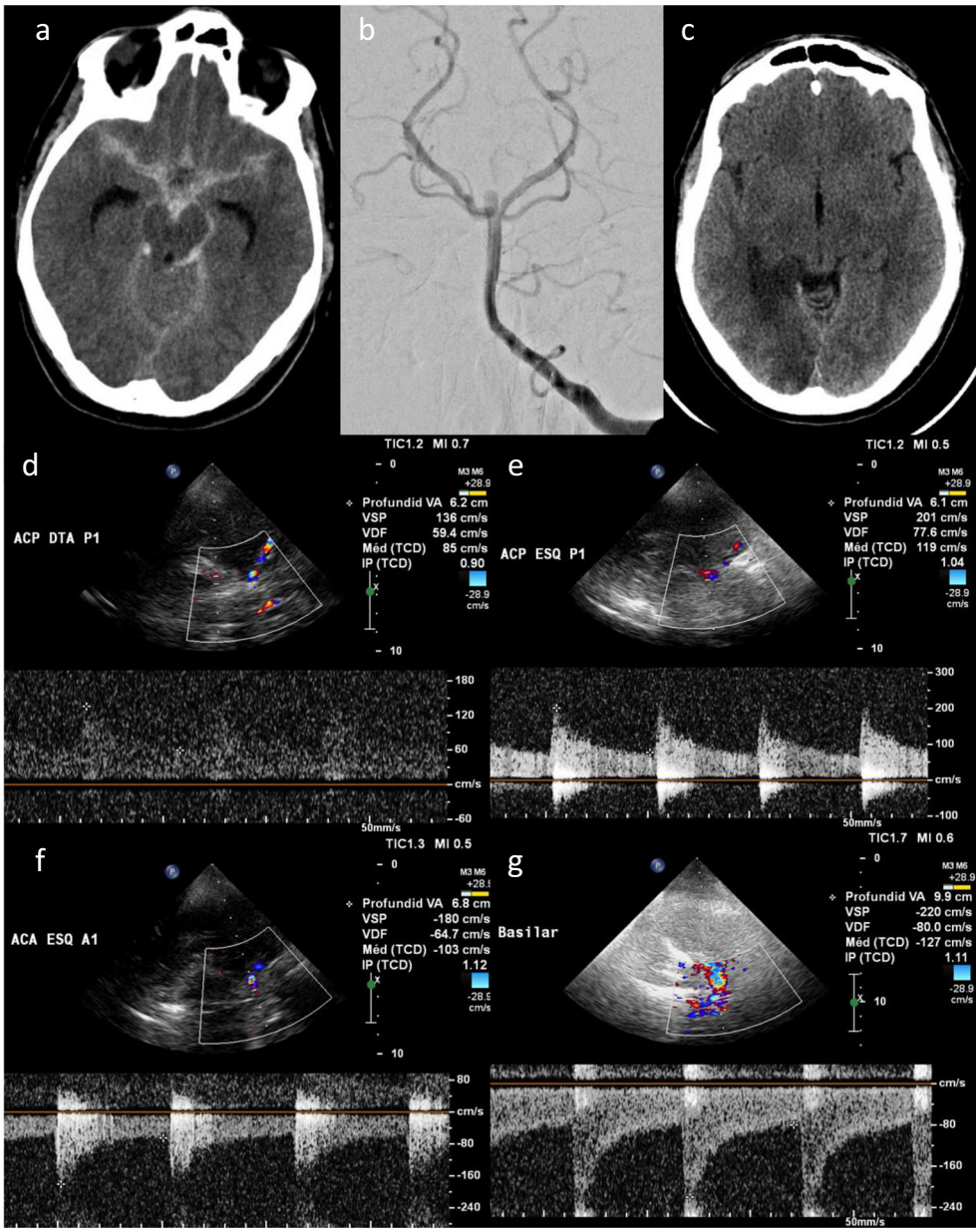

Fig. 3. Thirty-nine-year-old male with a ruptured basilar tip aneurysm that later developed vasospasm and cerebral infarct. CT scan at admission showed a diffuse modified Fisher grade 3 SAH (**a**), and DSA performed at admission (**b**) showed normal diameter vessels and a basilar tip aneurysm. CT scan repeated at day 7 post-SAH (**c**) shows an acute ischaemic infarct on the right PCA vascular territory. Same day TCD study shows increased mFV of the right PCA P1 segment (**d**), 85 cm/s, left PCA P1 segment (**e**), 119 cm/s, left ACA A1 segment (**f**), 103 cm/s, and basilar artery (**g**), 127 cm/s, suggestive of moderate vasospasm of the PCA P1 segments and left ACA A1 segments, and moderate to severe vasospasm of the basilar artery

Transcranial Doppler

Transcranial Doppler (TCD) allows dynamic monitoring of CBF velocity and pulsatility indexes (Fig. 3). Current American Heart Association's guidelines for the management aneurysmal SAH indicate TCD as a reasonable tool for vasospasm monitoring (class IIa, level B evidence) [3••]. In addition to mean flow velocity (mFV), the use of indices, such as Lindegaard ratio for MCA vasospasm and the Sviri ratio for basilar artery vasospasm, helps to distinguish increased velocities due to haemodynamic factors from vasospasm (velocity adjustment by calculating a ratio with the ipsilateral ICA and both the vertebral arteries, respectively) [74, 76]. A new intracranial arteriovenous index (AVI) between flow velocity in the MCA and the basal vein of Rosenthal has been proposed, with slightly higher reliability for differentiating vasospasm and hyperperfusion [75].

Over the years, several mFV threshold values for development of vasospasm have been proposed, either regarding a relative increase of mFV (increase of 20–50 cm/s) or absolute mFV values (> 120–200 cm/s) [99•, 100]. In 2001, a meta-analysis showed that TCD had higher specificity (99%) and sensitivity (67%) for MCA vasospasm, as compared to other arteries, with a positive predictive value (PPV) of 97% and a negative predictive value (NPV) of 78%, when compared to DSA [73]. In 2004, a consensus statement supported that, for MCA vasospasm, TCD is a reliable predictor for the absence of angiographic vasospasm at mFV < 120 cm/s and for the presence of angiographic vasospasm at mFV > 200 cm/s [101].

