

Subarachnoid haemorrhage

Jan van Gijn, Richard S Kerr, Gabriel J E Rinkel

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Department of Neurology,
Rudolf Magnus Institute of
Neuroscience, University
Medical Centre Utrecht,
3584CX Utrecht, Netherlands
(Prof J van Gijn FRCP,
Prof G J E Rinkel MD); and
Department of Neurosurgery,
Radcliffe Infirmary, Oxford, UK
(Mr R S Kerr FRCS)

Correspondence to:
Prof Jan van Gijn
J.vanGijn@umcutrecht.nl

Subarachnoid haemorrhage accounts for only 5% of strokes, but occurs at a fairly young age. Sudden headache is the cardinal feature, but patients might not report the mode of onset. CT brain scanning is normal in most patients with sudden headache, but to exclude subarachnoid haemorrhage or other serious disorders, a carefully planned lumbar puncture is also needed. Aneurysms are the cause of subarachnoid haemorrhage in 85% of cases. The case fatality after aneurysmal haemorrhage is 50%; one in eight patients with subarachnoid haemorrhage dies outside hospital. Rebleeding is the most imminent danger; a first aim is therefore occlusion of the aneurysm. Endovascular obliteration by means of platinum spirals (coiling) is the preferred mode of treatment, but some patients require a direct neurosurgical approach (clipping). Another complication is delayed cerebral ischaemia; the risk is reduced with oral nimodipine and probably by maintaining circulatory volume. Hydrocephalus might cause gradual obtundation in the first few hours or days; it can be treated by lumbar puncture or ventricular drainage, dependent on the site of obstruction.

Only one in every 20 strokes is caused by subarachnoid haemorrhage from an intracranial aneurysm, but because the disease strikes at a fairly young age and is often fatal, the loss of productive life years is similar to that for cerebral infarction or intracerebral haemorrhage.¹ The diagnosis and acute management of subarachnoid haemorrhage represents a challenge to neurologists, neurosurgeons, interventional radiologists, and intensivists.

Epidemiology

The incidence of subarachnoid haemorrhage was overestimated until brain imaging allowed accurate distinction between subarachnoid and intracerebral haemorrhage. In most populations the incidence is 6–7 per 100 000 person-years (after adjustment to age-standardised rates),^{2,3} but is around 20 per 100 000 in Finland and Japan.² Thus, a full-time general practitioner with 2000 patients will see, on average, one patient with subarachnoid haemorrhage about every 7–8 years. Although the incidence increases with age, half the patients are younger than 55 years at the time of subarachnoid haemorrhage.³ Ruptured aneurysms are the cause in 85% of patients, whereas 10% fit into the pattern of so-called non-aneurysmal perimesencephalic haemorrhage, a relatively innocuous condition. The remaining 5% are caused by various rare causes (panel 1). The case fatality rate is about 50% in population-based studies, with a trend towards gradual improvement.^{4,5} This proportion includes 10–15% of all patients with

subarachnoid haemorrhage who die at home or during transportation to hospital.⁶

Pathophysiology Aneurysms

Intracranial aneurysms are not congenital, as was once believed, but develop in the course of life.⁷ The best estimate of the frequency of aneurysms for an average adult without specific risk factors is 2.3% (95% CI 1.7–3.1); this proportion increases with age.⁷ Saccular aneurysms arise at sites of arterial branching, usually at the base of the brain, either on the circle of Willis itself or at a nearby branching point (figure 1). Most intracranial aneurysms will never rupture. The rupture risk increases with the size of aneurysm, but paradoxically, most ruptured aneurysms are small—ie, less than 1 cm; the explanation for this paradox is that 90% of all aneurysms are small and the small fraction of this majority that ruptures outnumber the greater fraction of the minority of large aneurysms that ruptures.

Modifiable risk factors for subarachnoid haemorrhage are hypertension, smoking, and excessive alcohol intake, all of which more-or-less double the risk.⁸ In terms of attributable risk, these modifiable risk factors account for two of every three haemorrhages, and genetic factors for only one of every ten.⁹ In patients with a positive family history of subarachnoid haemorrhage, the average age at which the haemorrhage occurs is younger than in patients with sporadic subarachnoid haemorrhage, and the aneurysms are more often large and multiple than in patients with sporadic subarachnoid haemorrhage.^{10–12} Nevertheless, since familial subarachnoid haemorrhage accounts for only 10% of all episodes, large and multiple aneurysms are more often associated with sporadic than with familial subarachnoid haemorrhage.

Genetic factors are obviously important in patients with familial subarachnoid haemorrhage. Candidate genes identified thus far include genes coding for elements of the extracellular matrix.¹³ In patients with autosomal dominant polycystic kidney disease intracranial aneurysms arise in about 10%,¹⁴ but account for less than

Search strategy and selection criteria

For literature searches we mainly used our personal database of references. This database has been prospectively built by daily search of PubMed in the past 10–15 years, by means of the following terms “subarachnoid hemorrhage [All Fields] OR subarachnoid haemorrhage [All Fields] OR aneurysm [All Fields] OR arteriovenous malformation [All Fields] OR perimesencephalic [All Fields]”. We also searched the Cochrane library with these terms. We mainly selected studies from the past 10 years, but did not exclude commonly cited older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are occasionally cited to provide readers with more details and references than this Seminar has room for.

Panel 1: Rare causes of subarachnoid haemorrhage**Inflammatory lesions of cerebral arteries**

- Mycotic aneurysms
- Borreliosis
- Behçet's disease
- Primary angiitis
- Polyarteritis nodosa
- Churg-Strauss syndrome
- Wegener's granulomatosis

Non-inflammatory lesions of intracerebral vessels

- Arterial dissection
- Cerebral arteriovenous malformations
- Fusiform aneurysms
- Cerebral dural arteriovenous fistulae
- Intracerebral cavernous angiomas
- Cerebral venous thrombosis
- Cerebral amyloid angiopathy
- Moyamoya disease

Vascular lesions in the spinal cord

- Saccular aneurysm of spinal artery
- Spinal arteriovenous fistula or malformation
- Cavernous angioma at spinal level

Sickle cell disease, coagulopathies**Tumours**

- Pituitary apoplexy
- Cerebral metastases of cardiac myxoma
- Malignant glioma
- Acoustic neuroma
- Angiolipoma
- Schwannoma of cranial nerve
- Cervical meningiomas
- Cervical spinal cord haemangioblastoma
- Spinal meningeal carcinomatosis
- Melanoma of the cauda equina

Drugs

- Cocaine abuse
- Anticoagulant drugs

1% of patients with subarachnoid haemorrhage.^{9,14} Factors that precipitate rupture of an aneurysm are complex, though a sudden increase in transmural arterial pressure seems a plausible element in at least a proportion of patients. Activities preceding subarachnoid haemorrhage, such as physical exercise, sexual intercourse, or straining are reported in up to 20%,¹⁵⁻¹⁷ but evidently these are not necessary factors.

