Vasospasm and Delayed Consequences

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Introduction

Subarachnoid haemorrhage-induced vasospasm is defined as the reduction in the diameter of the cerebral artery lumens, which is associated with microcirculatory disorders⁴² and structural anomalies of the vessel walls. Vasospasm is related to the presence of blood in the subarachnoid spaces but its pathophysiology remains unclear. It begins by a prolonged contraction of the smooth muscle with modifications of the vascular wall, including hyperplasia of the intima, subendothelial fibrosis, smooth muscle cell proliferation and collagen deposits³⁷. It is most commonly symptomatic in young subjects, current smokers, and those with a history of hypertension or diabetes¹⁰. It might be more common in severe cases of subarachnoid haemorrhage (SAH) with a poor clinical grade early in its course, but these relationships are variable according to the series and are being debated.

Vasospasm is the most common complication of SAH and is the main cause of delayed morbidity and mortality. It usually occurs 4 to 14 days after the initial accident, with a peak incidence at 7 days. Its rate of occurrence varies according to the authors from 40 to 70%³⁸. It is symptomatic in 17 to 40% of cases¹⁰. In addition, while some vasospasms are "asymptomatic", they may be the cause of ischemic lesions³⁹. Due to the development of new minimally invasive techniques (transcranial Doppler, PET scan, MRI diffusion-perfusion sequences), patients with SAH are now routinely evaluated for vasospasm. The therapeutic management usually includes a preventive approach with calcium inhibitors, and curative measures with hypertension and hypervolaemia. Percutaneous angioplasty possibly associated with local

vasodilator injection is effective but is not free of risk and its indication should be debated. While it is accepted that a significant spasm associated with a severe neurological deficit should benefit from a curative treatment, it is not known how to deal with severe asymptomatic vasospasms or those accompanied only by minor alterations in consciousness (confusion, disorientation, etc.).

Following SAH, a significant number (50%) of patients without physical disability present with a real psychological disability in the form of an astheno-emotional syndrome. These disorders, which are difficult to quantify, are probably underestimated. One hypothesis is that the vasospasm, though asymptomatic, could play a role in the occurrence of this syndrome. The reduced perfusion pressure resulting from the spasm may be responsible for diffuse cerebral lesions through neuronal depopulation.

Diagnosis

With the occurrence of ischemic lesions and their clinical manifestations, vasospasm is suspected with worsening headaches, fever or confusion³⁰. In unconscious patients, elevation of the S-100 protein is an early and sensitive sign. The non-invasive diagnostic exams, such as transcranial Doppler, are usually routinely performed and repeated at the usual starting period of the vasospasm.

Transcranial Doppler

Transcranial Doppler exploration has been found to be useful for the detection and evaluation of vasospasm^{8,24,27}. It is a highly specific,

non-invasive exam but has a low level of sensitivity. This exam is very operator- and patient-dependent and its value is debated. Different parameters have been suggested in the literature for quantifying the severity of the vasospasm. The mean velocity is the most commonly used interpretation criteria. As such, a spasm is defined as a mean velocity (MV) higher than 120 cm/sec on one or several of the explored axes, with a minor spasm being between 120 and 160 cm/sec, a moderate spasm between 160 and 200 cm/sec and a severe spasm being a MV greater than 200 cm/sec⁸. The ratio between the systolic velocities of the middle cerebral artery and the internal carotid artery, or Lindegaard index, is a useful accessory; a value greater than 3 indicates the presence of a vasospasm. However, there are several factors that can induce false negative or false positive diagnoses. Vasospasm of the anterior cerebral artery is poorly evaluated. A purely distal vasospasm, severe vasospasm of the carotid siphon or the presence of intracranial hypertension are common causes of false negative diagnoses. By decreasing the hematocrit level and blood viscosity, treatment-induced hypervolaemia increases blood velocity and can lead to false positive diagnoses. It is thus recommended that these speeds be considered in relation to the general appearance of the spectrum, the resistance index (systolic velocity-diastolic velocity/systolic velocity) and the maximum systolic velocity for classifying the patient into one of four groups. The essential item is the progression of the disease over repeated exams. A rapid increase of the mean velocity by 50 cm/sec or more over a 48-hour interval makes the occurrence of symptomatic spasm highly probable.