There have been recent advances in TCD: image-guided TCD and TCD automated analysis. Neulen et al. demonstrated the feasibility of image-guided TCD, in which the ideal ultrasonic bone window regions and ultrasonic trajectories were obtained from CTA images and uploaded on a hand-held image-guided device [77] Although time-consuming, image-guided TCD was feasible in aneurysmal SAH patients, with high spatial accuracy and inter-observer reproducibility. In order to facilitate continuous TCD-monitoring protocols, an automated algorithm for detection of vasospasm based on TCD audio signal analysis was developed, with promising results [78].

Non-invasive angiographic studies

CTA is a fast and widely available non-invasive angiographic imaging modality. It is considered fairly accurate for detection of radiographic proximal vasospasm, with a reported sensitivity of 80% and specificity of 93% [79]. Despite this, there is concern regarding its value to help guide clinical management, as it has only moderate inter-rater reproducibility [102]. Recent areas of research include volumetric analysis of the intracranial vessels, in which vessel volume of a given arterial segment could be used as an objective parameter for identification of vasospasm requiring endovascular treatment, as addressed in two pilot studies [80, 81].

Although MR is not a routine imaging study in acute SAH, the various modalities of magnetic resonance angiography (MRA) can diagnose proximal vasospasm, although less accurately than DSA [82–84]. Recently developed black-blood MR angiography (BBMRA) utilizes a non-T1-weighted contrast spin-echo sequence. A small retrospective study by Takano et al. showed

superior accuracy of BBMRA when compared to TOF-MRA and high sensitivity and specificity in detection of vasospasm when compared to CTA or DSA [85]. Also recently described is the association between intracranial MR vessel wall enhancement and the development of angiographic vasospasm in ruptured aneurysm patients [86]. Although larger studies are necessary, newer vessel wall imaging sequences may be promising in the evaluation of vasospasm.

