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Review Article

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Imaging predictors of outcome in acute spontaneous subarachnoid hemorrhage: a review of the literature

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Abstract

Spontaneous subarachnoid hemorrhage (SAH) accounts for about 5% of strokes, but has a very high morbidity and mortality. Many survivors are left with important cognitive impairment and are severely incapacitated. Prediction of complications such as vasospasm and delayed cerebral ischemia, and of clinical outcome after SAH, is challenging. Imaging studies are essential in the initial evaluation of SAH patients and are increasingly relevant in assessing for complications and prognosis. In this article, we reviewed the role of imaging studies in evaluating early brain injury and predicting complications as well as clinical and neuropsychological prognosis after acute SAH.

Keywords

Subarachnoid hemorrhage, delayed cerebral ischemia, early brain injury, magnetic resonance imaging, computed tomography, cerebral perfusion, diffusion-weighted imaging, prognosis

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Introduction

Spontaneous subarachnoid hemorrhage (SAH) is caused in most cases by a ruptured intracranial aneurysm and often affects young patients (1,2). Aneurysmal SAH is a serious clinical condition, with pre-hospital mortality reaching 50% and a global mortality in the range of 18–67% (2,3). Survivors are often left with physical or neuropsychological sequelae that prevent the return to normal premorbid life (4,5). Other types of SAH, such as perimesencephalic hemorrhage and non-traumatic convexity SAH, have different origins (venous hemorrhage, amyloid angiopathy, venous thrombosis, vasculitis, reversible cerebral vasoconstriction syndrome [RCVS], drugs) and different clinical courses.

Clinical outcome of patients with aneurysmal SAH is heterogeneous, with some patients promptly recovering completely and others worsening and becoming severely incapacitated, despite optimal medical and surgical treatment. Prediction of outcome in SAH is difficult considering the multifactorial pathogenesis of SAH, and the not yet fully explained mechanisms behind early brain injury (EBI) and delayed cerebral ischemia (DCI), the two main complications of SAH.

Imaging plays a central role throughout the course of this disease and, as in other diseases, has a growing role in predicting prognosis. This review focused on imaging studies and their role in assessing EBI and predicting complications such as DCI and vasospasm, clinical and neurocognitive prognosis after spontaneous SAH.

Initial imaging evaluation of SAH: clues to the prognosis

Computed tomography (CT) is usually the first imaging study performed in SAH. Magnetic resonance imaging (MRI) is the most sensitive imaging study to evaluate cerebral parenchyma, but is not a routine exam in

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SAH, because of less availability, longer scanning times, and logistical issues in severely ill patients.

The hallmark of spontaneous SAH is the presence of hyperdensities in the basal cisterns. Quantification of cisternal blood is important as a prognostic tool (Fig. 1, Table 1). Fisher grade (6) and the Modified Fisher scale (7) are widely used scales that correlate the amount of blood to the risk of vasospasm, DCI and clinical outcome (6–8). The Hijdra scale is a more complex method of quantifying cisternal blood (9, 10), that has been included in some prognostic scales as a predictor of vasospasm, DCI, and clinical outcome (10,11). The presence of a space occupying parenchymal hematoma also negatively influences prognosis, especially in patients with poor-grade SAH (12).

Acute hydrocephalus, affecting around 20% of patients (13), can be diagnosed in admission imaging studies and negatively influences neurological and functional outcome, particularly if associated with intraventricular hemorrhage.

In summary, from the first imaging assessment, we may infer that higher amounts of hemorrhage correlate with increased risk of vasospasm, DCI, and poor outcome. The early identification of patients at higher risk for vasospasm and DCI is clinically relevant, since these patients will need closer monitoring and eventually more aggressive pharmacological and endovascular approaches.