Correlations between transcranial Doppler and CT angiography are good for patients with severe vasospasms (PMV > 180 cm/sec) and for patients without vasospasms (PMV < 140 cm/sec) in the study by IONITA (20). On the other hand, correlations are less good for patients with asymptomatic spasms or with intermediate velocities and the authors recommend CT angiography in this case.

CT Scan

The simple CT scan is useful for ruling out other causes in the event of the occurrence of a deficit or worsening of the clinical state (re-

bleeding, ischemia in relation to the treatment for aneurysm, etc.). Unfortunately, it is too late for the vasospasm. When the ischemic lesions secondary to vasospasm appear, it is too late to perform a procedure that aims to correct the hypoperfusion that results from the vasospasm.

Multidetector CT scans enable the study of the vessels to be done with CT angiography, along with the study of arterial perfusion. These reasons, in addition to an easy access, especially for intensive care patients, explain the current interest of this method in the follow-up of SAH.

The perfusion CT scan enables the usual perfusion parameters to be easily accessed and this deficit to be quantified³⁸. Wintermark⁴¹ had thus correlated the perfusion CT scan and vasospasm with angiography. In his study, the CBF and MTT were the most pertinent, with a sensitivity of 92% and a specificity of 81% for an MTT > 6.4 secs., and a sensitivity of 83% and specificity of 95% for a blood flow less than 39.3 cm³/100 g/ minute; this resulted in a PPV of 94% and an NPV of 85%.

CT angiography has been widely used for this indication with a good correlation with angiography. In the study by Binaghi⁴, this sensitivity reached 100% for the A2, M2, M1 and the basilar trunk segments, slightly less good for the A1 segment (87.5%) and especially so for the carotid siphon (45%), with a PPV of over 98% for all the vessels. Chaudari¹¹ also found this low sensitivity for the carotid siphon. It was even lower for the P1 and posterior communicating artery segments. The negative predictive value thus remained excellent for all the studied arterial segments, being greater than 90%. The authors concluded that in their series of 33 patients, 83% of the arteriographies were superfluous. This good correlation was confirmed by all the authors and CT angiography gradually became the ideal method of patient selection for angioplasty. The main limitation of this technique is the artefacts due to the metallic coils or clips that can thus impede the visualization of one or several arterial segments.

MRI

The diffusion sequence enables a very early diagnosis of cerebral ischemia and then rapid intervention²³. It can also be predictive of

ischemia. The visualized cerebral lesions may be cortical, appearing triangular or in bands, which correspond to cortical laminar necrosis¹³, or they may be deep, with focal lesions of the white matter but with few overall true territorial infarcts.

The cortical lesions develop independent of visible spasms on angiography³⁶; they might occur earlier, in relation to the blood in the sulci, and might correspond to a spasm of pial and perforating arteries, or "cortical spreading ischemia" as described in experimental studies³⁹.

The diffusion MRI imaging usually first shows multiple small areas of ischemia within the zone of hypoperfusion³². Apparent diffusion coefficient (ADC) reduction is however more widespread from the beginning and we could demonstrate the existence of reduced ADC of the white matter, even in cases of asymptomatic vasospasm, usually with a regression of anomalies¹². Study of perfusion is possible with MRI, taking into account the usual restrictions of this technique. According to Hattigen¹⁷, the angiographic vasospasm correlates with a simultaneous reduction in the volume and blood flow in the territory of these arteries. The lack of an increase in local blood volume as a compensation for the flow decrease denotes dysfunctional vascular autoregulation.

