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REVIEW

# Update on subarachnoid haemorrhage

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**Abstract** Subarachnoid haemorrhage (SAH) is less frequent than ischaemic stroke or intracerebral haemorrhage, but has a high public health relevance because it can affect young and middle-age adults, has considerable mortality and morbidity, it is treatable and preventable. SAH is traditionally a topic for neurosurgeons. However as endovascular interventions are becoming effective alternatives to surgical treatment, SAH should turn out to be of interest to neurologists, in particular to those devoted to stroke, emergency and neurointensive care. Despite stable incidence, the mortality of SAH has decreased in the last two decades due to better neurosurgical techniques and neurocritical care and to advances in interventional neuroradiological procedures.

We review the recent advances in the clinical and diagnostic aspects of SAH and in the genetics of intracranial aneurysms. A systematic review of the treatment of SAH and grading of the available evidence is included.

**Key words** subarachnoid haemorrhage · intracranial aneurysm · vasospasm

## Abbreviations

| | |
|---|---|
| SAH | subarachnoid haemorrhage |
| RR | relative risk |
| OR | odds ratio |
| CT | computerized tomography |
| CSF | cerebrospinal fluid |
| MR | magnetic resonance |
| EEG | electroencephalogram |
| ECG | electrocardiogram |
| WFNSS | World Federation of Neurological Surgeons Scale |
| RCT | randomised controlled trial |
| ICU | intensive care unit |

## Introduction

In this review, we have included selected advances in the clinical and diagnostic aspects of SAH and a systematic review of the treatment of ruptured intracranial aneurysms, SAH and its complications that we judge to be relevant to the general neurologist or to those with an interest in stroke care. Since 2000 other reviews [1, 8, 55, 102, 104] on SAH and cerebral aneurysms have been

JON 2606

published. SAH represent only 5 % of all strokes, but it is responsible for 25 % of all fatalities related to stroke. SAH is more common in females (3:2). SAH is an emergency. Patients with SAH should be referred urgently to a tertiary care centre providing expert cerebral aneurysm treatment, including endovascular, neurosurgical and neurointensive care management [92].

### SAH as a cause of death

SAH is a serious condition: global mortality ranges from 32–67 % [32]. 20 to 30 % of the survivors are left with disabling sequele. Less than 1/3 of the patients regain their previous occupation and life style. Among those who reach a tertiary care centre, $^1/_4$ will die from complications of SAH (mainly vasospasm) or its treatment within 2 weeks. SAH is also a cause of sudden death. Around 20 % of SAH patients die before arriving at the hospital. The estimated risk is 12 % for aneurysmal SAH and 45 % for posterior circulation aneurysms [35]. Sudden death may be due to cardiac arrhythmias or to global cerebral ischaemia and oedema secondary to the sudden rise of intracranial pressure due to intracranial bleeding from a large arterial source.

## Epidemiology of SAH

Contrary to other stroke types, the incidence of SAH remains stable: ~10/100000/year (6 to 16) [50]. The most recent epidemiological studies showed that contrary to the traditional concept, the incidence of SAH increases with age [91]. The occurrence of SAH exhibits a seasonal (winter and spring), diurnal (late morning) and daily (Sunday) peak pattern [25].

### Risk factors for SAH

The risk factors for SAH are not exactly the same as for other types of stroke. The most important vascular risk factors for SAH are hypertension, smoking and high alcohol intake [90]. Feigin et al. [26] recently updated their previous systematic review of risk factors for SAH, using data from population-based and case-control studies and confirmed that hypertension (RR longitudinal studies 2.5, OR case-control studies 2.6), smoking – RR longitudinal studies 2.2, OR case-control studies 3.1) and excessive alcohol consumption (RR longitudinal studies 2.1, case-control studies 1.5) were risk factors for SAH. Non-white ethnicity was a less robust risk factor, while oral contraceptives had no effect and hormonal replacement therapy, high cholesterol and diabetes were protective factors for SAH. Smoking and hypertension were also the more important risk factors for SAH in Asian-Pacific cohorts [23]. "Binge" alcohol intake was a risk factor for SAH in some studies performed in Scandinavia but not in Asia. Unfortunately, more than 1/3 of smokers continue to smoke after surviving a SAH, in particular those who started their habit at a young age, and those with history of depression and alcohol abuse [4].

The ACROSS study confirmed moderate to extreme physical exertion as a trigger of SAH (but not heavy smoking or binge drinking) [3].

## Genetics of SAH and intracranial aneurysms

First degree relatives but not second degree relatives of SAH patients have an increased risk of SAH [80]. In the population based study performed in Scotland, the 10-year prospective risk was 1.2 for first degree relatives and 0.5 for second degree relatives. The risk was highest in families with 2 first degree relatives affected [89].

An exceedingly small percentage of aneurysmal SAH is due to rare monozygotic disorders with Mendelian inheritance. These include primary connective tissue diseases (Ehlers-Danlos – mutation in collagen type 3; Marfan's syndrome – mutations in fibriline-1 gene; pseudoxantoma elasticum – mutations in ABCC6 gene), neurofibromatosis type 1 and polycystic kidney disease (mutations in PKD1 and PKD2).

Other evidence for a genetic predisposition to SAH and intracranial aneurysms comes from association studies. Candidate genes included ELN and COL1A2 that code structural proteins of the extracellular matrix and ACE II polymorphisms [78, 87]. In genome-wide screen linkage studies, the following susceptibility genes and loci have been identified: chromosome 7q11, 14q22 and 5q22–31 in Japanese families, chromosome 19q13.3 in Finnish families, chromosome 2p13 in Dutch families, chromosome 1p34.3–36.13 in US families.

Other studies associated some genes with SAH prognosis. ApoE – E4 was associated with worse prognosis but no association was found in other studies; eNOS – 786TC was associated with increased susceptibility to vasospasm; PAI-1–4 g was associated with worse prognosis.

For recent reviews on this topic see [58, 95, 105].