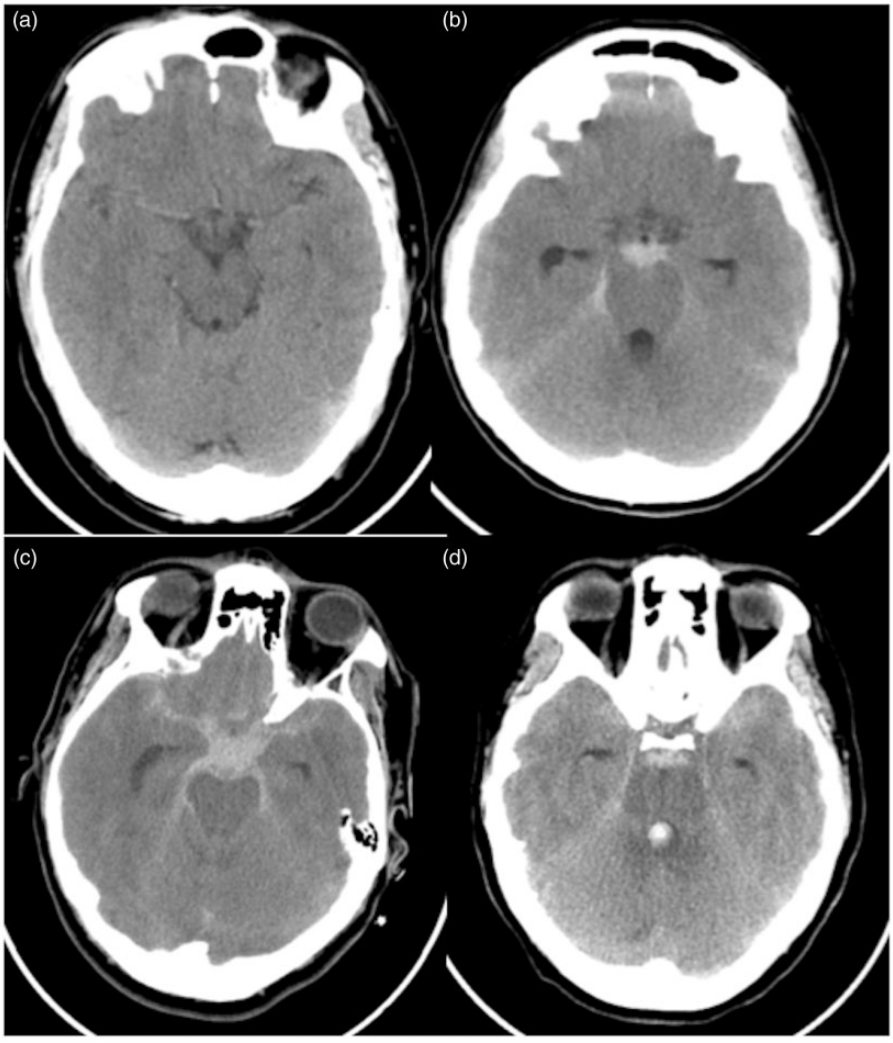

Fig. 1. Non-contrast admission CT scan of acute spontaneous SAH in four different patients, illustrating different Fisher grades: grade 1 (a), grade 2 (b), grade 3 (c) and grade 4 (d). Patient A had a ruptured anterior communicating artery aneurysm. Patient B had a perimesencephalic hemorrhage, and no identifiable aneurysm. Both Patients C and D had basilar aneurysms.

Table 1. Commonly used scales to quantify blood on admission CT after spontaneous SAH.

Fisher scale (6)	Modified Fisher scale (7)	Hijdra score (9)
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 Moderately filled = 2 Completely filled = 3
	Grade 2: focal/diffuse thin (< 1 mm) SAH and IVH	
Grade 3: localized clot/ SAH > 1 mm thick	Grade 3: focal/diffuse thick (> 1 mm) SAH, no IVH	Ventricular Hijdra (range = 0–12)
Grade 4: diffuse SAH and IVH and/or intracerebral hemorrhage	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 are considered: anterior inter-hemispheric fissure; lateral sylvian fissure; basal sylvian fissure; suprasellar cistern; ambient cistern and quadrigeminal cistern; and the four ventricles are considered.
IVH, intraventricular hemorrhage.

Early brain injury: insights from imaging studies

The concept of EBI was described in 2004 (14) and encompasses the global parenchymal insult occurring in the first 72 h after SAH, that primes the brain for further injury (15). EBI at the time of hemorrhage is an important cause of mortality in the first days after SAH (16).

Pathophysiological mechanisms involved in EBI are multiple (15): increased intracranial pressure; global cerebral hypoperfusion; impairment of autoregulation; microvascular constriction and thrombosis; injury of the blood–brain barrier; cortical spreading depolarization; and apoptosis. Some of these early pathophysiological changes can be translated in MR studies that may reveal acute ischemic lesions, global cerebral edema, or even vasogenic edema in normal-appearing white matter (17–22). There is an increasing number of studies demonstrating the potential interest of MRI in SAH, revealing lesions missed on CT studies. The impact of some of these subtle and until recently unknown MRI abnormalities on prognosis is not fully established.

Hyperacute ischemic lesions

Mechanisms behind acute DWI lesions in SAH are not fully understood, but possibly coincide with pathophysiological mechanisms of EBI: intracranial circulatory arrest after SAH; vasogenic edema; microcirculatory dysfunction; lesion of blood–brain barrier; activation of platelets; and cortical spreading depolarization (18). Hyperacute ischemic lesions in SAH occur in multiple patterns: punctate in up to 75% of patients, but also territorial and cortical (20). They affect distinct vascular territories (23,24), mostly cortical anterior cerebral artery and middle cerebral artery, but also basal ganglia and cerebellum (Fig. 2). The burden of early acute ischemia is proportional to the neurological status at admission, occurring in up to 86% in poor-grade SAH patients (17,18), and predicts DCI in the course of SAH (18–20,25).