Non-aneurysmal perimesencephalic haemorrhage

In this rather harmless type of subarachnoid haemorrhage, the extravasated blood is confined to the cisterns around the midbrain (figure 2).¹⁸⁻²⁰ Usually the centre of the haemorrhage is anterior to the midbrain or the pons,¹⁹⁻²² but in some patients the blood is confined to the

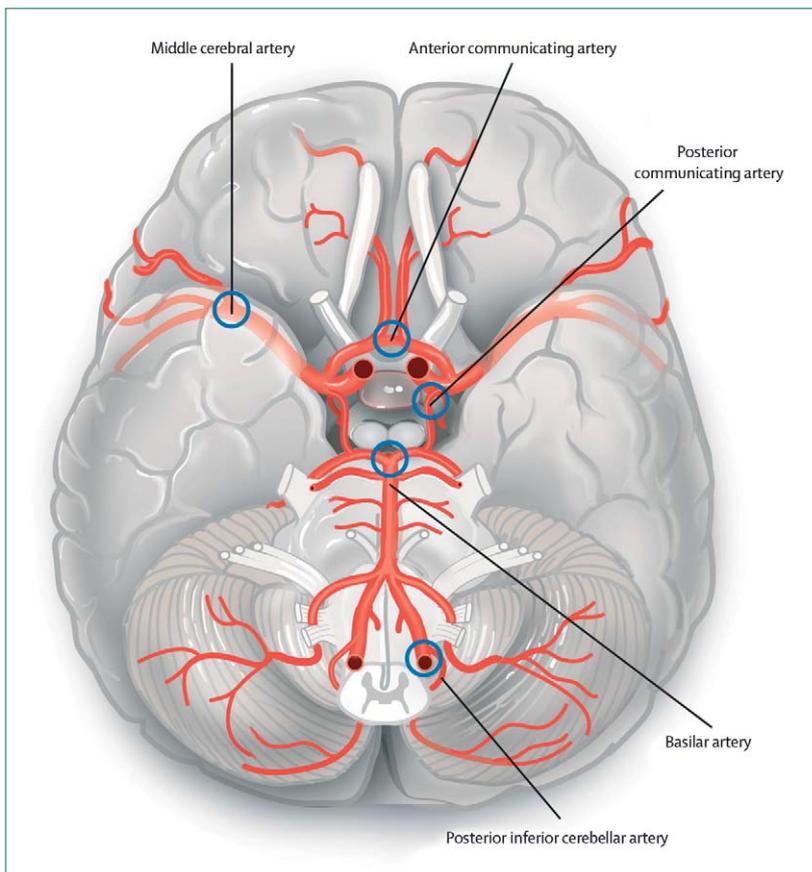


Figure 1: Base of brain, with most common sites of aneurysms (circles)

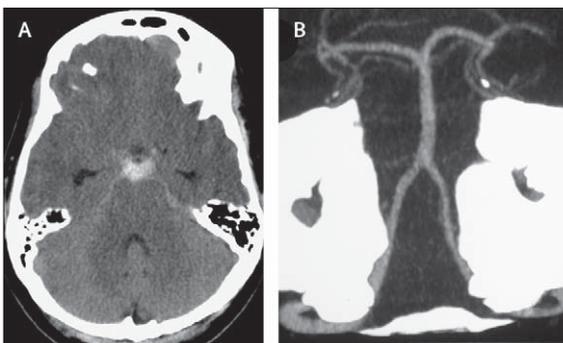


Figure 2: Perimesencephalic (non-aneurysmal) haemorrhage

(A) Typical example of perimesencephalic pattern of haemorrhage. Dense accumulation of blood in front of and around midbrain (interpeduncular cistern and ambient cisterns). Note that localised nature of haemorrhage and not density of cisternal blood characterises perimesencephalic pattern of haemorrhage. (B) CT angiogram ruling out a basilar artery aneurysm, thereby confirming diagnosis of perimesencephalic haemorrhage.

quadrigeminal cistern.²³ The condition is defined only by this characteristic distribution of blood in the subarachnoid space in combination with a normal angiographic study. The haemorrhage does not extend to the lateral Sylvian fissures or to the anterior part of the interhemispheric fissure. Some sedimentation of blood in the

ventricular system can occur, but frank intraventricular haemorrhage or extension of the haemorrhage into the brain parenchyma implies another cause.^{18–20} The perimesencephalic pattern of bleeding is not entirely specific, since one in 20–40 patients has a ruptured aneurysm of the basilar, or vertebral artery.^{19,24,25} To exclude such an aneurysm, a high quality CT angiogram is usually sufficient.²⁶

The onset of headache is more often gradual (in minutes rather than seconds) than in patients with aneurysmal rupture,²⁷ and on admission, patients are invariably alert; a few are slightly disoriented.²⁰ Rebleeding does not occur, in the short term or in the long term.²⁰ No convincing examples of delayed cerebral ischaemia have been reported. Only hydrocephalus can be a complication in the early phase.²⁸ The cause of the bleeding is unknown; the good outcome is the very reason no post-mortem studies have been done.^{29,30} The mild clinical features, the limited extension of the extravasated blood on brain CT, and the normal angiograms all militate against an aneurysm or, in fact, any arterial source of bleeding. Instead, rupture of a vein in the prepontine or interpeduncular cistern seems a likely source. Another indirect argument for this assumption is that in these patients, perimesencephalic veins often drain directly into dural sinuses instead of via the vein of Galen.³¹