## Clinical aspects of SAH

SAH produces a rather typical clinical picture: a sudden onset, very severe headache, occurring during activity, followed in some cases by a transient disturbance of consciousness or vomiting. Neck stiffness and other meningeal signs are the main findings in the physical exam. Fundoscopy may reveal a retinal, subhyaloid or vitreous haemorrhage (Terson's syndrome) [56]. Less

commonly, SAH produces motor defects, aphasia, seizures, ptosis, diplopia or a complete III nerve palsy (Posterior Communicating Artery Aneurysm), visual troubles (carotid aneurysms) and amnesia (Anterior Communicating Artery Aneurysm)

However, about 20 % of SAH cases are not recognised in their first medical encounter [21, 49]. Most common misdiagnosis is migraine, tension headache and headache related to high blood pressure. The difficulty arises from the fact that sudden onset headache is a common condition that is sometimes due to SAH or other serious condition but is mostly harmless. Landtblom et al. [47] performed a prospective study of 137 patients with sudden onset headache of thunderclap type and only 11 % had a SAH. Differential diagnosis of sudden onset headache is described in Table 1.

SAH is preceded in about 10 % of the cases by a "sentinel headache" or warning leak, an episode of headache similar to that of SAH, and preceding it by days or weeks. This is currently judged to be in fact a minor undiagnosed SAH. A recent systematic review concluded that their true incidence may vary from 0 to 40 %, depending on the rate of misdiagnosis in the community. Sentinel headache is more common in aneurysmal than in non-aneurysmal SAH, indicating that the majority of sentinel headaches are not due to recall bias [72].

Bleeding in the spinal subarachnoid space (Fig. 1), originating from a spinal source or from diffusion from an encephalic source, can produce radicular pain mimicking sciatica, back pain [44] or a "coup de poignard" syndrome, a sudden precordial pain simulating myocardial infarction or aortic dissection [5, 13].

SAH can also present as a psychiatric condition: a burst of aggressive or bizarre behaviour [73] or as delirium. Psychiatric manifestations are common in the acute phase: depression – 60 %, denial – 28 %, apathy – 28 % and delirium – 18 % [12]. Delirium is more frequent in patients with intraventricular bleeding, hydrocephalus and baso-frontal haematomas, reflecting the involvement of anatomical networks subserving sustained attention, declarative memory and the expression of emotional behaviour [11].

SAH in the elderly has some distinct clinical aspects: a larger proportion of elderly patients present in poor clinical condition. Complications, both medical and neurological, in particular hydrocephalus, are more common. The prognosis is worse than in younger patients. Half of the patients die and only 1 out of 6 SAH patients older than 75 will leave the hospital alive and independent [33, 67].

**Table 1** Differential diagnosis of sudden onset headache

| |
|---|
| Primary thunderclap headache |
| Primary exertional headache |
| Primary headache associated with sexual activity |
| Primary cough headache |
| Sudden onset migraine |
| Cervicogenic headache |
| Headache related to cerebrovascular disorders |
| Subarachnoid haemorrhage |
| Intracerebral haemorrhage |
| Ischaemic stroke |
| Carotid or vertebral dissection |
| Dural sinus thrombosis |
| Hypophyseal apoplexy |
| Intracranial neoplasms and cysts |
| Acute meningitis |
| Sinusitis |

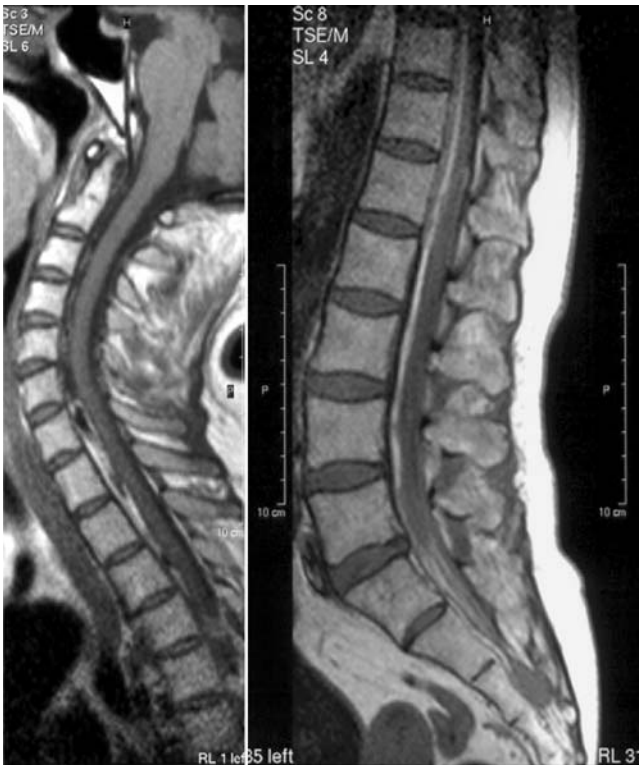


**Fig. 1** Spontaneous spinal subarachnoid haemorrhage. MR ($T_1$ sequence) of the dorsal and lumbar spine showing hematic hyperintensities anterior to the spinal cord

## Diagnosis of SAH

### Is lumbar puncture still necessary?

Subarachnoid haematic densities on an early brain CT are diagnostic of SAH. However if the amount of blood in the CSF is minute it may not be detected by CT. Sensitivity of new generation CTs ranges from 93 to 100 % [55]. The later the CT is performed, the lower the likelihood of having hyperintensities in the subarachnoid

space, because they will become gradually isodense. 30 % of the scans will be negative within 4 days and 50 % at one week after the initial bleeding.

In suspected cases with negative scans a lumbar puncture must be performed. Xanthochromia in CSF is due to bilirubin (from haemoglobin) and is diagnostic. Xanthochromia develops between 2 to 12 h after bleeding and takes at least 2 weeks to clear. Traumatic lumbar puncture (about 20 %) causes bloody CSF (decreasing in successive samples) but not xanthochromia (if centrifugation is not too delayed). Spectrophotometry of the CSF is the recommended method of analysis. This should be done on the final bottle of CSF collected [6]. Fig. 2 shows a proposed flow chart for the diagnosis of SAH.