Diagnosis and prediction of delayed cerebral ischemia

Arterial vasospasm was described more than 60 years ago, occurring in association with the rupture of aneurysms (26), and is, strictly speaking, a reduction in the caliber of cerebral arteries. Vasospasm usually starts after 72 h after SAH, has its peak at 6–8 days, and subsides after 2–3 weeks (27). Vasospasm occurs in up to 70% of patients (1,28), is diagnosed by non-invasive methods such as transcranial Doppler (TCD) and CT angiography, or by conventional subtraction angiography (Fig. 3). Vasospasm is potentially prevented with vasodilators and screening for vasospasm is current practice in SAH, because it is potentially treatable both pharmacologically and endovascularly (1). Clinical vasospasm (also called symptomatic vasospasm) corresponds to the clinical manifestation of ischemia secondary to arterial narrowing, and occurs in far fewer patients, around 25–30% (29). A wider concept was set forward in 2010 that incorporates clinical vasospasm and imaging: DCI. This is defined as a ''de novo'' neurological deficit in the absence of other causes and/or in the presence of ischemic lesions on imaging studies after the fourth day post SAH (to exclude lesions secondary to angiographic/surgical treatment of aneurysms) (30,31). DCI occurs in

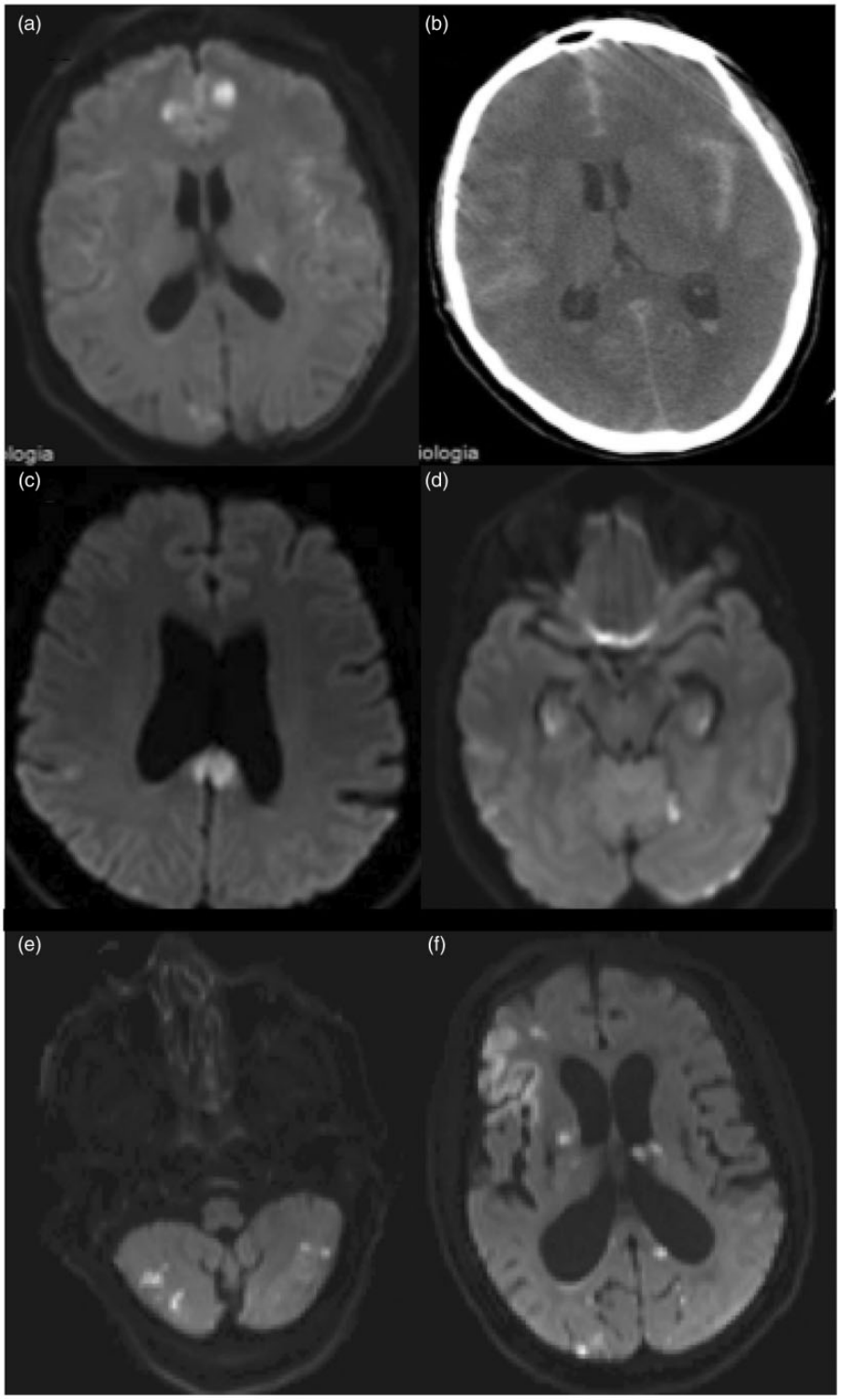

Fig. 2. Early brain injury lesions. (a) Axial DWI performed on the first 24 h after SAH, showing acute ischemia in both frontal lobes, right occipital lobe, insular cortex bilaterally, and posterior left thalamus. Lesions were not visible in a CT scan performed on the same day (b). (c–f) DWI images of different patients, illustrating different distributions of acute ischemic lesions: (c) corpus callosum splenium; (d) bilateral involvement of the hippocampi; (e) bilateral cortical and subcortical cerebellar lesions; (f) lesions involving several territories, including right frontal cortex, bilateral occipital cortex, bilateral deep basal ganglia and internal capsule, and left justaventricular white matter.