Diagnosis

Clinical features

Sudden headache is the most characteristic symptom of subarachnoid haemorrhage; in three out of four patients, the onset is within a split second or a few seconds.²⁷ It is the only symptom in about a third of patients in general practice.³² Conversely, in patients who present with sudden headache alone in general practice, subarachnoid haemorrhage is the cause in one in ten patients.³² Apparently, common headaches with an exceptionally rapid onset outnumber subarachnoid haemorrhage in general practice. Headache from subarachnoid haemorrhage is generally diffuse and often described by patients as by far the most severe headache they have ever had. It is, however, not the severity, but the suddenness of onset, which is the characteristic feature—but a feature that patients often forget to mention because it is the severity of the pain for which they seek medical attention. The headache usually lasts 1–2 weeks, sometimes longer. How short in duration a headache from subarachnoid haemorrhage can be is not known.

No single or combined features of the headache exist that distinguish reliably, and at an early stage, between subarachnoid haemorrhage and non-haemorrhagic thunderclap headache. Vomiting is not a distinctive feature either because almost half the patients with non-haemorrhagic thunderclap headache also report vomiting at onset.²⁷ The discomfort and cost of referring most patients for examination and investigation in hospital is probably outweighed by avoidance of the potential disaster

of rebleeding from an undiagnosed ruptured aneurysm. Seizures at onset of the haemorrhage occur in one of every 14 patients with subarachnoid haemorrhage.^{27,33,34} Since seizures are not reported by patients with perimesencephalic haemorrhage or non-haemorrhagic thunderclap headache,²⁷ the history of a seizure is a strong indicator for aneurysmal rupture as cause for the headache, even if patients have regained consciousness on arrival at hospital.

On admission two-thirds of all patients have depressed consciousness, of whom half are in coma.³⁵ The patient might regain alertness and orientation or might remain with various degrees of lethargy, confusion, agitation, or obtundation. An acute confusional state can occur and be misinterpreted as psychological in origin.^{36,37} Neck stiffness is a common symptom, caused by the inflammatory response to blood in the subarachnoid space. It takes some 3–12 h to appear and might not develop at all in deeply unconscious patients, or in patients with minor subarachnoid haemorrhage.³⁸ Therefore, absence of neck stiffness cannot exclude the diagnosis of subarachnoid haemorrhage in a patient with sudden headache.

Fundoscopy is essential in patients suspected of subarachnoid haemorrhage. Intraocular haemorrhages occur in one in seven patients with a ruptured aneurysm.³⁹ The chance of finding intraocular haemorrhages is higher in patients with reduced consciousness. These haemorrhages are caused by a sustained increase in cerebrospinal-fluid pressure, with obstruction of the central retinal vein as it traverses the optic nerve sheath.⁴⁰ Linear streaks of blood or flame-shaped haemorrhages appear in the preretinal layer (subhyaloid), usually near the optic disc. If large, the preretinal haemorrhage might extend into the vitreous body (Terson's syndrome).⁴¹ Patients might complain of large brown blobs obscuring their vision.

Focal neurological deficits occur when an aneurysm compresses a cranial nerve or bleeds into the brain parenchyma, or from focal ischaemia due to acute vasoconstriction immediately after aneurysmal rupture. Sometimes, therefore, the clinical manifestations of a ruptured aneurysm are indistinguishable from a stroke syndrome from intracerebral haematoma or cerebral infarction. Complete or part third-nerve palsy is a well recognised sign after rupture of aneurysms, mostly of the internal carotid artery at the origin of the posterior communicating artery. By contrast, sixth-nerve palsies have no localising value.

Systemic features that can be associated with subarachnoid haemorrhage in the acute phase are severe hypertension, hypoxaemia, and electrocardiographic (ECG) changes, which can mimic acute myocardial infarction and lead to erroneous examinations and treatment.⁴² In about 3% of patients, cardiac arrest occurs at onset of the haemorrhage; resuscitation is essential, because half the survivors regain independent existence.⁴³

CT scanning

CT scanning is the first investigation if subarachnoid haemorrhage is suspected. The ability to detect subarachnoid haemorrhage is dependent on the amount of subarachnoid blood, the interval after symptom onset, the resolution of the scanner, and the skills of the radiologist (figure 3). On the first day, extravasated blood will be present in more than 95% of patients,^{44,45} but in the following days, this proportion falls sharply as blood in the subarachnoid space is recirculated and cleared. The haemorrhage from an intracranial aneurysm might not be confined to the subarachnoid cisterns but can rupture into the brain tissue, the ventricular system or sometimes the subdural space. The location of the intracerebral haematoma usually indicates the site of the ruptured aneurysm, more reliably than cisternal blood alone (figure 4). A false positive diagnosis of subarachnoid haemorrhage is sometimes made, especially diffuse in brain swelling, when hyperdense material in the subarachnoid space represents blood in congested subarachnoid blood vessels (figure 5).⁴⁶

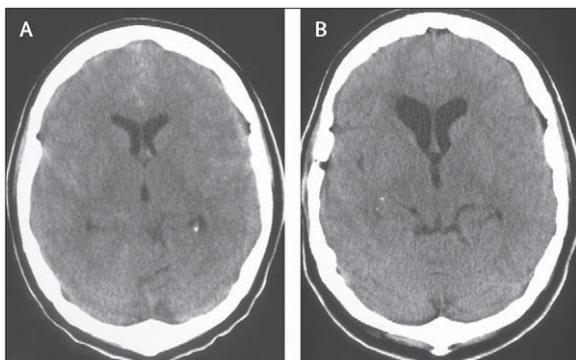


Figure 3: A subarachnoid haemorrhage that can be overlooked

(A) Small amount of subarachnoid blood in anterior interhemispheric cistern and lateral part of both Sylvian fissures, from an aneurysm of anterior communicating artery. (B) Repeat CT scan 2 days later, showing disappearance of cisternal blood.