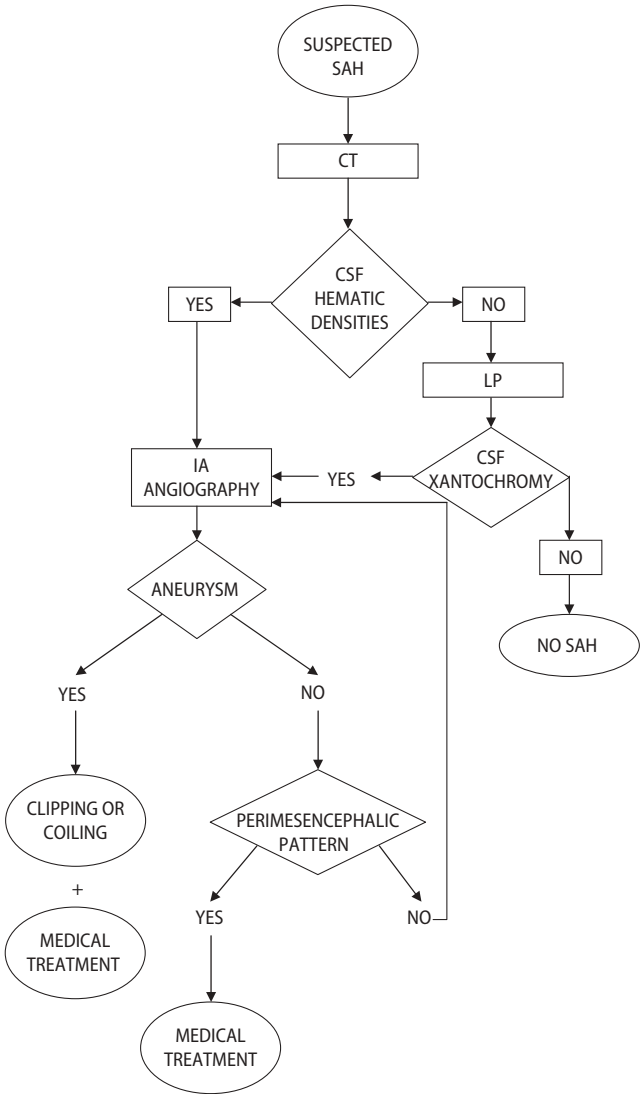


**Fig. 2** Flow chart for the diagnosis of SAH

### MR, CT or intra-arterial angiography?

MR can also be useful to detect cases with delayed presentation, by showing hyperintensity signals in the subarachnoid space (Fig. 3) [46, 60]. Intra-arterial angiography remains the gold standard for the diagnosis of aneurysms and should be performed as soon as possible, to hasten endovascular or surgical treatment of the aneurysm to prevent rebleeding (Fig. 4). Although it can detect aneurysm as small as 3 mm, MR angiography is not as sensitive as intra-arterial angiography and produces false positive results. In some cases (e.g. elderly patients or patients with severe limb or aortic atheroma) or in some institutions, CT angiography is used instead of intra-arterial angiography. However the sensitivity of CTA compared to intra-arterial angiography varies between 85 and 98 %.

## Etiology of SAH

About $^{3}/_{4}$ of the cases of SAH are due to ruptured intracranial aneurysms. Other causes are cranio-cerebral trauma, arterio-venous malformations, dural fistulae, dural sinus thrombosis, intracranial arterial dissection, mycotic aneurysms, bleeding diseases and drugs (cocaine) [34]. The majority of these causes can be identified by clinical history and MR. In about 20 % of the cases no cause is found. Angiography must be repeated in such patients in a variable interval (days to 2 weeks) after the first one, but the yield of repeat angiography is very low (~2 %). In a few patients, hematic densities are limited to the perimesencephalic cisterns, with no blood on the convexity, the interhemispheric fissure or the vertical part of the Sylvian fissure (Fig. 5). These patients have a perimesencephalic pattern of SAH [103] that is rarely due to aneurysmal rupture (< 10 %). It is considered to be of venous origin or due to intramural dissection. This pattern only applies to patients with early (< 4 days) scans. Perimesencephalic SAH has a benign course although it can be complicated by hydrocephalus. In one case-series, the presence of intraventricular blood was associated with the development of acute hydrocephalus, a higher complication rate and a poorer outcome in comparison with patients without intraventricular blood [27]. In patients with perimesencephalic SAH repeat angiography is not warranted if the first angio is negative.

There are multiple aneurysms in about 25 % of the cases. Patients with multiple aneurysms are younger than those with single aneurysms, pointing towards a stronger genetic component.

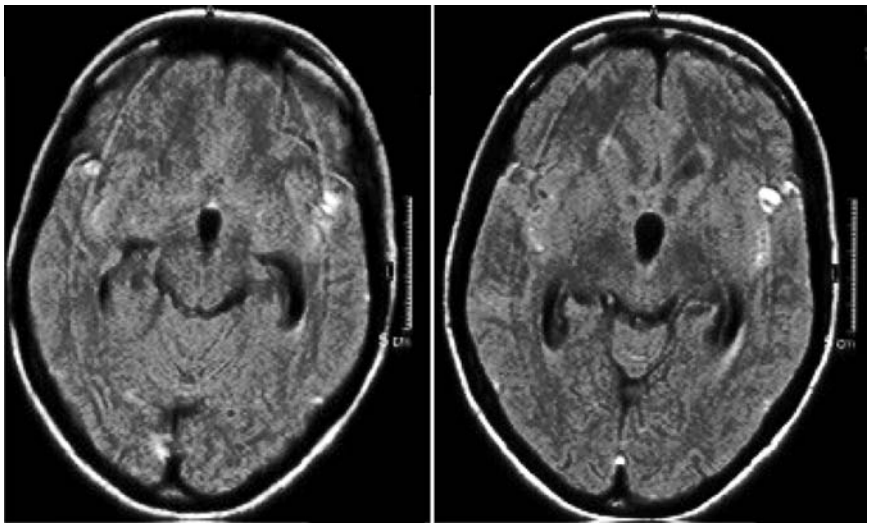

**Fig. 3** MR hyperintensities in the Sylvian and calcarine fissures in a patient with subarachnoid bleeding a week before