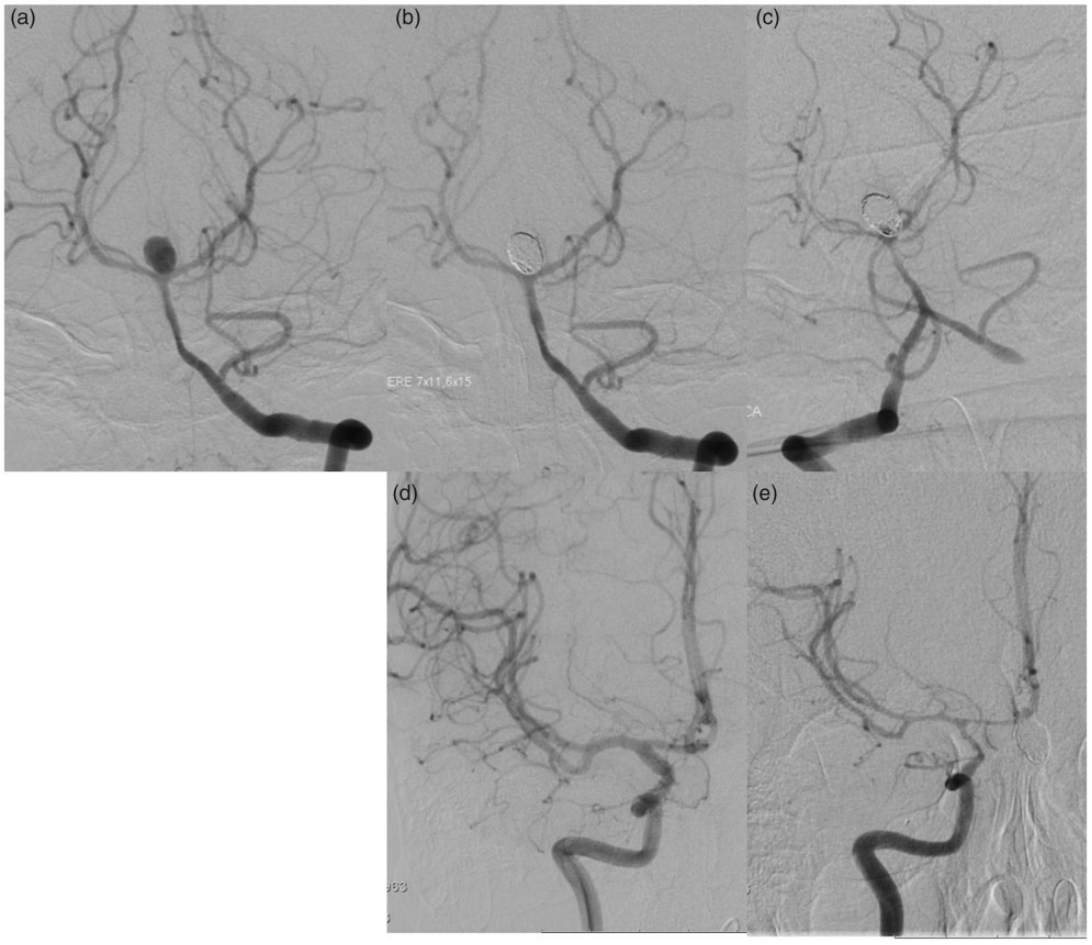

Fig. 3. Digital subtraction angiography images from a patient with a ruptured basilar tip aneurysm. (a, b) Angiography performed on day 1, showing the final result post coiling of the aneurysm. (c) Angiography performed on day 7 shows marked reduction of the basilar and posterior cerebral arteries caliber, secondary to vasospasm. Other territories were also affected in this patient: (d) anteroposterior view of the right internal carotid artery on day 1; (e) severe angiographic vasospasm of the middle and anterior cerebral arteries on day 7.

20–40% of patients and is associated with worse clinical and cognitive prognosis (27,31). It is the leading cause of morbidity and mortality in patients that survive early brain injury after SAH (2,32).

There is growing evidence that DCI is multifactorial in origin, and although vasospasm might be a contributing factor, it is not its only determinant. Although there is a strong association of severe vasospasm in TCD and angiographic studies with the occurrence of cerebral infarction (32,33), the presence of angiographic vasospasm is not linearly associated with ischemia and DCI (32), and cerebral infarction can appear in territories unaffected by vasospasm (32,34,35). The best method to predict DCI remains uncertain. In the following paragraphs, we will refer to the main imaging techniques used for the diagnosis of vasospasm and DCI, and we will discuss the relative contribution of each in predicting DCI.

Can transcranial Doppler ultrasonography predict DCI?

TCD is routinely used to screen for the emergence of cerebral vasospasm, with a high negative predictive value (36). The use of indices such as the Lindegaard Ratio (that corrects middle cerebral artery velocities by calculating a ratio with the ipsilateral internal carotid artery) help to distinguish increased velocities due to hemodynamic factors from vasospasm (36). Although useful for proximal large vessel vasospasm, TCD is insensitive to distal spasm (37). Regarding DCI, the positive predictive value and sensitivity of TCD vasospasm is only 67% (32) and 63% (37), respectively, as would be expected considering that vasospasm and DCI are not linearly associated. Therefore, TCD seems to be insufficient to identify patients at risk for DCI.