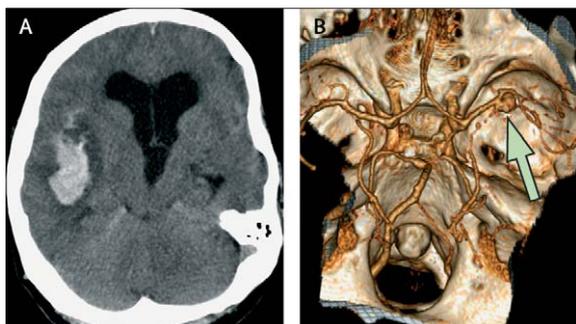


Figure 4: Ruptured aneurysm mimicking primary intracerebral haemorrhage

(A) Intracerebral haematoma from a ruptured aneurysm of right middle cerebral artery. Aneurysmal origin (instead of a hypertensive haemorrhage originating in basal ganglia) can be recognised from lateral extension of haematoma, close to Sylvian fissure. (B) Reconstruction of CT angiogram showing aneurysm (to viewer's right, arrow).



Figure 5: CT scan of brain showing pseudosubarachnoid haemorrhage from brain swelling

Lumbar puncture

In an important small minority of patients (about 3%) with sudden headache and normal head CT scan within 12 h the cerebrospinal fluid shows metabolites of haemoglobin and angiography subsequently confirms a ruptured aneurysm.⁴⁴ Therefore, a lumbar puncture is necessary in any patient with sudden headache and a normal head CT scan, even though the cerebrospinal fluid will be normal in most patients. According to a retrospective review in a large Scottish teaching hospital, lumbar puncture is still omitted in half of all eligible patients.⁴⁷

Once the decision has been taken to do a lumbar puncture, the next requirement is to do it well. This is less simple than it seems.⁴⁸ The first rule is to wait until at least 6 h and preferably 12 h have elapsed after the headache onset. This delay is essential because if cerebrospinal fluid is obtained earlier and turns out to be blood-stained, it is forever impossible to distinguish between blood that was there before (genuine subarachnoid haemorrhage) and blood that was introduced by the needle (a traumatic tap). Only in the former case will bilirubin have been formed in the interval, from the breakdown of erythrocytes in the cerebrospinal fluid.³⁸ Even the smoothest puncture can hit a vein. The three tube test (a reduction in numbers of red blood cells in consecutive tubes) is unreliable.⁴⁹ Immediately proceeding with CT or MR angiography in all patients with bloodstained cerebrospinal fluid is not a good idea, since a small (<5 mm) unruptured aneurysm can be expected in every 50th adult,⁷ yet such incidental findings require no treatment.

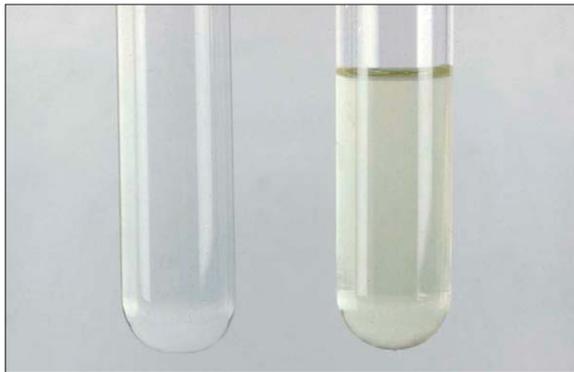


Figure 6: Xanthochromia of cerebrospinal fluid
Haemorrhagic cerebrospinal fluid after centrifugation shows a yellow colour (right) compared with water (left), which proves that blood was not introduced during puncture.

If the cerebrospinal fluid seems clear, the pressure should be measured, since sudden headache can be a first manifestation of intracranial venous thrombosis.⁵⁰ Conversely, low cerebrospinal fluid pressure can signify spontaneous intracranial hypotension. Clear cerebrospinal fluid should also be sent for culture, because meningitis, especially pneumococcal meningitis, can present acutely. If the cerebrospinal fluid is blood-stained, it should be spun down immediately. If the supernatant is yellow (compared with water against a white background), the diagnosis of subarachnoid haemorrhage is practically certain (figure 6), though formally the presence of bilirubin needs to be established. Bilirubin can be formed only *in vivo*, whereas haemoglobin can also be broken down to oxyhaemoglobin, in a test tube that has been left unattended before it was spun down. The specimen should be stored in darkness, preferably wrapped in tinfoil because the ultraviolet components of daylight can break down bilirubin—not only in icteric newborn babies, but also in test tubes. Spectrophotometry can not only confirm the presence of bilirubin but also exclude it,⁵¹ although experienced neurologists and neurosurgeons can confidently exclude xanthochromia by visual inspection alone.⁵²

MRI

Because of the greater availability and feasibility of CT imaging in patients with suspected subarachnoid haemorrhage, few studies of MRI in the acute phase after subarachnoid haemorrhage have been reported. These suggest that in the first few hours and days, MR with proton density and FLAIR images is as sensitive as CT imaging.⁵³ After the initial days, when hyperdensity on CT scans decreases, MR is better for detecting blood, with fluid attenuation inversion recovery (FLAIR) and T2-star images being most sensitive techniques.⁵⁴

Angiography

Angiographic studies in general serve not only to identify one or more aneurysms as potential causes in a patient

with subarachnoid haemorrhage, but also to study the anatomical configuration of the aneurysm in relation to adjoining arteries, which allows optimum selection of treatment (coiling or clipping).

CT angiography is a continuously improving technique. The sensitivity for detecting ruptured aneurysms, with conventional angiography as the gold standard, is currently about 95%.^{55–57} In many patients, the endovascular or neurosurgical procedure can be based on CT angiography as diagnostic work-up.^{58,59} A great advantage of CT angiography over MR angiography and catheter angiography is the speed with which it can be undertaken, preferably immediately after the CT scan of the brain by which the diagnosis of aneurysmal haemorrhage is made, and while the patient is still in the scanner. Magnetic resonance angiography and CT angiography have similar test characteristics.⁶⁰ MR angiography is done without radiation and without contrast enhancement. The absence of risks makes it well suited as an instrument for screening people at high risk of intracranial aneurysms, but the procedure is less feasible for patients who are restless or need mechanical ventilation, and is therefore less suitable in subarachnoid haemorrhage.