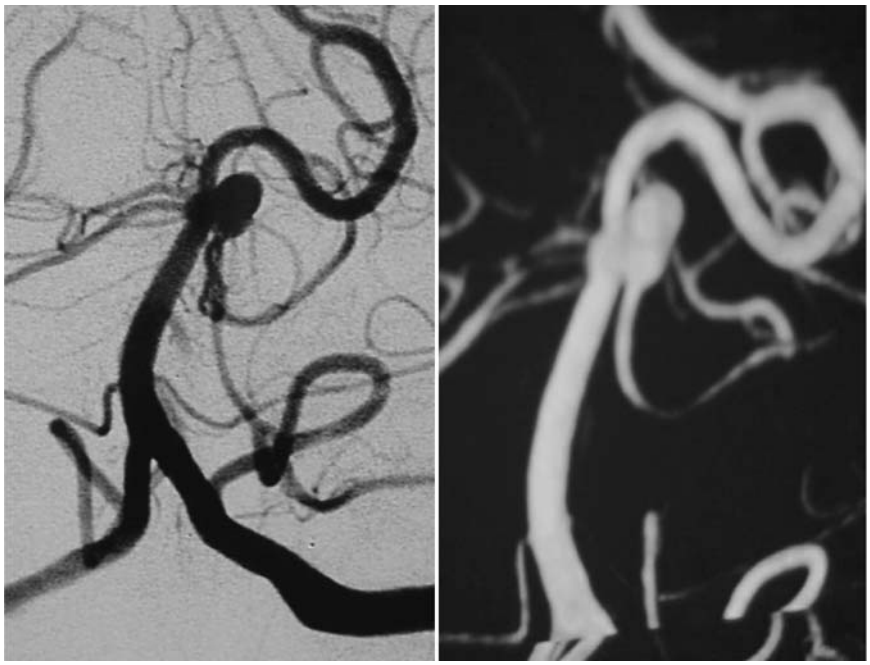

**Fig. 4** Intra-arterial angiography. 2-D (left) and 3D (right) views of a basilar aneurysm

## Complications of SAH

The clinical course of SAH can have several complications. The most important neurological complications are rebleeding [65], intracerebral haematoma and intraventricular haemorrhage, vasospasm, hydrocephalus and seizures. Continuous EEG monitoring may detect non-convulsive status epilepticus in about 8 % of SAH patients and unexplained coma or neurological deterioration [19].

### Rebleeding

Rebleeding is the most feared complication and peaks in the first few days after the first bleeding. Rebleeding is more frequent in patients with poor clinical condition and in those with large aneurysms. Rebleeding carries a dismal outcome. If the aneurysm is not treated, the risk of rebleeding within 4 weeks is estimated to be of 35–40 % [31]. After the first month the risk decreases gradually from 1–2 %/day to 3 %/year [111].

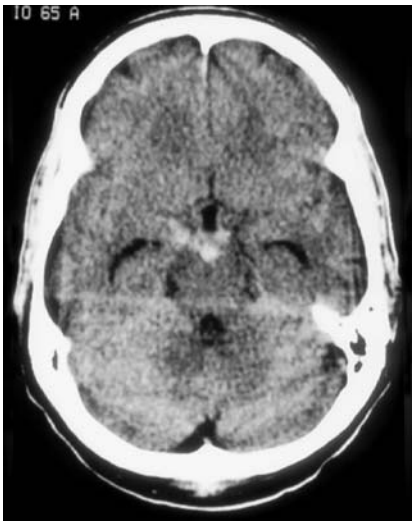


**Fig. 5** Acute cranial CT of a patient with a perimesencephalic pattern of SAH

## Cardiac complications of SAH

ECG changes are common in acute SAH, being present in about $^{3}/_{4}$ of acute SAH patients and include: sinus bradycardia or tachycardia, QT prolongation, bundle branch block, ST depression or elevation, T wave changes and pathological Q waves. Some of these changes may mimic those of acute myocardial infarction [42, 54, 79]. In addition, enzyme elevation, echocardiogram wall motion abnormalities, abnormal thallium scans, pulmonary oedema and myocardial pathological changes at autopsy have been reported. These cardiac changes are thought to be mediated through systemic release of adrenaline and noradrenaline and through sympathetic and parasympathetic cardiac nervous connections. As mentioned in the introduction, SAH can cause cardiac arrest and sudden death. Most cases of cardiac arrest occur at the time of initial or recurrent SAH. Resuscitation is worthwhile as it is often successful and the outcome of survivors is not worse than that of other SAH patients [96].

## Diagnosis of vasospasm

Transcranial Doppler is used for diagnosis of vasospasm in SAH patients. Compared to angiography, for the middle cerebral artery, transcranial Doppler has a high specificity (99%) and high positive predictive (97%) values. However the sensitivity is moderate (67%); for the anterior cerebral artery specificity is 76% and sensitivity is 42%; for the other arteries there is lack of evidence of accuracy of transcranial Doppler [53].

## Prognosis of SAH

The major prognostic factor in SAH is the severity of the initial bleeding, measured either clinically by grading scales such as the Glasgow Coma Scale, Hunt and Hess or the WFNS scales (Table 2) and from the amount of haematic densities in the admission scan, measured by the Fisher's or the Hidja's scales (Table 2) [76]. Other variables with influence in prognosis are age, intracerebral and intraventricular haemorrhage, blood pressure values, location [16] and size of the aneurysm and time to diagnosis.

Long-term neuropsychological consequences (memory and executive deficits) are well known among SAH survivors. Less known is neuroendocrinal dysfunction [45] showed pituitary deficiency in 18 of 40 SAH survivors. Many patients who survive an episode of SAH have disorders of sleep and wake, which are related to their quality of life [81].