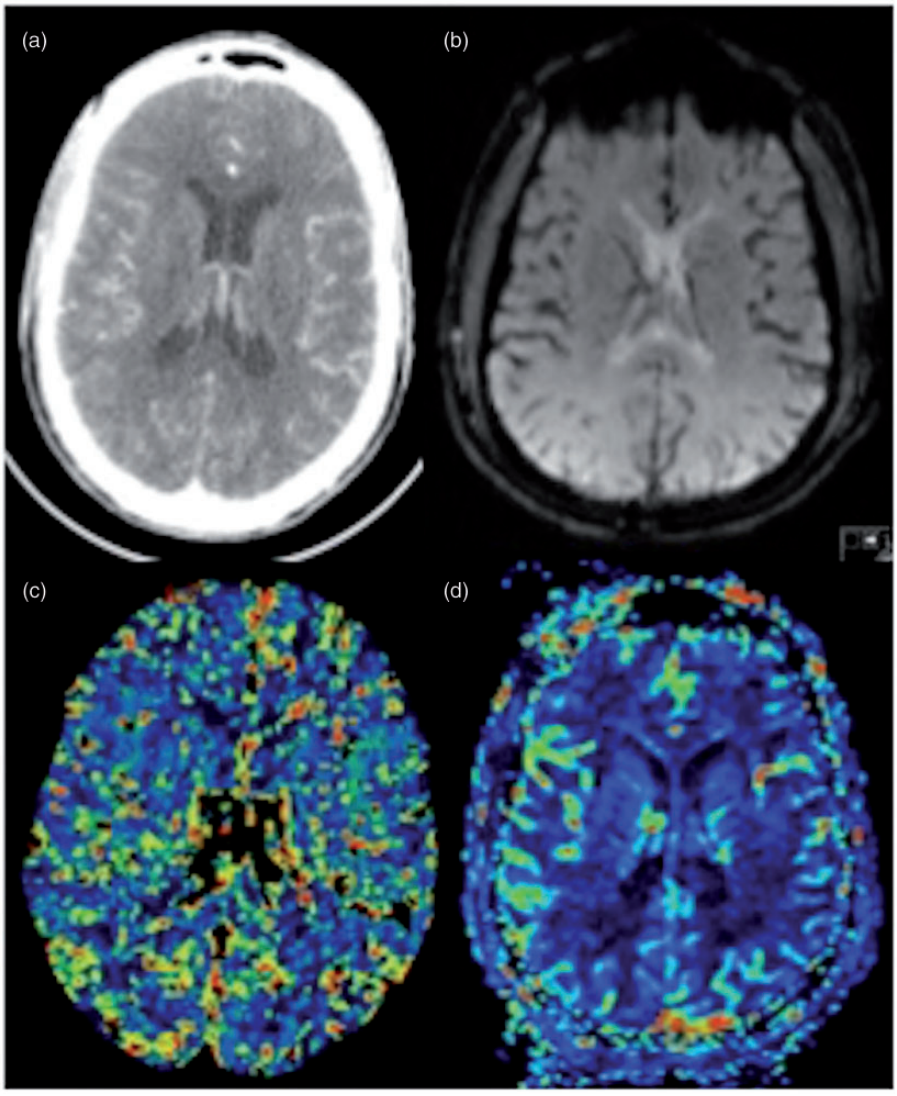

Fig. 4. Source images of perfusion studies on CT (a) and MR (b). After postprocessing, color maps of the several parameters can be obtained. CBF maps on CT (c) and MR (d) of the same patient show relatively symmetric perfusion of both hemispheres.

Cerebral perfusion imaging and prediction of DCI

Cerebral perfusion is affected both in the acute stage of SAH (38,39) and during the time window of vasospasm (40–43). Among the available methods for studying perfusion, CT (Fig. 4) is practically the only one used in clinical practice, since the availability of PET, SPECT, and Xenon perfusion is limited. There are very few studies using MR perfusion in acute SAH, and only one study using arterial spin labelling (44), but results are not consistent respecting the utility of MR perfusion to diagnose or predict DCI.

Perfusion imaging has been used both for the diagnosis and the prediction of DCI.

Vasospasm is associated with perfusion deficits detected by CT perfusion studies, manifested by increased mean transit time (MTT) and reduced cerebral blood flow (CBF) (38,40,42,43,45). The reduction of cerebral perfusion usually correlates with the onset of neurological symptoms. Values of perfusion parameters overlap between patients with and without DCI, but there is a trend for higher MTT and lower CBF in patients with DCI (46). Thresholds for diagnosis of DCI at the time window for vasospasm were set by many authors, with MTT values in the range of 5.0–6.4s (46,47), and for CBF in the range of 30.5–44.3 mL/100 mg/min (47).