Perfusion studies

CT perfusion studies can assess perfusion deficits secondary to vasospasm, manifested by increased MTT and reduced CBF [55, 87–93]. A high degree of agreement between CT perfusion and DSA has been documented [94], and a meta-analysis showed a sensitivity of 74,1% and specificity of 93% of CT perfusion for the diagnosis of vasospasm [79]. Various studies found MTT to be the most sensitive parameter [88–91, 93]. MTT threshold values of 4,6–6,4 s [88, 93] and a CBF value of 44,3 mL/100 g/min [93] have been described. However, because of equipment and post-processing software differences between centres, validation of these values is challenging and should be interpreted with caution. Some authors have suggested a combined CTA and CT perfusion approach as the preferred method in the diagnosis of vasospasm [103, 104]. MR perfusion studies in SAH have mainly addressed prediction or early detection of DCI, with very few having focused on prediction or diagnosis of vasospasm. Combination of DWI and perfusion-weighted imaging (PWI) in patients with vasospasm enabled the detection of small regions of early ischaemic injury within larger regions of abnormal relative CBF and MTT, compatible with vascular supply regions of vessels with angiographically demonstrated vasospasm [97] (Fig. 4). Diffusion-perfusion mismatch, translated by elevated MTT and no signs of parenchymal ischaemia on DWI, has also been suggested for early identification of vasospasm and prediction of its evolution to ischaemia [96, 98].

In summary, TCD is still the preferred technique for screening the appearance of vasospasm. Although operator-dependent, it is a non-invasive, widely available bedside technique that can effectively detect and monitor cerebral artery vasospasm, with a high positive predictive value. Image-guided TCD and TCD automated analysis are being developed and seem promising for improving monitoring accuracy and facilitate its implementation on critical care units.

Prediction and diagnosis of DCI

Delayed cerebral ischaemia is the end result of a complex cascade of events after SAH that include early brain injury (that results from microvascular changes, coagulation dysfunction, cortical spreading depression, activation of inflammatory mediators) and delayed vasospasm [10••]. Although DCI negatively influences patient prognosis, the best method to predict this complication remains uncertain.

Computed tomography and MR imaging

In patients that suffer neurological deterioration after SAH, non-contrast CT is a rapid and widely available technique, allowing the exclusion of hydrocephalus,

