How Intracranial Aneurysm Rupture Damages the Brain

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Summary

Intracranial aneurysm rupture causes arterial bleeding into the subarachnoid space (SAH). In the acute stage lasting around 5 minutes intracranial pressure (ICP) rises rapidly up to the level between systolic and diastolic blood pressures, which slows down the outflow of blood, facilitates clot formation in the site of rupture and leads to arrest of bleeding. Increased ICP lowers cerebral perfusion pressure, causing brain ischemia, which is unevenly distributed throughout the brain as a result of interhemispheric pressure gradients, arterial spasms and other factors. No-reflow phenomenon in the capillaries following temporary arrest or considerable slowing of circulation produces areas of hypoperfusion and reduced capacity of blood flow autoregulation scattered irregularly in the brain in the subacute stage up to 30 minutes following haemorrhage. Disturbed regional cerebral blood flow is accompanied by spots of damaged blood brain barrier resulting in brain oedema. After SAH the brain remains vulnerable to reduction of blood flow and hypoxaemia, which explains greater brain damage after secondary haemorrhage, and in some cases persistent neurological deficits or global brain dysfunction.

Introduction

Intracranial aneurysm rupture causes in most cases very severe disturbances of the brain function, which are often life-threatening. Over 10% of individuals suffering subarachnoid haemorrhage (SAH) die before reaching medical attention, 25% die within 24 hours,

and 40-50% within 3 months. Mortality rate has been estimated to be as high as 65%, with most deaths occurring early in the clinical course.

Mortality and morbidity of aneurysmal SAH has been attributed to cerebral ischaemia resulting from arterial spasm. Spasm of cerebral arteries immediately following aneurysm rupture is a physiological reaction of the bleeding vessel that helps to control the bleeding. It is a short lasting event induced by neurogenic reflexes. Late spasm occurs after a few days and is attributed to activity of a variety of vasoactive mediators released from the dissolving blood clot in the subarachnoid space¹⁻⁴.

There is however a number of specific features of the post-haemorrhagic brain ischemia that can hardly be explained solely by spasms of the brain arteries. Blood enters subarachnoid space in a number of clinical conditions that are not related to aneurysm rupture, like trauma, surgery, bleeding from an arteriovenous malformation or tumour. The occurrence of post haemorrhagic brain ischaemia and arterial spasm in those cases is rare.

Results

Brain ischaemia in aneurysmal SAH is reported in 60% of cases, in arteriovenous malformation in 12%, SAH of unknown causes in 12%, posttraumatic below 10% and it is extremely rare in postoperative condition⁵.

It often happens that localization of hypoperfused areas in the brain are remote from the site of spastic arteries identified with angiography or transcranial Doppler sonography, and often occurs in patients without arterial

spasms. Therefore other specific mechanisms of ischemic brain damage resulting from aneurysmal bleeding were investigated^{6,7}.

It is the acute stage of the haemorrhage that can make the difference between the aneurysmal bleeding and SAH from other sources. An aneurysmal wall has deficient structure resulting in loss of capacity to spasm. Unlike an injured wall of a normal vessel that constricts around the site of rupture to limit outflow of blood, a breach in the aneurysmal dome remains wide open. Blood flows freely under the driving force of pressure gradient between the arterial lumen and subarachnoid space. Cerebrospinal fluid in the cerebrospinal cisterns is displaced by blood, flowing into the subarachnoid cistern around the bleeding point. Bleeding is terminated when the transaneurysmal wall pressure gradient drops considerably as a result of substantial elevation of intracranial pressure, enabling clot formation in the slowly flowing or stagnant blood⁶⁻⁹.

The volume loading of CSF space with blood rapidly elevates ICP, typically reaching peak levels in 30 seconds. The ICP level off at an equilibrium point representing the balance of volume loading by effusing blood and cerebral compliance due to displacement of CSF.

If volume loading of the subarachnoid space continues long enough cerebral compliance will be reduced and eventually exhausted. Then prolonged and profound global ischaemia associated with reduced CPP and loss of consciousness may occur.

There are only a few investigations of the course of aneurysmal bleeding and pathophysiological changes associated with early phase of SAH. Human data immediately after SAH are isolated chance observations and those available are limited to second or subsequent haemorrhage event rather than a primary event. Chance observations in patients who have suffered a haemorrhage while awaiting aneurysm repair have been reported. Those observations document SAH with pre-existing cisternal clot, an injured brain, low cerebral pressure compliance, elevated resting ICP and abnormal CSF outflow resistance^{2,3}.

Evidence of pathophysiology at the time of aneurysmal bleeding, ICP changes and other phenomena has been extrapolated from the data provided by experimental investigations. In animal models influence of blood injected in the subarachnoidal space has been extensively

studied providing information on the reaction of blood vessels to the blood and a variety of blood products^{10,11}. Bleeding from an artery has been also reproduced in a number of ways and those observations showed that ICP rises very rapidly during the bleeding, usually reaching a level of between the systolic and diastolic blood pressure. The inflow of blood into the subarachnoid space is initially high, and then slows down following reduction of transmural pressure gradient equal to cerebral perfusion pressure (CPP) and within a short time after reaching a plateau the bleeding stops. The time of bleeding is estimated to last around 2-3 minutes. This is then followed by gradual reduction of ICP when pressure regulation mechanisms come into action. The ICP does not return to pre-SAH values in many hours^{8,12}. Two-thirds of the volume of extravasated blood is delivered in one-third of the bleeding time⁸. At first blood mixes with the cerebrospinal fluid bilaterally in the basal cisterns and over the hemispheres, and then fills mostly subarachnoid space in the vicinity of the bleeding site. During the bleeding and shortly after its termination there is a pressure gradient building up between the hemispheres. This is higher with higher levels of ICP, and then gradually decreases with falling ICP^{9,13}.