Catheter angiography is not an innocuous procedure. In patients with subarachnoid haemorrhage, the rate of ischaemic neurological complications (transient or permanent) is 1.8%,⁶¹ that of aneurysm rerupture during the procedure 1–2% overall.^{62,63} In a patient with a pattern of haemorrhage on CT scanning that is compatible with a posterior circulation aneurysm, an angiogram cannot be termed negative until both vertebral arteries have been visualised, since aneurysms arising from the posterior inferior cerebellar artery or other proximal branches of the vertebral artery will be missed with imaging of a single vertebral artery only. Also three-dimensional imaging of the region in which the aneurysm is suspected can identify an aneurysm not visible on routine projections.

Management

Recommendations for general management and nursing are shown in panel 2. On admission, the first concern is to identify the cause of any reduction in consciousness or focal deficit, before these signs are attributed to the effect of the initial event; some of these causes require immediate intervention. In patients who survive the initial hours after the haemorrhage, three main neurological complications can threaten the patient with a ruptured intracranial aneurysm: rebleeding, delayed brain ischaemia, and hydrocephalus. Additionally, several systemic complications can have a considerable effect on outcome.

Treatable causes of initially poor clinical condition

Intracerebral extension of the haemorrhage occurs in at least a third of patients. Patients with a large haematoma and depressed consciousness might require immediate evacuation, preferably preceded by occlusion of the aneurysm,⁶⁴ or extensive hemicraniectomy that allows

external expansion of the brain.⁶⁵ Subdural haematomas are rare (2% of all subarachnoid haemorrhages),⁶⁶ but might be life-threatening and in that case should be removed.⁶⁷ Massive intraventricular extension of the haemorrhage is associated with poor outcome.⁶⁸ Observational studies suggest that insertion of an external ventricular catheter is not helpful, but is more promising in combination with fibrinolysis.^{69,70}

Prevention of rebleeding

In the first few hours after the initial haemorrhage, up to 15% of patients have a sudden deterioration of consciousness that suggests rebleeding.⁷¹ In patients who survive the first day, the risk of rebleeding is more-or-less evenly distributed during the next 4 weeks,³⁵ with a cumulative risk of 40% without intervention.⁷² After rebleeding the prognosis is poor: 80% of patients die or remain disabled.⁷³ Few, if any, prognostic factors predict an increased risk of rebleeding.⁷²

During the past decade, endovascular occlusion by means of detachable coils (coiling) of aneurysms has largely replaced surgical occlusion as the intervention of choice for the prevention of rebleeding, at least in specialised centres. The technique consists of packing the aneurysm with platinum coils, with a system for controlled detachment (figure 7), and is generally done under general anaesthesia. Randomised trials in which coiling was compared with neurosurgical clipping have included 2272 patients,⁷⁴ of which 2143 were from the International Subarachnoid Aneurysm Trial (ISAT).⁷⁵ Most patients were in good clinical condition and had a small (<1 cm) aneurysm on the anterior circulation. After a year of follow-up, the relative risk reduction for poor outcome (death or dependency) for coiling versus clipping was 24% (95% CI 12–33%). The absolute risk reduction of poor outcome was 7% (4–11%). Patients older than 70 years were under-represented in this comparison—in view of the perceived advantage of coiling in elderly people—as were patients with aneurysms of the middle cerebral artery, because the anatomical configuration is often unfavourable for coiling, with branches arising near the neck of the aneurysm. Ideally, after coiling, the remaining lumen becomes occluded by a process of reactive thrombosis, but early or late rebleeding can occur after technically correct procedures.^{76,77} Nevertheless, in ISAT, the 7% absolute advantage over surgical treatment in the rate of death or dependence was maintained after 1 year, and the early survival advantage was maintained for up to 7 years.⁷⁸ Uncertainty exists about the length of time that patients need to be followed up after coiling, about the most suitable radiological technique, and about the need for a second procedure for aneurysm necks that have recanalised by impaction of the coils, through re-coiling⁷⁹ or surgical occlusion.⁸⁰

Surgical clipping for occlusion of the aneurysm has now become second choice for most patients (figure 8). Modern surgical techniques are estimated to provide an absolute

reduction in the risk of poor outcome of almost 10% (95% CI 7–14%) and a relative risk reduction of 19% (13–27%).⁷² Clipping of aneurysms is usually done early—ie, within 3 days of the initial bleed, and within 24 h if possible—despite absence of support from the only randomised trial,⁸¹ or from observational studies.⁸²

Antifibrinolytic drugs prevent rebleeding after aneurysmal rupture, but because they increase the risk of cerebral ischaemia, they have no useful effect on overall outcome.^{83,84}

Prevention of delayed cerebral ischaemia

Unlike thromboembolic stroke, cerebral ischaemia after subarachnoid haemorrhage has a gradual onset and often involves more than the territory of a single cerebral artery

Panel 2: Recommendations for nursing and general management of patients with subarachnoid haemorrhage

Nursing

- Continuous observation (Glasgow Coma Scale, temperature, ECG monitoring, pupils, any focal deficits)

Nutrition

Oral route

- Only with intact cough and swallowing reflexes
- Keep stools soft by adequate fluid intake and by restriction of milk content; if necessary add laxatives

Nasogastric tube

- Deflate endotracheal cuff (if present) on insertion
- Confirm proper placement on radiograph
- Begin with small test feeds of 5% dextrose
- Prevent aspiration by feeding in sitting position and by checking gastric residue every h
- Tablets should be crushed and flushed down (blood phenytoin concentrations will not be adequate in conventional doses)

Parenteral nutrition

- Should be used only as a last resort

Blood pressure

- Do not treat hypertension unless mean arterial pressure is ≥ 130 mm Hg or if clinical or laboratory evidence of progressive end organ damage

Fluids and electrolytes

- Intravenous line mandatory
- Give at least 3 L per day (isotonic saline, 0.9%)
- Insert an indwelling bladder catheter
- Compensate for a negative fluid balance and for fever
- Monitoring of electrolytes (and leucocyte count), at least every other day

Pain

- Start with paracetamol 500 mg every 3–4 h; avoid aspirin
- Midazolam can be used if pain is accompanied by anxiety (5 mg via infusion pump)
- For severe pain, use codeine (30–60 mg every 4 h, as needed), tramadol (50–100 mg every 4 h, as needed) or, as a last resort, piritramide 0.2–0.3 mg/kg intramuscularly (maximum 80 mg/24 h, in four doses).