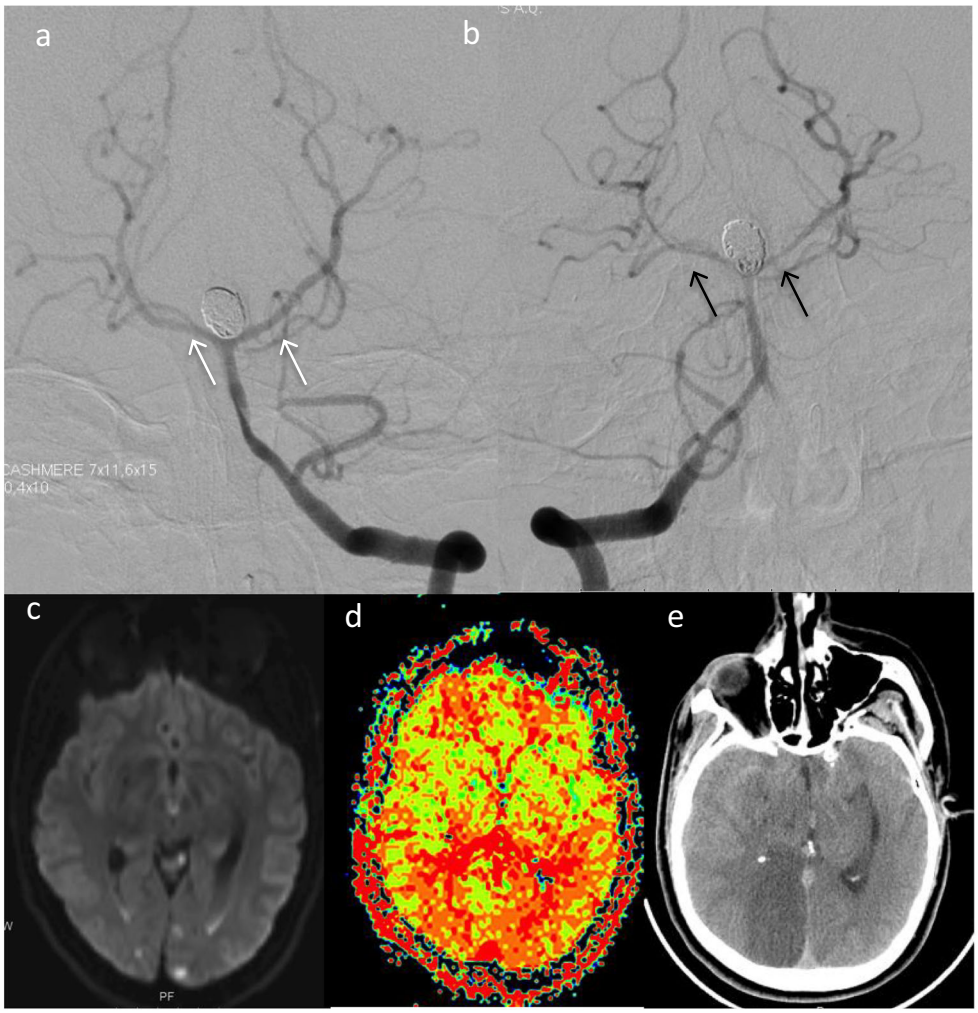

Fig. 4. Forty-one-year-old patient with a ruptured basilar tip aneurysm. **a** DSA at admission, after coiling of the aneurysm. Normal diameter of basilar artery and posterior cerebral arteries (PCA) (white arrows). **b** DSA at day 7 post-SAH, showing reduction of the diameter of the basilar artery and both PCAs (black arrows). MRI performed at day 4 post-SAH showed small acute ischaemic lesions on both PCA territories, on DWI (**c**), and an increase of TTP on the same territory (**d**), reflecting hypoperfusion, with a DWI/PWI mismatch. **e** CT scan at day 10 after SAH, showing an acute ischaemic lesion on the right PCA territory, and global cerebral edema, that progressed despite aggressive treatment of vasospasm.

rebleeding or cerebral edema that may occur in the subacute stages of SAH. CT can diagnose cerebral infarctions related to DCI in up to 35% of patients in the course of SAH (Fig. 3); however, if MR imaging is used, ischaemia can be detected in up to 81% of patients [105](Fig. 5). Besides clinical and imaging predictors present at admission, there are other possible imaging predictors of DCI during the early phase of SAH and in the period of vasospasm (Table 4).