Perfusion studies seem to be effective in diagnosing vasospasm and DCI; however, it would be important if they could predict their occurrence earlier in the course of SAH. Accordingly, some studies suggested that perfusion studies could be used to identify patients at risk of developing vasospasm and DCI (Fig. 5) (38,39,41,48–51). Patients who later in the course of

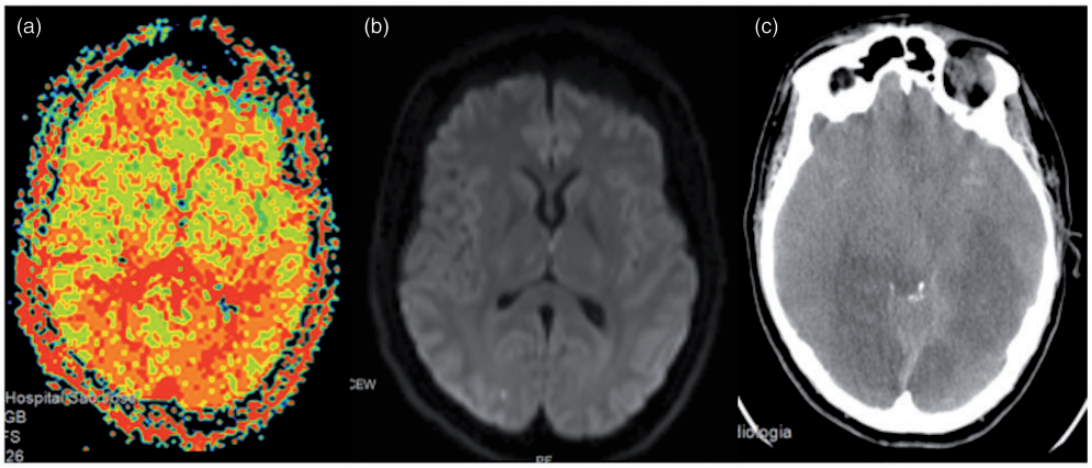

Fig. 5. (a) MR perfusion study showing increased TTP (red and orange) in the left temporal lobe (middle cerebral artery territory) and in both occipital lobes (posterior cerebral artery territory) on the first 24 h after SAH. (b) DWI performed on the same day shows small punctate acute ischemic lesions and no territorial infarction on the hypoperfused areas. (c) CT scan ten days after showing acute ischemic lesions due to severe vasospasm, affecting the hypoperfused territories.

SAH developed DCI presented early lower global and focal CBF values, lower cerebral blood volume (CBV), and raised MTT values (52–55), indicating not only cerebral hypoperfusion, but also an inability to compensate for the reduced perfusion.

However, there is still controversy concerning the value of CT perfusion in prediction DCI. In fact, one meta-analysis including 345 patients (41) described a 23-fold increased probability of DCI in patients with early CT perfusion changes, but another meta-analysis published in the same year including 570 patients failed to reliably associate early perfusion findings to the occurrence of DCI (48).

Although the rationale of evaluating CT perfusion to predict DCI is logical, the clinical validation and application of these studies have failed so far, in part due to the problems with standardizing CT perfusion protocols between centers and also due to the heterogeneity of studies design, with mostly retrospective analyses, different timings of measurement, diverse definitions of outcomes, and insufficient adjustment for variables that could be associated with both brain perfusion and outcome.

Cerebral autoregulation evaluation and prediction of DCI

Autoregulatory dysfunction predisposes to DCI and is aggravated by the installation of vasospasm (52–55). The assessment of cerebral autoregulatory capacity may be a tool for identifying patients at risk for DCI. There are several techniques available to assess cerebral autoregulation.

Monitoring of cerebral autoregulation during SAH is possible using indexes derived from TCD, such as the mean velocity index, that has been shown to associate with vasospasm and outcome, or direct measures of tissue oxygenation through near-infrared spectroscopy, that allow continuous monitoring of cerebral blood flow (56). A recent study reported that patients with DCI have a distinct autoregulatory profile (57). In a study using perfusion-weighted MRI, reduced CBF and reduced CBV in the basal ganglia were found in patients with SAH, even in the absence of vasospasm, suggesting dysfunctional vascular autoregulation in this region (58). At present, regardless of its interest and relevance, the assessment of autoregulation is not used in the clinical setting.

Imaging of blood–brain barrier and DCI

The analysis of blood–brain barrier dysfunction, in studies of permeability, is a yet unexplored tool to evaluate endothelial dysfunction in SAH and its association with vasospasm or DCI. There are very few studies on permeability after SAH (59). Permeability can be measured using CT or MR perfusion techniques, and the few existing studies have found a relation of increased blood–brain barrier permeability and vasospasm (60), but not with DCI or prognosis (53).

In conclusion, despite all the recent developments and extensive research, the effectiveness of imaging studies in predicting DCI is still uncertain.

Imaging predictors of clinical outcome

Although hospital mortality has decreased in recent years, functional outcome after SAH remains poor (61). Of the surviving patients who regain independence at daily life activities, up to 50% are left with different

degrees of cognitive impairment (62) and many are not be able to return to work due to deficits in memory, attention, executive functioning, and also mood disturbances and anxiety that last for years after hemorrhage (4,5).

Imaging studies have been used to help predict long-term outcome after SAH, such as mortality, functional independence, or cognitive impairment. As previously discussed, non-contrast CT can provide important information concerning short- or long-term prognosis, but its role is quite limited in assessing the full impact of SAH in cerebral parenchyma, such as the burden of acute ischemic lesions or cerebral edema.