Epilepsy occurs in 7–12% of SAH survivors and it is predicted by cerebral infarction and subdural

**Table 2** Commonly used clinical and imaging SAH scales

**World Federation of Neurological Surgeons grading system**

| WFNS grade | Glasgow Coma Scale Score | Focal deficit |
|---|---|---|
| I | 15 | Absent |
| II | 14–13 | Absent |
| III | 14–13 | Present |
| IV | 12–7 | Present or absent |
| V | 6–3 | Present or absent |

**Hunt and Hess grading system**

| Category* | Criteria |
|---|---|
| Grade I | Asymptomatic or minimal headache and slight nuchal rigidity |
| Grade II | Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy |
| Grade III | Drowsiness, confusion, or mild focal deficit |
| Grade IV | Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances |
| Grade V | Deep coma, decerebrate rigidity, moribund appearance |

* Serious systemic disease, such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography result in placement of the patient in the next less favourable category

**Fisher scale**

| |
|---|
| Group 1: No detectable blood on CT |
| Group 2: Diffuse blood that does not appear dense enough to represent a large, thick homogenous clot. |
| Group 3: Dense collection of blood that appears to represent a clot greater than 1 mm thick in the vertical plane or greater than 5x3 mm in longitudinal and transverse dimensions in the horizontal plane; severe spasm predicted. |
| Group 4: Intracerebral or intraventricular clots, but with only diffuse blood or no blood in basal cisterns. |

haematoma and is associated with poor functional recovery and quality of life [15]. Seizures are infrequent in cases treated only with coil embolization [10].

## Treatment: a review of the evidence

We performed a literature review for each of the therapeutic interventions listed below in the Medline, Cochrane Library, Neurosurgical and Neurological Intensive Care books. Priority was given to randomised controlled trials, meta-analyses and systematic reviews. If lacking, data provided by other clinical trials and expert opinions were considered. The level of evidence was classified according to Brainin et al. [7].

The search strategy was planned using the key words: aneurysm*, subarachnoid, haemorrhage (or hemorrhage). For each of the treatments and intervention other key words were specifically used (e.g. surgery OR surgical OR clipping OR neurosurg* endovascular OR coil* OR "interventional neuroradiology" OR catheter* OR neurovascular). Tables 2 and 3 describe the level of evidence for each of the interventions mentioned in the text, accordingly to the evidence grading system used in this review (Brainin et al. [7]).

### Prevention of rebleeding

The main strategy to prevent rebleeding is to treat the aneurysm, excluding it from the arterial circulation. Should this be done by surgery (clipping) or through an endovascular procedure (coiling)? And how soon after the initial bleeding should it be done? Three other measures may decrease the risk of rebleeding: physical rest and avoidance of valsalva's manoeuvre, blood pressure control and antifibrinolitics.

#### Clipping or coiling? (Fig. 6)

Two RCTs have been performed [43]. In the Koivisto et al. trial, which included 109 patients, clinical and neuropsychological outcomes at one year were comparable after early surgical and endovascular treatment. The ISAT trial [37, 61] showed that in patients with a ruptured intracranial aneurysm, for which endovascular coiling and neurosurgical clipping are therapeutic options, survival free of disability at 1 year was significantly better with endovascular coiling. This survival benefit continues for at least 7 years. The risk of seizures was also lower with coiling. Although the long-term risks of further bleeding are very low with either treatment they are somewhat more frequent after coiling.

Some important features of the ISAT trial should be considered when transposing its results into practice [9]. It followed the incertitude principle and therefore many patients were treated surgically or by endovascular techniques outside the trial; it only included aneurysms of the anterior circulation; the majority of treated aneurysms were < 10 mm in size; patients were treated very shortly (mean 2 days) after the diagnosis, so the results cannot be generalised to centres where the endovascular procedures cannot be performed on an emergency basis. Finally, to transpose ISAT results into practice it is crucial to know the local figures for morbidity and mortality after coiling and clipping. The selection of the best treatment depends also on the morphology and location of the aneurysm (e.g. aneurysm with large necks are not convenient for coiling; posterior circulation aneurysms are best treated by endovascular techniques) [39, 51].

Incomplete treatment is more frequent after coiling. There is also less certainty concerning the long-term occlusion of the aneurysm. Therefore coiled patients need

**Table 3** Treatment interventions for subarachnoid haemorrhage. Classification of levels of evidence (according to Brainin M et al. 2004) [6]

| Treatment strategies | Evidence classification |
|---|---|
| Rebleeding, prevention | |
| Aneurysm treatment (surgical or endovascular) | II |
| Endovascular if both feasible early | |
| Early aneurysm treatment | III – surgical treatment<br>IV – endovascular treatment |
| Avoidance of Valsalva manoeuvre, physical rest and blood pressure control | IV |
| Antifibrinolytics proved harmful | II |
| Vasospasm, prevention | |
| Nimodipine per os 60 mg 4/4 h | II |
| No benefit for triple H therapy | IV |
| Avoid hypovolemia | III |
| No benefit for tirilazad | I |
| Vasospasm, symptomatic | |
| Triple H therapy | IV |
| Balloon angioplasty (if refractory to medical treatment) | IV |
| Intra-arterial vasodilator (if refractory to medical treatment) | IV |
| Acute hydrocephalus | |
| Ventricular drainage | IV |
| Hyponatremia, prevention | |
| Fludrocortisone or hydrocortisone | III |
| Treatment with steroids | IV |
| Treatment strategies waiting further evidence | |
| Intracysternal thrombolytics for preventing vasospasm | |
| Intraventricular vasodilators for preventing vasospasm | |
| Nicardipine prolonged release implants for preventing vasospasm | |
| Antiplatelet agents for preventing vasospasm | |
| Statins for preventing vasospasm | |
| Endothelin antagonists for preventing vasospasm | |
| Intraventricular fibrinolytics for intraventricular haemorrhage | |