The MR angiography is more controversial, as the three-dimensional TOF always results in overestimation of stenosis. However the combination of TCD, MRA, perfusion and diffusion MRI provides a reliable indication for the procedure⁶.

Angiography is still considered the gold standard for the diagnosis of vasospasm but its invasive nature and good correlations with CT angiography make it so that it is now reserved for cases of discordance between non-invasive examinations, especially in the pre-treatment phase when angioplasty is being considered.

Treatments^{1,2,22,26}

Preventive medical treatment. Intravenous nimodipin at a dose of 2mg/hr or orally at a dose of 360 mg/day for 21 days (possibly shortened to 14 days in the absence of spasm) is effective in reducing the risk of delayed neurological deficit. Its use is highly recommended²⁶.

Reinforcement of medical treatment, including the control of blood volume (avoidance of hypovolaemia) and especially control of hyper-

tension when the aneurysm is treated, is recommended²⁶.

Local vasodilator infusions. The use of papaverin was introduced in the beginning of the 1990's. It is infused in the carotid or vertebral artery at a dose of 300 mg diluted in 100 ml of normal saline over 30 to 60 minutes²⁵. It induces an increase in the calibre of the vessels, which is visible on angiography, and reduces cerebral circulatory transit time. Unfortunately, it has a short half-life and its effects are transitory over a length of 90 minutes¹⁴. It may be repeated, but the beneficial clinical effects of isolated papaverin infusion have been recorded in less than half the cases. It may be used together with angioplasty, either to facilitate the procedure, or as a complement by perfusion of the distal branches that are unattainable by angioplasty¹.

The infusion must be done at a rate less than 5 ml/min, otherwise transitory manifestations may result including mydriasis, bradycardia, increased intracranial pressure, etc. Nimodipin may also be used by intra-arterial injection in the same conditions and at a dose of 2 mg over 30 minutes in each spastic vessel and a total of 5 mg maximum with identical effects and less side effects. In 2004, Biondi⁵ reported 25 patients with radiological improvement in 52% of cases and clinical improvement in 76%.

Percutaneous angioplasty was proposed by Zubkov in 1984⁴³. It subsequently became accepted as the most efficient treatment. Technically-speaking, angioplasty is done using a distensible, very flexible balloon and in a gentle, progressive manner. The inflations are done manually at a very low pressure and over a short length of time. The technique progresses from the carotid siphon towards the initial segments of the anterior and middle cerebral arteries and from the vertebral artery towards the initial segments of the posterior cerebral arteries. The balloons that were initially used were simple and non-perforated, which enabled only dilation of the carotid siphon and the middle cerebral artery for the anterior circulation and with risks of overinflation and thus arterial rupture. The material currently used includes a perforated balloon mounted on a guidewire. The guidewire helps to direct the balloon, and therefore reach the segments such as the anterior cerebral artery, and to occlude the balloon while inflated. In the event of overinflation, the dilation of the distal orifice avoids increased

pressure and arterial rupture. It results in an immediate increase of the arterial calibre, reduction in cerebral circulatory transit time and especially an absence of relapse^{2,35}. Long-term follow-up has not shown modification of the lumen secondary to the angioplasty.

The main risk is arterial rupture during the dilation, which always has a fatal outcome; fortunately, it is a rare occurrence. Other complications have been reported, including thrombosis secondary to a dissection by the guidewire; untreated aneurysm rupture or hemorrhagic transformation of an established infarction. These risks are less than 4-5%. If the angiographic and cerebral perfusion results are consistently good, the clinical aspects on the other hand are essentially variable depending on the time period between the appearance of the deficit signs and the angioplasty². The procedure must be carried out as early as possible, but imperatively within 12 hours to achieve clinical improvement. According to Rosenwasser³³, the rate of favourable outcome thus reaches 70% if the procedure is done within 2 hours.