Brain MRI and clinical outcome

One important predictor of outcome is the burden of ischemic lesions, not only in the acute stage of SAH, but also during the vasospasm time window. The presence of acute ischemia seems to be a marker of worse immediate and long-term clinical outcome (17,63,64). A higher number of ischemic lesions and volume of ischemia, even if asymptomatic, relates to worse survival rate and poor clinical outcome: the number of ischemic lesions and volume of ischemia predicts severe disability and death with high sensitivity and specificity (20,65). Infarcts related to aneurysm treatment also impact on clinical outcome (66). Location of infarcts has impact on prognosis (67), since even small lesions in strategic locations may cause important symptoms (23), and the combined occurrence of cortical and deep infarcts is associated with poor cognitive and functional outcome (Fig. 6) (67,68).

Global cerebral edema, a marker of EBI, was suggested to be an independent predictor of mortality and poor clinical prognosis (22,69).

The premorbid existence of white matter cerebral lesions in FLAIR was found to associate with worse clinical outcome, in a similar manner as in stroke patients, where higher volumes of chronic white matter injury relate to worse outcomes (19). Global brain atrophy is also correlated to worse long-term functional outcomes (70,71).

Advanced modalities such as diffusion tensor imaging (DTI) studies are starting to be used to assess the prognosis of SAH patients. DTI allows for quantification of the microstructural integrity of white matter tracts and therefore can theoretically increase the sensitivity to detect parenchymal lesions, even in normal-appearing brain. The utility of DTI as a predictor of outcome has already been established for other diseases, such as traumatic brain disorders (72,73). We recently suggested the role of fractional anisotropy (FA) and ADC as independent predictors of DCI and clinical outcome at three months (74,75). Sener et al. measured DTI parameters at day 12 after SAH and found an association between reductions in FA and white matter tracts and mortality at six months (73). Although promising, DTI is yet not validated as a tool to predict prognosis in SAH.

Cerebral perfusion imaging and prediction of clinical outcome

In addition to the possible role in predicting DCI as discussed above, CT perfusion studies were also studied as tools to predict clinical outcome. The few published studies included mostly early CT perfusion evaluations, before the vasospasm time window. One recent study found that the earliest the perfusion changes occur, the higher likelihood of poor outcome in patients with DCI (76). From all perfusion parameters, MTT seems to be the most significant regarding outcome prediction. Lagares et al. reported that an MTT of > 5.9 s is associated with a 20-fold risk of poor outcomes on the Glasgow Outcome Scale with a 90% positive predictive value (77). Etminan et al. reported an association of early elevated MTT together with higher blood burden on admission CT with poor clinical outcome at six weeks (49). Mathys et al. reported an MTT threshold > 4 s predicts unfavorable outcome at 23 months (78). Tateyama et al. described global MTT as an independent predictor of poor outcome (39). However, there are contradictory reports on CT perfusion value as a predictor of outcome and some did not confirm the association between early MTT or CBF changes and long-term outcome (53).

In summary, there is already considerable and sound evidence that imaging studies are important in the prediction of outcome after SAH. However, the main limitation is the lack of validation and standardization of these imaging tools that prevent their application in prognosis scales. In the future, the use of automated software may allow for a more uniform application of DWI, DTI, and eventually perfusion studies in prognostication.

Imaging prediction of cognitive outcome

Despite good clinical outcome in neurologic grading scales, up to 50% of patients with aneurysmal SAH are left with neuropsychological deficits that impact on daily activities and on the return to normal life (5). Cognitive dysfunction is both global and domain-specific, affecting mood, memory, and speech (5). The cause for cognitive dysfunction after SAH is not fully understood. Patients with vasospasm and DCI have associated worse neuropsychological outcomes (28,62,79,80). Some studies have identified associations between acute SAH imaging findings and long-term cognitive