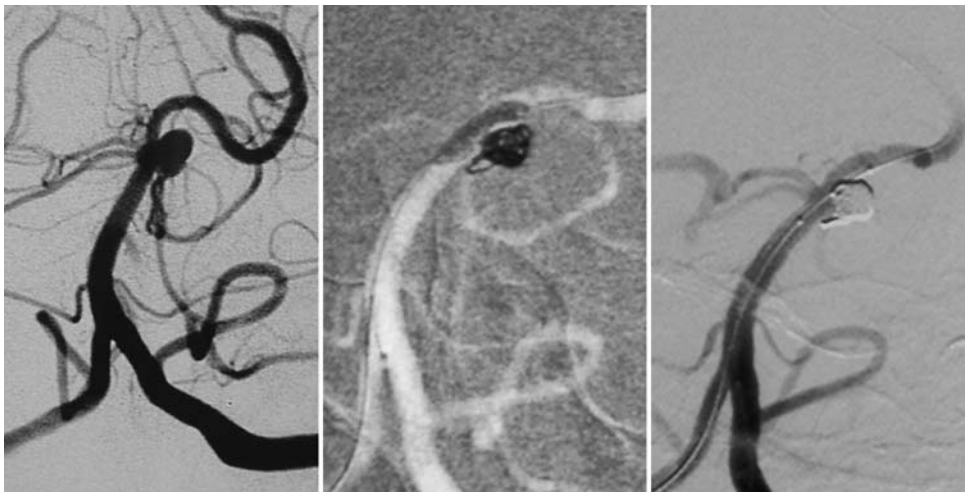

**Fig. 6** Treatment of a basilar aneurysm by endovascular intervention. Untreated aneurysm (left). Due to the large neck of the aneurysm, a balloon was temporarily placed in the lumen of the artery while coils were detached to fill the aneurysm sac (centre). The treated aneurysm is excluded from the circulation (right)

periodically angiographic control, which should also be performed in clipped patients.

Based on the available evidence, it is recommended that in a patient with acute aneurysmal SAH in whom both treatments are feasible, coiling is the preferred choice [101], if it can be performed within 72 h after SAH.

There is considerable uncertainty regarding the best treatment options for SAH patients grades IV and V on admission. Evidence from case series in the literature, local practice results, ethical issues and cost should be taken into consideration. These patients have in general a poorer prognosis than patients in grades 0–III, but a subgroup appears to benefit from aggressive management (ICU care, ventricular drainage, angiography and endovascular or surgical treatment of the aneurysm) at a cost-effective ratio [110].

### Early or late treatment?

There are two systematic reviews [18, 108] and a RCT evaluating the impact of time of surgery [68]. There are no studies of comparable quality in respect to endovascular treatment, nor in relation to specific subgroups of patients, such as those in poor condition and elderly patients. The evidence indicates that patients with aneurysmal SAH grades I–III should be treated as soon as possible (< 72 h) (evidence class III, for surgical treatment).

### Treatment of blood pressure

There are no RCTs or systematic reviews on this topic. Reduction of blood pressure decreases the risk of rebleeding and increases the risk of ischaemia if vasospasm develops. An arbitrary cut-off of 180/100 mmHg is currently used in patients with untreated aneurysms, to treat BP.

### Antifibrinolytic treatment

A systematic review of nine clinical trials was published [77]. Fibrinolytics decreased the probability of rebleeding, but increased cerebral ischaemia and consequently poor outcome. Therefore, available evidence (class II) does not support their use.

## Prevention of vasospasm and delayed cerebral ischaemia

There are three options to prevent and treat vasospasm: calcium channel blockers, triple H therapy (hypertension, haemodilution, hypervolaemia) and other treatments, including vasodilators, intracisternal thrombolytics, antiplatelets, neuroprotectors, statins, magnesium and endothelin antagonists.

### Calcium channel blockers

There are several trials and five published meta-analyses evaluating the effect of calcium channel blockers (mainly nimodipine) in the prevention of vasospasm and delayed cerebral ischaemia [74].

Treatment with oral nimodipine, 60 mg 4/4 h, should be started immediately after the diagnosis and maintained for 21 days. Intravenous nimodipine is not recommended routinely due to potentially harmful decrease of blood pressure and because the majority of the trials used oral nimodipine.

Nicardipine prolonged-release implants were used successfully and safely for preventing vasospasm in a non-randomised, non-blind, controlled study [40, 41].

### Triple H therapy

The basis for the triple H therapy (hypervolemia, hypertension and haemodilution) is the finding that delayed cerebral ischaemia is enhanced by dehydration and limitation of fluid intake. Triple H treatment is used in the majority of the centres. It improves cerebral blood flow, but it remains unclear if it decreases delayed cerebral ischaemia. This therapy has several side effects, both neurological (cerebral oedema, rebleeding) and systemic (dilutional hyponatremia, cardiac failure with pulmonary oedema) [48, 84].

The evidence concerning triple H is poor. There is an inconclusive systematic review [97] and a meta-analysis of 2 small RCTs of hypervolemia with plasma expanders [74]. After the review three other RCTs trials were published. Again no benefit on functional outcome was demonstrated [22].

Hypovolemia should be avoided. Because of safety concerns, albumin should not be used. There is no evidence that hypervolemia is better or safer than normovolemia. If prescribed prophylactically as an option, triple H therapy should be limited to a few days to decrease the risk of complications. However it is more sensible to start triple H therapy when deficits develop and are thought to be related to vasospasm and delayed cerebral ischaemia.

### Other treatments

**Cysternal thrombolytics.** A meta-analysis [2] indicates a positive effect of this therapy in decreasing mortality and delayed cerebral ischaemia. However a RCT could not demonstrate such efficacy. There are insufficient data regarding safety of this intervention. New RCTs are necessary before direct cysternal injection of thrombolytics can be recommended as a routine. In any case this treatment can only be performed after coiling or clipping the aneurysm.

**Cysternal or intraventricular vasodilators.** In a non-randomised study with no controls sustained release papaverine was associated with a better functional prognosis [17]. Sodium nitroprussiate was used to prevent vasospasm in high risk patients and to treat refractory vasospasm, with no important side effects [93]. These treatments should be considered experimental.