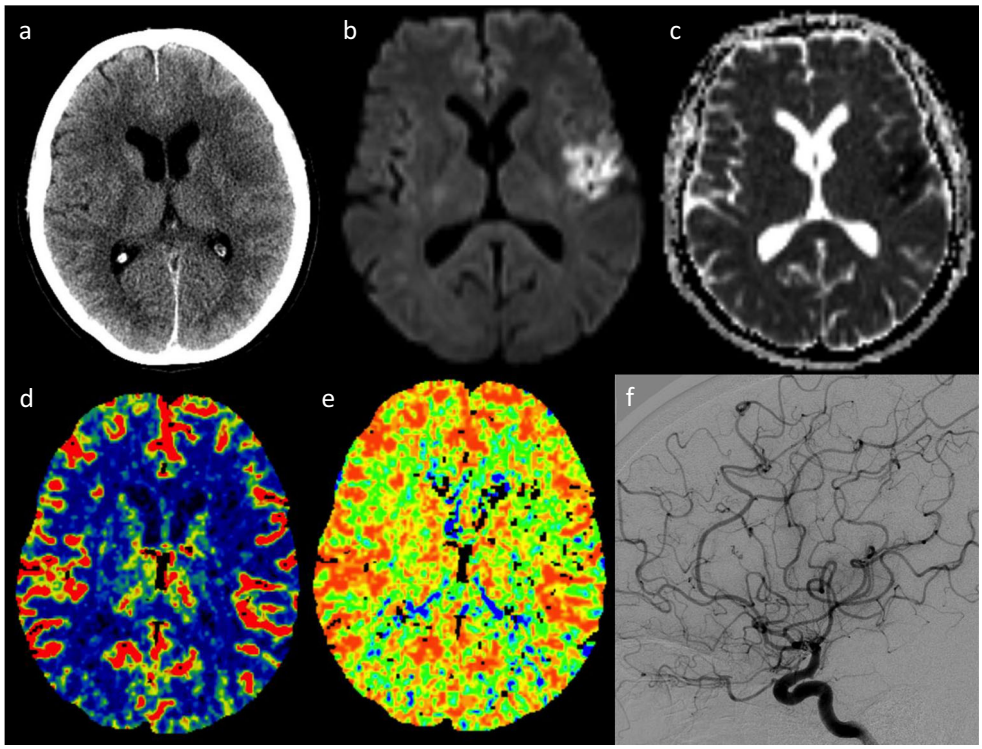

Fig. 5. Fifty-nine-year-old patient with a ruptured communicating artery aneurysm treated with coils. Follow-up CT scan at day 9 after SAH (**a**) shows a very subtle hypoattenuating lesion in the left insular and temporal lobes. Same day MRI, DWI (**b**) and ADC map (**c**), clearly depict the acute cerebral infarct, illustrating the lower sensitivity of CT in diagnosis of acute cerebral ischaemia. CT perfusion performed 2 days earlier showed a very slight decrease in CBF (**d**) in the infarct area and no asymmetry on the MTT map (**e**). DSA performed at day 10 (**f**) shows no signs of angiographic vasospasm.

Transcranial Doppler

TCD is the most used monitoring tool for vasospasm after SAH; however, evidence of the value of TCD in predicting DCI is still conflicting. Meta-analysis found that the diagnosis of moderate/severe vasospasm by TCD (defined by mFV > 120 cm/s) can accurately predict DCI, with high sensitivity and high negative predictive value [106]. However, centres that routinely screened for vasospasm using TCD did not have higher rates of DCI diagnosis compared to non-screening centres [120].

Perfusion studies

Although CT perfusion can detect areas of cerebral hypoperfusion that correlate with arterial vasospasm, there are conflicting results regarding its association with DCI, which again underlines the multifactorial origin of DCI. Several CT perfusion studies have shown significantly lower CBF and CBV values and higher MTT values in patients with DCI, during the vasospasm window period [88, 114, 115]. Two meta-analyses, one including 345 patients [116] and the other including 444 patients [62], confirmed these findings. In the first one, a 23-fold increased probability of DCI was found in patients with CT perfusion changes demonstrating perfusion deficits [116]. Different threshold values have been proposed for diagnosis of DCI at the time window for vasospasm,

Table 4. Prediction and diagnosis of DCI

Imaging modality	Findings	Source of evidence type of studies	Advantages	Disadvantages
TCD	TCD diagnosed vasospasm (mFV > 120 cm/s)	Meta-analysis [106]	Non-invasive; widely available; inexpensive; portable/bedside technique; repeatable; no ionizing radiation	Operator-dependent; time-consuming; suboptimal insonation windows; assessment of cerebral autoregulation or CVR not used in the clinical setting
	Cerebral autoregulation	Prospective [107–109] Retrospective [110]		
	CVR acetazolamide test	Prospective [111]		
	CVR carbon dioxide test	Prospective [112, 113]		
CT perfusion	Lower CBF and CBV and higher MTT values	Prospective [88, 114], Retrospective [115] Meta-analysis [62, 116]	Qualitative and quantitative analysis of cerebral haemodynamics; rapid, widely available; non-invasive	Lack of uniformization of post-processing parameters between different scanners and institutions; difficult interpretation; ionizing radiation; requires contrast administration
Functional MRI (BOLD)	CVR carbon dioxide challenge	Case series [117]		Not used in the clinical setting
Permeability imaging	kTrans, permeability surface product (PS)	Prospective [118, 119]		Not used in the clinical setting