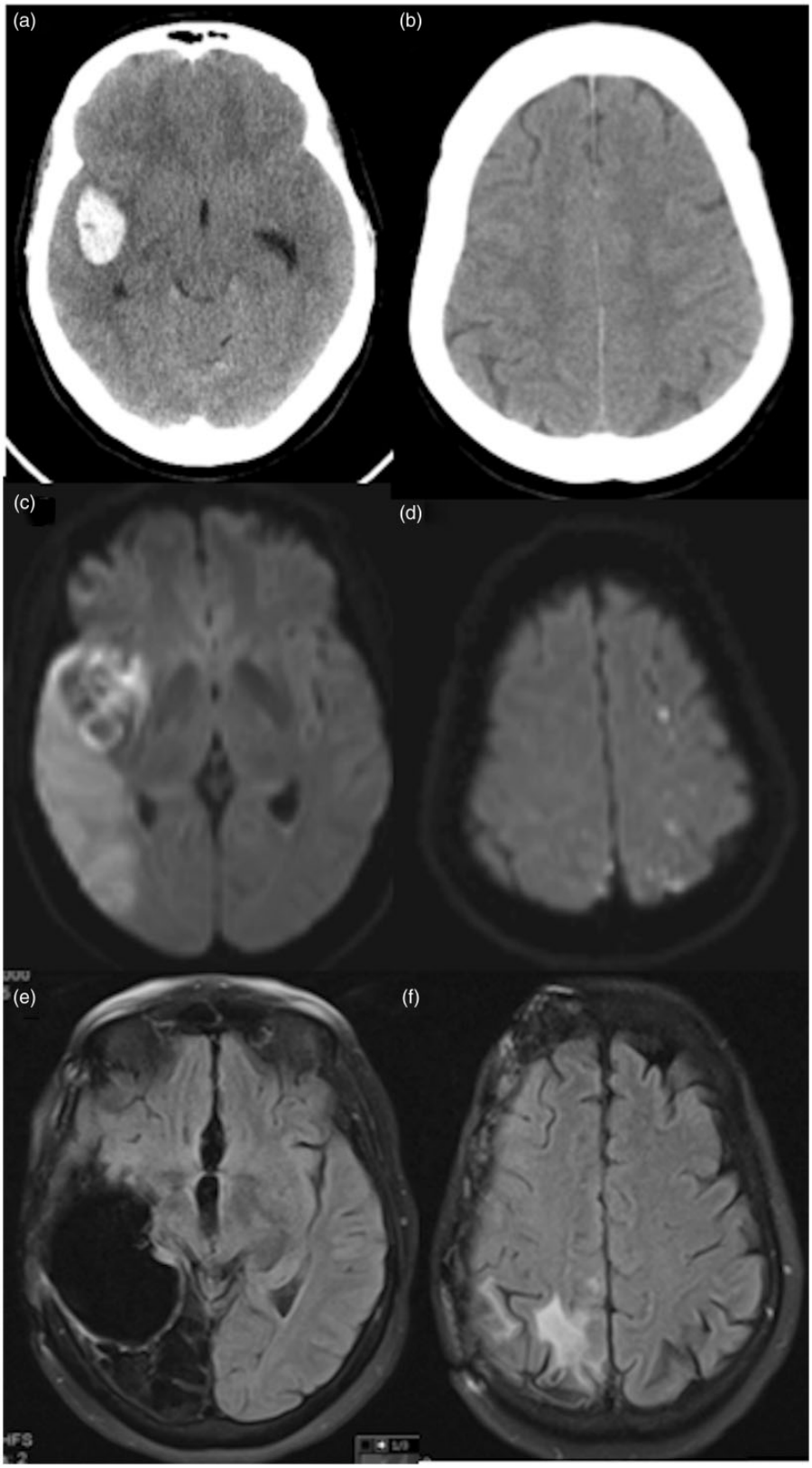

Fig. 6. (a, b) Admission CT images of a 50-year old patient with acute SAH and right temporal hematoma, and bilateral middle cerebral artery aneurysms. (c, d) DWI images at 48 h after SAH showing acute ischemic lesions in the right middle cerebral artery territory (c) and watershed infarcts on the left hemisphere (d). MRI performed four years after shows large areas of encephalomalacia on the right temporal and occipital lobes (e), and no evidence of residual left hemispheric lesions (f). The patient had no motor sequelae but was not able to return to her professional activity as a hairdresser and needs constant assistance for daily activities due to severe memory disturbance.

prognosis: higher Fisher grades and acute hydrocephalus on admission associate with brain atrophy, that ultimately associates with long-term cognitive impairment (81,82); global cerebral edema is strongly associated with cognitive impairment in multiple domains (83).

The increased detail in MRI studies may allow a better understanding of the impact of structural lesions in cognitive outcome. Reduced volume of the hippocampi is associated with increased incidence of mood disorders in surgically treated SAH patients (84). Volumetric changes in MRI studies have been described also at the chronic stage of SAH, globally affecting the gray and white matter (71,82,85) and focally affecting specific areas such as the left prefrontal lobes and striatum (86), and the mammillothalamic tract (87); these changes in imaging studies correlate with neuropsychological and cognitive outcome (70,82).

Finally, there are very few data on functional MRI (fMRI) studies in SAH. One study showed differences in BOLD-fMRI in SAH patients with memory impairment (88). Although still experimental, fMRI studies might serve as an additional tool to predict subtle cognitive changes after SAH.

In conclusion, neuroimaging studies are presently essential in the diagnosis of spontaneous SAH and are adjunctive methods to better identify several complications and understand patients' outcomes. They are also emerging as promising tools to predict the occurrence of DCI and clinical prognosis.

At the first examination, the amount of blood on CT is one of the most important factors to predict patient prognosis. MRI, although not currently performed at initial stage of SAH, has the potential to provide data on early brain injury and ischemia lesions occurring soon after the ictus. With increasing use of MRI studies in SAH patients, advanced modalities such as DTI and brain volumetry may expand their role in predicting outcome, either when performed at the acute phase of SAH or in later phases.

Cerebral perfusion is affected at early stages of SAH and during the vasospasm period, and it can be assessed by CT perfusion studies. Although routinely used in many centers, there are still some difficulties in establishing validated thresholds of perfusion to predict DCI and prognosis, which limits its generalization. Future advances in imaging techniques and active research in imaging of SAH will certainly contribute for a better understanding of the pathophysiology of this complex disease and, most importantly, in a more precise determination of its prognosis.

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