Review Article

Cerebral vasospasm: Aetiopathogenesis and intensive care management

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Abstract

Cerebral vasospasm is the prolonged, intense constriction of the larger conducting arteries in the subarachnoid space which are initially surrounded by subarachnoid clot. Significant narrowing develops gradually over the first few days after the aneurysmal rupture. The spasm usually is maximal in about a week's time following haemorrhage. Vasospasm is the one of the leading causes of death after the aneurysmal rupture along with the effect of the initial haemorrhage and latter rebleeding. The purpose of this article is to outline the importance in early diagnosis and aggressive treatment of this otherwise challenging clinical entity.

Key Words: Cerebral vasospasm, SAH, Intensive care

Introduction

Vasospasm is the prolonged, intense constriction of the larger conducting arteries in the subarachnoid space which are initially surrounded by subarachnoid clot. The narrowing of the vessels is best demonstrated by cerebral angiography. It is likely that spasmogens released from the breakdown of red blood cells trapped by a fibrin mesh in the abnormal environment of the subarachnoid space are responsible for causation of this vasospasm. Significant narrowing develops gradually over the first few days after aneurismal rupture,[1] and the vessel narrowing usually is not severe enough to cause ischemic symptoms for four days or so. The spasm is usually maximal about a week after the hemorrhage. Symptoms from infarction are also most common at around this time. The chance of the patients beginning to develop symptomatic infarction after two weeks on the basis of vasospasm is extraordinarily low or negligible.[2]

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For patients in all neurologic grades following the aneurysmal rupture the chance is about 50-50 that significant angiographic vasospasm will develop. Between one-quarter and one-fifth of patients will get symptoms of delayed ischemia, and in between one-third and one-half there will be CT evidence of infarction due to cerebral vasospasm. Vasospastic infarction severe enough to cause death will occur in between one in twenty and one in six patients. Vasospasm is one of the leading causes of death after aneurysmal rupture along with the effect of the initial hemorrhage and later rebleeding.[3]

The more severe the initial hemorrhage and the larger the volume of subarachnoid clot, the more likely is the severity of diffuse vasospasm which will develop. For infarction to develop, there usually has to be an extreme degree of narrowing over a long segment of the vessels and a failure of collateral flow. Many other factors also play an important role which includes the circulating blood volume, cardiac output, blood pressure, intracranial pressure, and the age of the patient.

Time Course

Vasospasm is almost never observed angiographically in the first three days following aneurysmal rupture. If it

is seen on the first angiogram it probably indicates that the patient had a previously unsuspected bleeding episode prior to the one that brought the patient to medical attention. The vasospasm is maximal around seven to eight days following rupture and usually subsides by two or three weeks.[3]

Aetiopathogenesis

The exact mechanism by which SAH induces arterial vasospasm continues to be a subject of considerable research and debate.

Arterial spasm most likely involves some alteration in the structure of the vessel wall. Studies have shown that arterial vasospasm results primarily from prolonged smooth muscle contraction. Hypertrophy, fibrosis, and degeneration as well as other inflammatory changes in the vessel wall are secondary effects that occur on a delayed basis. Extensive research has shown that the big event that leads to the initiation of vasospasm is the release of oxyhemoglobin (blood breakdown product). However, the exact mechanism by which oxyhemoglobin induces vasoconstriction is unknown. This mechanism appears to be a multifactorial process that involves the generation of free radicals, lipid peroxidation and activation of protein kinase C as well as phospholipase C and A2 with resultant accumulation of diacylglycerol and the release of endothelin-1. These events appear to create a positive feedback loop that, in turn, produces a tonic state of smooth muscle contraction and inhibition of endothelium-dependent relaxation. Serotonin, prostaglandins, catecholamines, histamine released from the breakdown of platelets and erythrocytes are also implicated as causative factors.

Classification

Cerebral vasospasm is classified as either angiographic or symptomatic. Angiographic vasospasm is narrowing of a cerebral arterial territory, seen on angiography, without clinical symptoms. Symptomatic vasospasm is the clinical syndrome of cerebral ischemia associated with angiographically documented narrowing of a major cerebral territory.

Clinical Presentation

Patient presents with progressive impairment in level of consciousness, especially after 72 to 96 hrs following SAH. There may be increase in focal defects. ECG shows q waves, ST elevation, peaked T waves, prolonged PR Interval and large U waves. Differential diagnosis include post operative bleed, electrolyte abnormality specially decreased serum sodium concentration, hypoxia, sepsis and hydrocephalus.

Diagnosis

Clinical

Progressive impairment in level of consciousness or increase in focal neurologic deficit occurring after four days of the bleeding episode should raise the suspicion of vasospasm. If surgery has been conducted early the differential diagnosis should include postoperative bleeding, swelling, electrolyte abnormality (particularly hyponatremia), hypoxia from respiratory complications, developing hydrocephalus, or sepsis. It is important not to use vasospasm as a catch-all explanation for any late deterioration.[3,4]

Transcranial Doppler and Angiography

As the caliber of major conducting arteries is reduced, the velocity of blood going through them generally increases. A progressive increase in this velocity may be a harbinger of problem due to vasospasm. Patients who develop clinical evidence of ischemia from vasospasm often have mean velocities in the middle cerebral arteries of over 200 cm/s.[1,4] Occasionally; the existence of intracranial hypertension will cause a spuriously low mean middle cerebral velocity. There are many exceptions to the linkage between increased velocities and ischemia; hence a close clinical correlation is required. Angiographic confirmation of severe diffuse vasospasm remains the gold standard.

Flow Studies: Xe-CT, PET, Isotopes

Several technologies currently are available for obtaining regional cerebral blood flow estimates. The xenon-CT scan and positron emission tomography (PET) scan provide excellent quantitative data but are not generally available. Single photon emission tomography is generally more commonly used, but the data are not quantitative.