TCD transcranial Doppler; *mFV* mean flow velocity; *CVR* cerebrovascular reactivity; *CBF* cerebral blood flow; *MTT* mean transit time; *CBV* cerebral blood volume; *MRI* magnetic resonance imaging; *BOLD* blood oxygenation level dependent; *kTrans* volume transfer constant

including MTT values of 5,0–5,85 s [88, 114, 115] and CBF values of 30,5–36,3 mL/100 mg/min [114, 115]. The ability of CT perfusion changes to predict DCI appears to be higher during the period of vasospasm, between 4 and 10 days after SAH. MR perfusion imaging is much less used in SAH patients, and therefore, less studies have focused on this technique. Positron emission tomography (PET) studies have also shown that hypoperfused and oligemic areas of the brain frequently occur in regions without vasospasm, and these physiologic parameters might better predict DCI [121].

Future research: autoregulation and permeability

Failure of autoregulatory mechanisms is one possible mechanism in the development of vasospasm and DCI. A few studies have suggested the utility of a transient hyperemic response test (THRT) in the early phase to predict cerebral autoregulation failure and development of clinical vasospasm [107, 108, 110]. This test is based on temporary compression of the common carotid artery while insonating the ipsilateral MCA. Upon decompression, an increase of more than 9% of the baseline systolic velocity is expected, when autoregulation is normal. A negative THRT was associated to development of symptomatic vasospasm and DCI [109]. A reduced cerebrovascular reactivity (CVR) assessed by carbon dioxide or acetazolamide TCD was also associated with DCI [111–113]. In a small pilot study, blood oxygenation level-dependent (BOLD) technique functional MRI measurements of CVR, by means of carbon dioxide challenge, seemed to have good spatial correlation with areas of future ischaemic events, in the context of DCI [117]. Assessment of cerebral autoregulation or CVR is still not used in clinical practice.

Finally, blood-brain barrier (BBB) dysfunction has been implicated as one of the many contributors to DCI. Its assessment by means of permeability imaging (through CT or MR perfusion techniques) might add as a tool for predicting DCI. Two recent studies have found an association between increased BBB permeability and DCI [118, 119]; however, permeability imaging is still not used in the clinical setting.

In summary, although DCI is one of the most important complications of SAH, it is very difficult to predict. TCD, although useful in the diagnosis of vasospasm, has questionable value in predicting DCI. CT perfusion performed during the period of vasospasm might help identify patients that will have DCI. Diagnosis of DCI relies on non-contrast imaging, and MRI is the best technique, with higher sensitivity than the most commonly performed CT studies. Research is ongoing on other techniques, such as the evaluation of autoregulatory mechanisms and BBB dysfunction, and might add as future tools for prediction of this important complication of SAH.

Conclusion

Imaging studies have been traditionally used to diagnose acute spontaneous SAH and to investigate the presence of a ruptured aneurysm. However, imaging studies performed early in the course of SAH also provide clues for prediction of its major complications: vasospasm and DCI. The volume of subarachnoid blood is a strong predictor of both these complications, but recent technical improvements such as automatized quantification of blood

on CT, and colour-coding post-processing of DSA images, have added value in identifying patients that will develop vasospasm and DCI. MRI, still not routinely performed in SAH patients, has the potential to diagnose early brain injury and help predict DCI.

Monitoring of vasospasm is still important in SAH patients, and TCD is still the preferred technique for this purpose in most centres. Patients with suspected symptomatic vasospasm on TCD will undergo DSA, the gold standard technique to confirm vasospasm, offering the possibility of endovascular treatment.

The occurrence of DCI has significant impact on the outcome of patients with SAH; however, and despite extensive research, it is very difficult to predict. Of all imaging methods, CT perfusion performed during the period of vasospasm, at 7–10 days, might help identify patients that will have DCI. However, CT perfusion thresholds are still not validated across centres. Other techniques, such as the evaluation of autoregulatory mechanisms and BBB dysfunction, are under research and might be future tools to help predict of this important complication of SAH. Combining clinical and imaging parameters might increase sensitivity and specificity in the prediction of vasospasm and DCI after SAH.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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