Prevention of deep vein thrombosis and pulmonary embolism

- Compression stockings or intermittent compression by pneumatic devices, or both

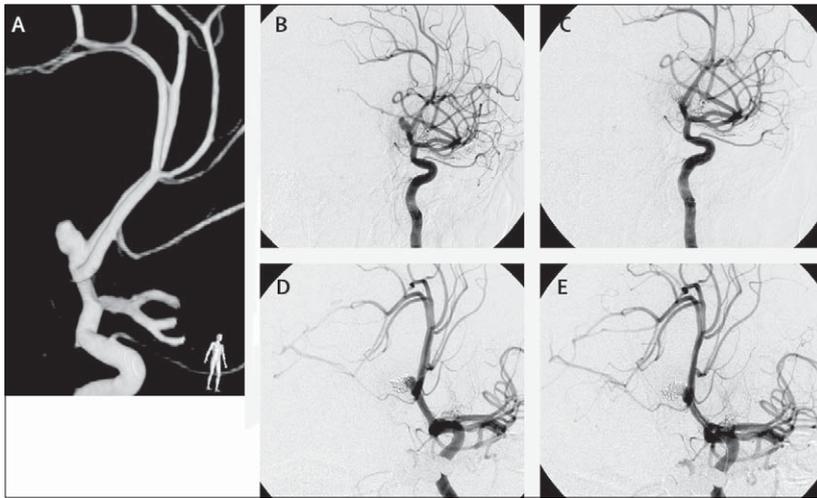


Figure 7: Coiling of an aneurysm of anterior communicating artery

(A) Catheter angiogram (with three-dimensional imaging) showing a small anterior communicating artery. (B) Catheter angiogram of aneurysm before packing with platinum coils. (C) Catheter angiogram of aneurysm after packing with platinum coils. (D) Repeat angiogram 6 months after coiling procedure, showing partial reopening of aneurysm. (E) Catheter angiogram after recoiling, with complete occlusion as result.

or one of its branches.⁸⁵ The clinical manifestations evolve gradually, over several hours, and consist of hemispheric focal deficits in a quarter of patients, a reduction in the level of consciousness in another quarter, and of both signs in the remaining half.⁸⁶ The peak frequency of cerebral ischaemia is from 5 to 14 days after subarachnoid haemorrhage. A simplistic explanation is vasospasm, but arterial narrowing—a complex process in itself—is neither a necessary nor a sufficient condition.⁸⁷ Powerful and independent predictors are; firstly, the total amount of subarachnoid blood, but not its distribution,^{85,88} and only if the source is arterial; and secondly, loss of consciousness at the time of the haemorrhage.^{88,89} The latter factor suggests that global ischaemia during the initial event could well be a key factor.⁹⁰ Other determinants are hypovolaemia and hypotension.^{91,92} Because patients are already under medical attention, opportunities exist for prevention.

Calcium antagonists improve outcome in patients with aneurysmal subarachnoid haemorrhage, with a relative risk reduction of 18% (95% CI 7–28%) and an absolute risk

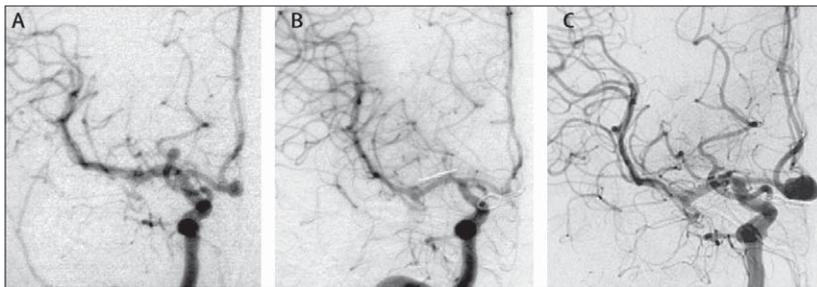


Figure 8: Clipping of two aneurysms (and regrowth after 10 years)

(A) and (B) Angiograms from 1993 showing a ruptured aneurysm of anterior communicating artery and an additional aneurysm of right carotid artery (A), and obliteration of aneurysms after surgical clipping (B). (C) Catheter angiogram from 2003 showing regrowth of the anterior communicating artery aneurysm.

reduction of 5.1%, according to a Cochrane review.⁹³ The relative risk reduction for clinical signs of secondary ischaemia is 33% (24–40%). The evidence consists of 12 trials, but is heavily weighted by a single large trial of nimodipine.⁹⁴ The current standard is the regimen used in that trial: 60 mg orally every 4 h, to be continued for 3 weeks. Intravenous administration is expensive, of unproven benefit,⁹³ and even potentially harmful because of the associated hypotension.

Magnesium sulphate might be useful because hypomagnesaemia occurs in more than 50% of patients with subarachnoid haemorrhage and is associated with the occurrence of delayed cerebral ischaemia and poor outcome.⁹⁵ A small randomised trial was necessarily inconclusive,⁹⁶ whereas a larger trial was more promising but intended as a preliminary (phase II) study, with delayed cerebral ischaemia and not overall outcome as the primary measure of effectiveness.⁹⁷

Antiplatelet agents reduced the rate of delayed cerebral ischaemia according to a systematic review,⁹⁸ but this finding was not in accord with the findings of a subsequent trial.⁹⁹ No evidence exists that antiplatelet agents reduce the proportion of patients with poor outcome.^{98,99} Circulatory volume expansion to prevent delayed ischaemia is not lent support by sound evidence.¹⁰⁰ Similarly, other drugs or measures have either failed in properly controlled trials or shown benefit only in non-randomised comparisons.