**Antiplatelet agents and anticoagulants.** Following SAH there is an activation of platelet aggregation and an increased release of thromboxane A2, in particular in those who develop vasospasm. A systematic review indicated that aspirin produces a decrease in delayed cerebral ischaemia. The nº of patients was too small to allow conclusions regarding functional outcome and haemorrhagic risk [57]. Therefore, aspirin cannot be recommended routinely in acute SAH. A single RCT of 170 patients with enoxaparin [85] showed that enoxaparin did not improve outcome but increased intracranial bleeding slightly.

**Statins.** Prior statin use was associated with better functional outcome in a matched controlled cohort study [69], although in another study statins were associated with an increased risk for vasospasm, probably due to abrupt statin withdrawal [86]. In a phase II RCT of 80 patients, pravastatin 40 mg/d was safe and reduced cerebral vasospasm, delayed ischemic deficits and overall mortality [98].

**Neuroprotectors.** Several RTCs tested the efficacy of free radical scavengers, namely the aminosteroid tirilazad, to prevent vasospasm. A meta-analysis of such trials concluded that tirilazad does not improve the outcome of SAH patients (class I) [20].

**New pharmacological treatments.** Several new compounds are undergoing pharmacological investigation as potential treatments for vasospasm and secondary ischaemia after SAH. Examples are nitric oxide donors, endothelin antagonists [99], potassium channel activators, erythropoietin [29, 38] and magnesium [100].

## Treatment of established vasospasm and delayed cerebral ischaemia

Despite its limitation, transcranial Doppler is the most used and useful technique to monitor vasospasm. The following values of middle cerebral artery flow velocities are indicative of vasospasm: mean middle cerebral artery flow velocity $>120$ cm/s (cut-off with highest negative predictive value) or $>200$ cm/s (cut-off with highest positive predictive value) or a daily increase $>50$ cm/s; the index middle cerebral artery/internal carotid artery should be $>3$. Alternatives or complements to transcranial Doppler for monitoring vasospasm include single photon emission tomography, Xenon CT and novel devices such as a thermal diffusion microprobe [94].

If a patient with vasospasm develops symptoms the most commonly used treatment is the triple H therapy. If symptoms persist, endovascular interventions (intra-arterial vasodilators and/or balloon angioplasty are used as a rescue treatment.

### Triple H therapy

Triple H therapy is routinely used to treat symptomatic vasospasm, despite lack of evidence from RCTs or systematic reviews [38]. There are several controlled and uncontrolled case series demonstrating that triple H

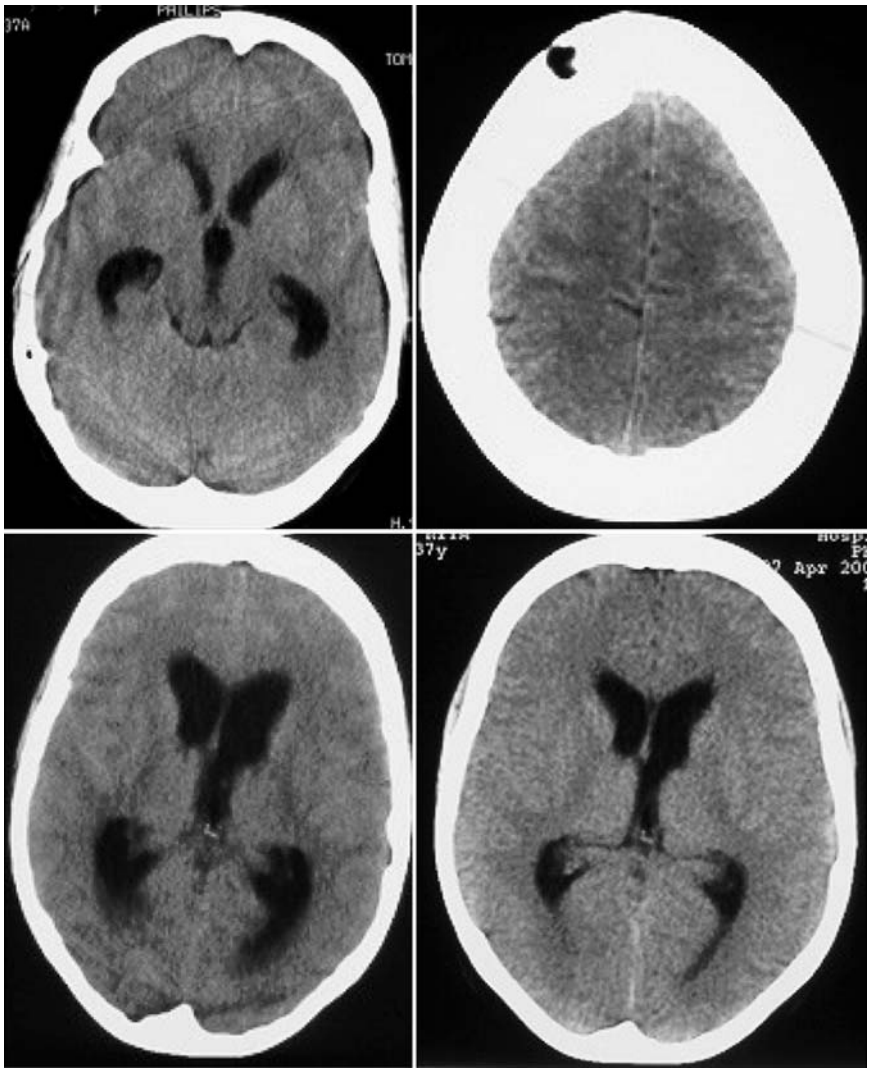

**Fig. 7** Acute hydrocephalus (left), treated by external drain (right)

therapy reverses vasospasm and its symptoms and a few trials of questionable methodological quality evaluating only one of the components of this therapy. In one R- and one quasi-RCT volume expansion failed to improve prognosis or to decrease the occurrence of secondary ischaemia and tended to increase the rate of complications. In another quasi-RCT hypervolemia reduced secondary ischaemia in the pre-operative period [74].