Blood clots filling the subarachnoidal space obstruct cerebrospinal fluid flow and result in acute but in many cases also in a chronic increase of cerebrospinal fluid outflow resistance, which in the chronic stage can be further augmented by blockade of arachnoidal granulations by blood cells and eventually result in hydrocephalus. The volume of blood extravasated during SAH is larger with larger diameter of arterial wall breach, higher blood pressure, reduced clotting properties of the blood and larger volume of subarachnoid space⁶⁻⁸.

The most likely mechanism of haemorrhage arrest in the intracranial aneurysm rupture is rapid reduction of CPP to near zero as a consequence of ICP rise. When ICP rises as high as the mean arterial blood pressure, arrest of the cerebral circulation occurs. Because there are intraparenchymal as well as interhemispheric differences in pressure and locally occurring early or acute spasms of the arteries, cerebral blood flow is reduced to a varying degree and time^{12,13}. Systemic blood pressure rises when brain perfusion is inadequate, an event known as Cushing reflex but this does not enough

to maintain adequate CPP which is falling with the rise of ICP. Studies of regional cerebral blood flow in experimental animals confirmed deprivation of blood flow and reduction of metabolic and electrical activity of the brain^{6,9}. Reduced brain perfusion leads to loss of consciousness and may result in permanent neurological deficit⁶.

In the acute stage lasting around 5 minutes a surge of catecholamines may lead to life-threatening cardiac arrhythmias, pulmonary oedema. Apnea has been noted in primate models as a symptom of brain stem dysfunction.

ICP elevation during acute stage of SAH is explained by various mechanisms. The straightforward levelling of pressure in two connected fluid compartments: arterial lumen and subarachnoid space is accompanied by obstruction of cerebrospinal fluid outflow by large volume of blood causing immediate decrease of CSF outflow. Continued haemorrhage with existing outflow obstruction causes rapid elevation of ICP. Another explanation is offered based on an observation of transcranial Doppler ultrasonography measuring intracranial blood flow at the time of SAH in patients experiencing secondary aneurysm rupture. This showed a reactive vasodilatation of distal cerebral arterioles and this was regarded by Grote and Hassler as the most important causative factor of increase of ICP.

After 5 minutes acute stage of SAH turns into a subacute stage with characteristic pathophysiological events representing earliest secondary response to SAH injury taking place in the next 30 minutes. Elevated ICP begins to resolve, but this does not necessarily is uniform in the intracranial compartments. Pressure in one hemisphere may remain significantly higher than that in the other hemisphere, resulting in brain shift which may adversely affect the local cerebral blood flow. The time course of ICP changes varies between individuals. When ICP remain high it represents a "tamponade" type of SAH course, leading in most cases to development of diffuse brain ischemia and death. In the majority of cases ICP falls steadily, but it does not reach the pre-SAH level in many hours or even days. Pressure autoregulation remains impaired in humans several days following SAH.

Already in the subacute stage beginning of cerebral blood-brain barrier disruption takes place. It develops within 4 hours after SAH and

local scattered foci may become confluent with time producing generalized brain oedema¹⁴.

Cerebral blood flow that drops considerably in the acute stage of SAH recovers at a varying rate and magnitude. Its process correlates with the degree of long term neurological damage. The regional cerebral blood flow recovers faster in the cortex than in the subcortical nuclei, which has been attributed to heterogeneity of no-reflow phenomenon in those structures. Regional cerebral blood flow studies show at the subacute stage, and shortly after hyperperfused areas of the brain often in the vicinity of the ischaemic foci.

In studies of temporary circulatory arrest in the brain Ames described a no-reflow phenomenon. Brain capillaries become blocked by slugging erythrocytes during flow arrest and not all of them are reopened when circulation in the bigger diameter vessels recover. This occurs also in the brains after aneurysmal SAH¹³.

Conclusion from early effects of aneurysmal SAH suggest that cerebral ischemic damage is induced at the time of aneurysmal rupture, and the degree is determined by the a number of presented factors, including amount and distribution of effused blood¹⁵.

It is assumed that early brain injury during SAH is responsible for 30% of deaths and arterial spasms to 10% of deaths.

Hydrocephalus develops in 10 to 20% of the patients after initial SAH. It can occur in the subacute stage as a result of disturbed circulation of cerebrospinal fluid through the blood clots obstructed cisterns at the base and the subarachnoid space. In the chronic stage blockade of arachnoid villi, the places of absorption of CSF, swelling of the villi and fibrosis of the leptomeninges may turn hydrocephalus into a permanent state.

Delayed arterial spasm occurs between day 3 and 14 from SAH. In majority of reports there it has not been proven angiographically, but neurological deterioration is ascribed to, and described as arterial spasm. Many authors propose that post-SAH neurological deficit occurring in the chronic stage of SAH is better called delayed neurological deficit (DND) unless a narrowing of the arteries can be confirmed. Arterial spasm in angiography is present in over 70% of patients in some stage following SAH. It is symptomatic in only half of those patients. Ischaemic symptoms may disappear even in cases with continuing spasms.

Conclusion

Intracranial aneurysm rupture triggers a cascade of pathophysiological events damaging the brain. The extent, severity and distribution of the damage depends on a variety of factors,

many of which were identified. After aneurysmal SAH the brain has a reduced capacity to withstand ischaemic or hypoxic stress and is more vulnerable than a healthy brain, even if symptoms of damage do not manifest in neurological clinical status of the patient.

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