Treatment of delayed cerebral ischaemia

The diagnosis of delayed cerebral ischaemia is often defined poorly or not at all in studies.¹⁰¹ Laboratory examinations and a repeat brain CT scans are needed to exclude other causes, especially hydrocephalus and systemic complications. MRI is more sensitive in detecting early changes in the brain, especially with diffusion-weighted imaging,¹⁰² but the procedure is often too long for ill and restless patients. Transcranial doppler sonography and even catheter angiography are used in some centres to detect impending cerebral ischaemia by means of the increased blood flow velocity or arterial narrowing, but the positive and negative predictive value of these tests are disappointing.^{87,103} Induced hypertension, hypervolaemia and haemodilution is a moderately plausible but unproven intervention strategy.¹⁰⁴ Controlled trials are sadly missing. The same applies to transluminal angioplasty and vasodilating drugs, despite the popularity of these measures in some specialised centres.^{105,106}

Management of hydrocephalus

The typical presentation of acute hydrocephalus is that of a patient who is initially alert, followed by a gradual reduction in consciousness in the next few hours.¹⁰⁷ Alternatively, consciousness is impaired from the onset, or the course is unknown because the patient was alone at the time of haemorrhage. Downward deviation of the eyes and small unreactive pupils indicate dilatation of the proximal part of the aqueduct with dysfunction of the

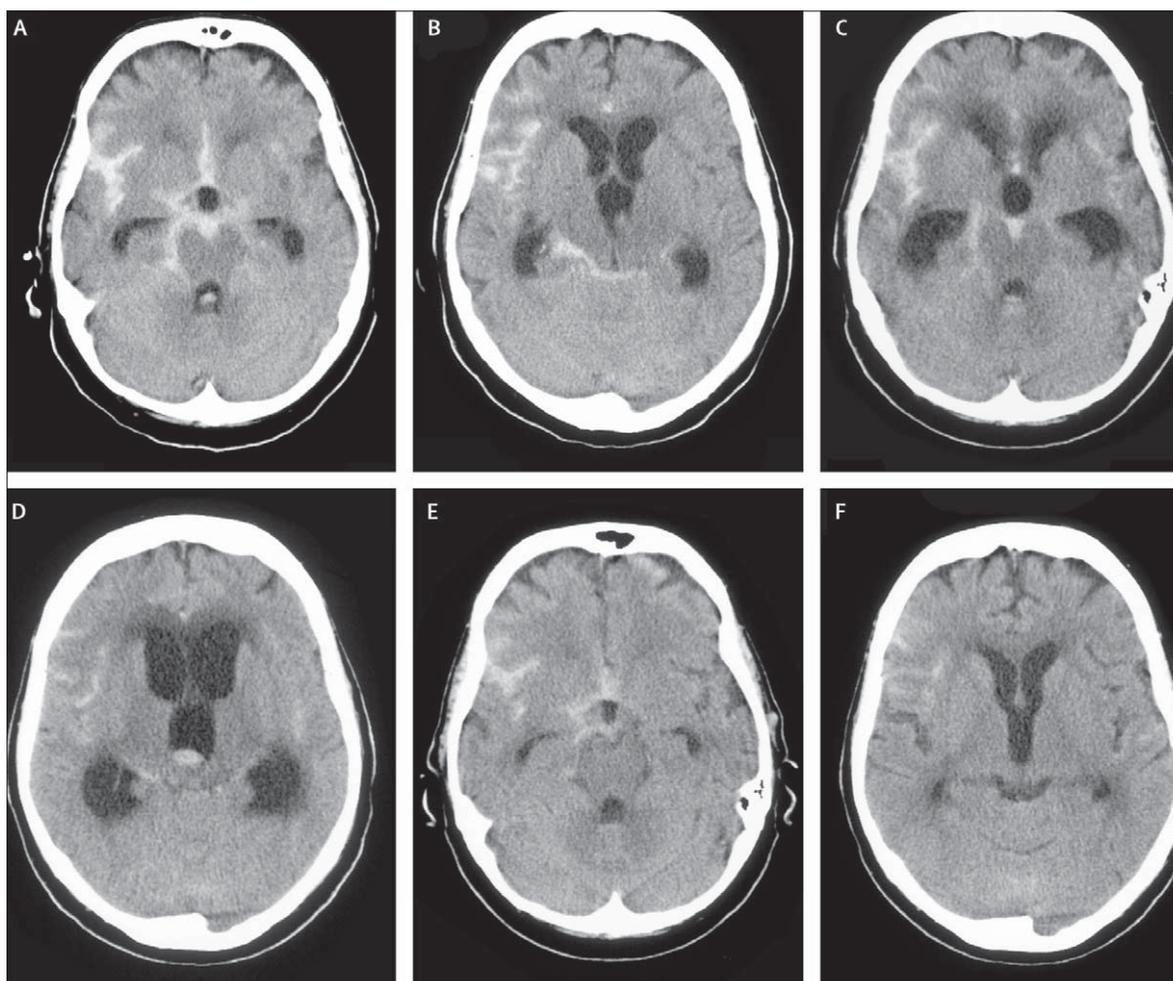


Figure 9: Acute hydrocephalus after subarachnoid haemorrhage

(A) and (B) CT scan on admission showing already enlarged ventricles. Patient was alert but disoriented. (C) and (D) repeated CT scan a few hours after admission when consciousness had gradually deteriorated, showing further enlargement of ventricles. (E) and (F) repeated CT scan after lumbar puncture. Patient had regained consciousness and hydrocephalus has disappeared.

pretectal area; these eye signs help to corroborate, but not to exclude, the diagnosis.¹⁰⁷ Repeat CT scanning is needed to diagnose or exclude hydrocephalus. Patients with intraventricular blood or with extensive haemorrhage in the perimesencephalic cisterns are predisposed to developing acute hydrocephalus (figure 9). In individual patients, the size of the ventricles inversely correlates with level of consciousness, but this relation is erratic across patients.^{107,108} On average, one in five patients with subarachnoid haemorrhage will have enlarged ventricles on the initial CT scan; and about one in five of these will be alert.^{107,108} A policy of wait-and-see for 24 h is eminently justified in patients with dilated ventricles who are drowsy and stable, because spontaneous improvement can be expected in about half.¹⁰⁸

Lumbar puncture can restore consciousness in patients with acute hydrocephalus who do not improve or further deteriorate and who do not have a space-occupying

haematoma or gross intraventricular haemorrhage.¹⁰⁹ Problematically, deciding whether the probable site of obstruction is indeed in the subarachnoid space and not in the ventricular system is not always easy. Whether the risk of rebleeding is increased by lumbar punctures or lumbar drainage is also uncertain.¹¹⁰

External drainage of the cerebrospinal fluid by a catheter inserted through a burr hole is the usual method of treating acute hydrocephalus. The impression that this increases the risk of rebleeding might have to be explained by confounding factors;¹¹¹ if drainage increases the risk at all, it does so by a small degree.¹¹² Ventriculitis is a common complication, especially if drainage is continued for more than 3 days.¹⁰⁸ Regular exchange of the intraventricular catheter is not helpful,^{113,114} but tunnelling of the drain away from the insertion site and a strict protocol for handling of the drain seem to reduce the risk of infection.¹¹⁵ To minimise the period in which ventricular catheterisation is necessary, test occlusion

should be applied early.