The surrogate goals of triple H therapy are to reach a central venous pressure of 8–12 cm$H_2O$, 30–35 % haematocrit and mean arterial pressure 20 % above baseline, using IV crystalloids (e.g. 2000 ml 5 % dextrose + 2000 ml normal saline or colloids (500–1000 ml)). Vasopressor amines (phenylephrine, dopamine, dobutamine) are used to raise blood pressure.

## Endovascular treatment

**Ballon angioplasty.** In vasospasm refractory to medical treatment, arterial dilatation can be accomplished by balloon angioplasty [112]. This technique is effective in achieving proximal (but not distal) arterial dilatation, but is associated with risk of arterial rupture, re-bleeding and reperfusion syndrome. Despite several case series claiming optimistic results, there is only one controlled non-randomised retrospective case-study of 38 patients with neutral results [70].

**Intra-arterial vasodilators.** Intra-arterial injection of vasodilators has also been shown to reverse vasospasm. However, this effect is short-lived and these drugs can cause severe hypotension and brainstem depression. Some case series using AT877 and nimodipine [62] were reported, but there is only one non-randomised retro-

spective case-control study of 31 patients treated with intra-arterial papaverine [71].

### Treatment of intraventricular haemorrhage and acute hydrocephalus

Acute hydrocephalus is a frequent complication of SAH. When symptomatic it can be treated with external ventricular drainage (Fig. 7). Repeated lumbar punctures are used in some centres although they carry the theoretical risk of re-bleeding if the aneurysm is not treated before. None of these therapeutic options was tested in clinical trials.

Intraventricular haemorrhage is associated with a poor prognosis, in particular if the amount of intraventricular blood is massive and there is accompanying hydrocephalus. In these cases clots can occlude the ventricular drain, making the relief of hydrocephalus more troublesome.

Some case series report the use of intraventricular fibrinolytics to prevent and treat hydrocephalus associated with intraventricular haemorrhage in SAH. Results are favourable when compared with non-treated patients, but the studies were non-randomised and the number of treated patients small. The meta-analysis of external ventricular drainage and fibrinolytics in SAH was inconclusive [66].

#### Steroids

Steroids are potentially useful in acute SAH by decreasing vasogenic oedema, inflammation and improving cerebral blood flow. However it is well known that they have a series of dangerous side effects, mostly increased risk of gastro-intestinal bleeding, infections and diabetes. A meta-analysis of three trials of steroids in SAH was unable to demonstrate evidence of either benefit or harm [24]. If steroids (e.g. dexamethasone 4 mg every 6 h for a few days) are prescribed, gastric protection with omeprazole or ranitidine should be used.

### Treatment and prevention of hyponatremia

Hyponatremia is secondary to increased natriuresis. Vasopressin and desmopressin are commonly used to correct hyponatremia, despite the lack of evidence from RCTs. Several case series and controlled trials point out that hydrocortisone or fludrocortisone may be useful in the prevention of excessive natriuresis [30, 63, 64, 109].

Although oral NaCl 4–12 g/d, normal saline IV or hypertonic saline IV may be used to correct hyponatremia, they usually produce increased natriuresis and osmotic diuresis. Therefore, fludrocortisone 0.3 mg/d, 3x/d (class IV) is the preferred option, when it is necessary to correct hyponatremia.

### Treatment of SAH in particular subgroups of patients

#### Elderly patients

Despite the lack of information of good quality (no RCTs specifically designed for this age group, very few elderly patients included in RCTs of SAH treatment, no matched or stratified case-control studies) [33, 52, 67, 82, 88], the available evidence of case-series from centres in different world regions indicates that both surgical repair and endovascular treatment are feasible in this age group with acceptable rates of morbidity. Elderly patients more likely to benefit are those in good condition prior to the intervention [33, 52, 66].

#### Pregnancy

SAH during pregnancy is an important cause of maternal death. Ruptured aneurysms during pregnancy should be treated, surgically or by coiling. If the gestational age allows, it is better to carry out the delivery by caesarean before aneurysmal treatment [75, 83].

## Screening for new and asymptomatic aneurysms

Contrary to current beliefs, aneurysms are not congenital but develop continuously during lifetime. Unruptured aneurysms have a risk of rupture of ~1 %/year, depending on their size.

Current evidence indicates that in patients with a life expectancy of at least 20 years, only those in the anterior circulation < 7 mm should be left untreated. Screening for unruptured aneurysms is controversial [59].

#### Polycystic kidney disease

Patients with autosomal dominant polycystic kidney disease have a relative risk of SAH of 4.4 % compared to the general population. Risk-benefit analysis failed to show any benefit of screening for unruptured aneurysms in these patients [28, 36].

#### Relatives of SAH patients

Screening with MR-angio or CT-angio for aneurysms in first degree relatives of SAH patients with more than one first degree relative with SAH or unruptured aneurysms is recommended by the American Heart Association 2000 guidelines. Angiography will reveal aneurysms in about 10 %. Knowing to harbour an aneurysm has a negative impact in quality of life. The decision to screen

must incorporate the life expectancy and preferences of the person to be screened and the local complication rates for aneurysm treatment. In patients with familial aneurysm the motivation for screening appears to be high. Once the decision had been taken to screen an individual, screening probably needs to be repeated, because new aneurysms may develop and SAH has been described after an initial negative screening [107].

### SAH patients

In patients with aneurysmal SAH, new aneurysms develop at a rate of 0.28 to 1.62 %/year for both de novo aneurysms and for a second aneurysm [14]. In a decision model analysis Wermer at al. [106] found that the expected number of QALYs 10 years after clipping was the same for screening and for no screening. In general, screening for new aneurysms should not be recommended. However, in patients who fear a recurrence, screening increases QALY at acceptable costs. The identification of a subgroup of patients who have a high risk of aneurysm formation and rupture is necessary before screening can be recommended.

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