Treatment

Prophylaxis

Early surgery permits the mechanical removal of fresh blood clot by suction and irrigation.[3,5] Once the offending aneurysm has been secured by a clip it is possible

to place tissue plasminogen activator within the subarachnoid space, either at the time of surgery or subsequently through catheters, to facilitate the early fibrinolysis of the clot, thus reducing the amount of decaying blood pressing against the arteries. This appears to be an effective way of preventing vasospasm. These fibrinolytic agents have a potential to cause bleeding by dissolving normal clot, so only patients at high risk of developing vasospasm should be chosen for this type of prophylaxis.

Calcium Antagonists

The one drug currently approved for use after subarachnoid hemorrhage in North America is the calcium antagonist nimodipine. Its use was associated with a reduced tendancy toward postaneurysmal cerebral infraction. Its clinical effectiveness was not based on its ability to prevent or reverse angiographically demonstrable vasospasm. Nimodipine can be used either orally, intravenous or intra-arterial. The drug is potent and long lasting than papavarine, is lipid soluble and crosses the blood brain barrier.[3,6]

The treatment should ideally commence within 96 hours and to be instituted up to 21 days either as infusion (1-2 mg/hr) or orally 60mg every 4 to 6 hourly to a maximum daily dose of 360 mg,[7,8] the role of Nicardipine a Calcium antagonist analogue is yet to be established.[8]

Endothelin Antagonists

Endothelin is the most potent naturally occurring vasoconstrictor. It can be produced by vascular endothelium and smooth muscle cells. In animal models, endothelin antagonists have been associated with reduced incidence of chronic vasospasm following clot placement. Such compounds have not yet gone to clinical trials. Nitric oxide has been tried with no established results.

Induced Hypertension

While this therapeutic modality has never been subjected to prospective clinical trial, it is nevertheless widely employed in the setting of delayed ischemia after aneurysmal rupture.[1,4,6] All experienced neurosurgeons have seen instances of dramatic reversal of focal neurologic deficits by induction of arterial hypertension. This is usually done in association with normalization of the circulating blood volume with fluid administration or transfusion. Very close clinical observation is indicated when patients are receiving agents such as dopamine or dobutamine in this setting. Xenon blood flow studies have demonstrated that in certain patients induced hypertension is associated with reduction in regional cerebral blood flow. While such patients are undoubtedly exceptional, this is an important caveat.

Hypervolemia

The avoidance of hypovolemia is perhaps more important than the institution of hypervolemia. The old days of intentional dehydration are gone forever. The optimal hematocrit varies from patient to patient, but it is probably reasonable to maintain it within the normal range. Crystalloid solutions are given to meet normal daily requirements. Glucose solutions are avoided. Human serum albumin is commonly used as a volume expander in dose of 1 g/kg per day divided in 4 to 6 doses/day, each administered over 30 to 60 min.

In critically ill patients or in those with compromised pulmonary function, a Swan-Ganz catheter should be in place and appropriate monitoring used to avoid circulatory overload and pulmonary edema, as well as to ensure the optimization of cardiac output.[1,2,5]

Angioplasty

If the patient is in imminent danger from severe diffuse vasospasm refractory to hypertension and hypervolemia, these spastic arterial segments may be forcibly dilated by means of small, sausage-shaped balloons placed through intra-arterial catheters.[9,12-14] In expert hands, this is associated with the permanent reversal of vasospasm and clinical improvement in one-half to two-thirds of patients. There is a serious risk of arterial rupture, hence the procedure should be restricted to experienced interventional neuroradiologists on the advice of experienced clinicians.[1,4]

Intraarterial Papavarine

The proximal segment of the anterior cerebral artery, the posterior cerebral arteries, and distal middle cerebral arteries are not amenable to balloon dilatation because of size or angle of take-off. The instillation over several hours of high concentrations of intra-arterial papavarine has been associated with reversal of spasm in some cases.[4,10] There has been a tendency for spasm to recur, and the infusion may have to be repeated, but it is

sometimes associated with clinical improvement.[11,15] Again, this is not a therapy to be undertaken lightly or before the failure of more conventional means.[17-19]

Other pharmacologic interventions

The intrathecal administration of recombinant tissue plasminogen activator (rtPA) has been shown to dissolve subarachnoid clots, thereby preventing vasospasm in humans. The use of rtPA in human trial has reduced the severity of angiographic vasospasm and improved the clinical neurologic grade of the patients. The other agents tried to varying results are Streptokinase and Urokinase. Tirilazad, a 21 amino steroid glucocorticoid with anti inflammatory properties has shown promising results and stays as a new drug with great expectations, the results of which require authentication.

Alternatively, the super-selective intra-arterial infusion of papavarine[19-22,24] (2 mg over 10 s) has been shown to be effective in dilating spastic distal vessel not accessible to angioplasty techniques.[23,25]

Intrathecal sodium nitroprusside was recently suggested as a treatment for cerebral ischemia in patients with severe, medically refractory vasospasm after sub arachnoid haemorrhage (10 to 40 mg single dose and 2 to 8 mg/hr as infusion)

Alprostadil – Prostaglandin E1 may be of value in the treatment of vasospasm. The efficacy is yet to be established. Intra arterial Nimodipine, has also been tried, but it does not work as well as papavarine, though it has a more long lasting effect. Nitroglycerine used intra arterial, has shown some success.

The general measures of good intensive care, proper ventilation and provision of optimal nutrition promote faster recovery and helps in better outcome.

Conclusion

Vasospasm is a clinical challenge. Timely diagnosis and aggressive treatment are essential goals for a better outcome, which otherwise carries a high morbidity and mortality.

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