The indication is widely accepted for a deficit refractory to medical treatment in a conscious subject, even with the occurrence of the deficit in a patient presenting with worsening headaches or confusion, recurrence of fever with velocimetric signs or basilar spasm on CT angiography and/or hypoperfusion on CT scan or perfusion MRI. For some patients, angioplasty should be considered even for an asymptomatic spasm if confirmed on diagnostic exam. Prophylactic angioplasty has been proposed for patients at risk of developing spasm and a multicentre, randomised phase II study was done on 171 patients presenting with Fischer grade 3 SAH on CT scan. Eighty-five were treated with preventive angioplasty⁴⁵ within 4 days following the haemorrhage. The incidence of late neurological deficits was lower in the treated group, with an absolute reduction in the risk of progression of 5.9% and a relative reduction of 10.4% , but 4 complications of the procedure were noted, and the angioplasty did not overall significantly improve the 3-month clinical score.

Long-term consequences of SAH and the role of vasospasm

A meta-analysis reports 30% mortality in patients with vasospasm and poorer results for long-term neurological aspects³. According to

Charpentier¹⁰, vasospasm is an independent factor of neurological sequelae at 6 months (OR 4.7, CI 95%, 1.77-12.6).

Even in independent patients and free of neurological deficits, modifications in the patient quality of life were noted, with 59% of cases in the Wermer study⁴⁰ having personality modifications, including irritability (37% of cases), emotionality (29%), and depression, anxiety (10%). This depressive state affected 37% of patients in the Buchanan study⁷. Cedzich⁹ found 87% of patients having a moderate change in the quality of life and 19% of cases reporting a severe change. This included lowered performance, e.g. reduced speed of processing information in 72.5%, and reduced capacity of working memory in 25% in the Fertl study¹⁵. This decreased quality of life is felt by the patient and his spouse¹⁸. For 63 patients in the Rodholm study³¹, these symptoms decreased over time, with 60/49/38% having fatigue-emotional disorders (fatigability, concentration and memory problems) at 3/6/12 months, respectively, and which might be correlated with a pre-existing SAH. The same occurred for Samra³⁴, with 36% having neurocognitive disorders at 3 months, and recovery for 26% at 9 months.

The parenchymatous consequences. In an unpublished study on 91 patients with an MRI 6 months after SAH, we found Periventricular hypersignals in 62.6% of patients, most commonly around the ventricular horns or at the fornix, or more rarely along the ventricular bodies. At least one periventricular or fornix anomaly was found in 65% of patients who presented with spasm and in 76% of cases of severe spasm, but without significant relation between these lesions and the occurrence of a spasm ($p=0.54$). The intensity of the spasm did not appear to be a factor promoting the occurrence or intensity of these anomalies ($p=0.28$).

Anomalies of the deep white matter were found in 92% of patients in the study, with the same prevalence in the control group (92.1%) and in the spasm group (92.5%). This frequency is higher than in the normal population at the same age. These lesions of the white matter were also found to occur in an abnormally frequent manner by Hadjivassiliou¹⁶ and Kivisaari²¹. Cerebral infarct sequelae were present on MRI in 19 patients, 16 of whom presented with vasospasm and 14 were symptomatic. In 18 patients the infarction was supratentorial and occurred most commonly in the area of the

middle cerebral artery (13 patients). The incidence of cerebral infarction was significantly linked to the presence of a vasospasm ($p=0.01$), with a clear increase in the frequency of cortical infarction ($p=0.04$) in moderate and severe vasospasms. Atrophy was present in 61% of cases in the spasm group and was significantly more common with moderate or severe spasms ($p=0.002$). Likewise, subcortical atrophy was significantly more common when the spasm was moderate or severe ($p=0.05$), even after

exclusion of patients who presented with hydrocephaly requiring placement of an external shunt.

The anomalies of the periventricular or subcortical white matter and the mainly subcortical atrophic phenomena were common in our patients with SAH from aneurysm rupture. Vasospasm does not seem to play a significant role in the genesis of white matter hypersignals. On the other hand, it is significantly related to the occurrence of cerebral atrophy.

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