Systemic complications

Non-neurological complications often occur in patients with aneurysmal subarachnoid haemorrhage. These include fever, anaemia, hypertension and hypotension, hyperglycaemia, hypernatraemia and hyponatraemia, hypomagnesaemia, cardiac failure and arrhythmias, and pulmonary oedema and pneumonia. These complications should be dealt with in close collaboration with physician-intensivists. Altogether, such complications occur in more than half the patients and are an important contributor to poor outcome after subarachnoid haemorrhage.^{116,117} Accordingly, grading scales in which these complications are taken into account are more accurate predictors of outcome after subarachnoid haemorrhage than those that take account of neurological characteristics alone.¹¹⁸

Long-term complications

Late rebleeding can occur in patients with successfully occluded aneurysms from *de novo* aneurysms, or from regrowth of the aneurysm that caused the first bleed. The risk of late rebleeding is a concern after coiling, but little information is available about the rate of rebleeding in the long term, apart from the first results from ISAT (0.7% between 1 month and 1 year)⁷⁸ and a cohort from Tilburg, the Netherlands (5 of 393 or 1.3% between 1 month and almost 4 years).⁷⁷ Late rebleeding can also occur after clipping of the ruptured aneurysm, with estimates around 2–3% in the first 10 years after treatment of the ruptured aneurysm.^{119,120} In about half the patients, the second episode was caused by a newly developed aneurysm.¹²¹

Epilepsy develops after discharge in one of every 14–20 patients.^{122,123} Putative risk factors include focal lesions, such as subdural haematoma and cerebral infarction, disability on discharge,^{122–124} insertion of an external ventricular drain or shunt,¹²⁵ and probably surgical treatment of the aneurysm.⁷⁸

Anosmia is a sequel in almost 30% of patients, fairly often after operation and with aneurysms of the anterior communicating artery, but loss of smell is not limited to these subgroups (Wermer M and colleagues, personal communication, University Medical Centre, Utrecht).

Cognitive deficits and psychosocial dysfunction in the first year after subarachnoid haemorrhage are common in patients who make a good recovery in terms of self-care.^{126–128} Although improvement occurs between 4 and 18 months after the haemorrhage, many former patients and their partners experience deficits and reduced quality of life 1–2 years after the haemorrhage.¹²⁹ The psychosocial effect at even longer follow-up is considerable. In a survey of 610 patients who were interviewed after a mean period of 8.9 years after subarachnoid haemorrhage, a quarter of the employed patients had stopped working and another quarter worked shorter hours or had a position

with less responsibility.¹³⁰ 60% of the patients reported changes in personality, most commonly increased irritability (37%) or emotionality (29%). All in all only 25% of those independent in activities of daily living reported a complete recovery without psychosocial or neurological problems.

Prevention

Three categories need to be considered here. First, there are patients with incidental aneurysms. Second, patients with subarachnoid haemorrhage might have one or more unruptured aneurysms. Last, the question of screening for aneurysms arises in patients who survive an episode of subarachnoid haemorrhage, and in first-degree relatives of patients with subarachnoid haemorrhage.

Incidental unruptured aneurysms

If an intracranial aneurysm is a surprise finding on an imaging study undertaken for another purpose, the dilemma arises whether the risk associated with preventive clipping or coiling of the aneurysm is outweighed by the risk of death or disability from rupture of the untreated aneurysms sometime later in life. Age is the most helpful factor, because the potential gain in life years decreases with increasing age, whereas the risk of complications of preventive treatment increases.¹³¹ On the other hand, the risk of rupture increases with age.⁷ Even an approximate age limit, such as 70 years, would be an over-simplification. Other factors that should be taken into account are the size of the aneurysm (increased risk of rupture with increasing size), the location of the aneurysm (greater risk of rupture if in the posterior circulation), sex (women have a higher risk of rupture), country (risk is higher in Japan and Finland),² comorbidity, and family history. If a patient has lost a parent or sibling because of subarachnoid haemorrhage, their aneurysm might have a high risk of rupture; moreover, they will find it difficult to accept even a small risk of rupture. The uncertainty surrounding these decisions is heightened because whether the growth rate of aneurysms and the risk of rupture are evenly distributed over time or whether there are critical periods is not known. Patients should not be burdened with the notion of a time bomb but instead be referred to a specialist clinic where they can make an informed decision about their treatment.

Unruptured aneurysms in patients with subarachnoid haemorrhage

Patients who survive an episode of subarachnoid haemorrhage and in whom the ruptured aneurysm is occluded, might have additional unruptured aneurysms. In general, treatment by endovascular or operative route will be offered, except if the aneurysm is very small or difficult to reach. An important reason for offering treatment is a psychological one: these people are not healthy individuals, but patients whose normal life has

already been interrupted by a sudden, life-threatening disease. Another reason is the assumption of a fairly high risk of rupture in patients with a previous episode of subarachnoid haemorrhage, although this belief is based on analysis of a subgroup (aneurysms smaller than 7 mm).¹³¹

Screening for aneurysms in relatives of patients with subarachnoid haemorrhage

Individuals with an affected first-degree relative have a 5–12 times greater life time risk of subarachnoid haemorrhage than the general population, corresponding with a life time risk of 2–5%.^{10,132} The chance of finding an aneurysm by screening in an individual with a single affected relative is only 1.7 times higher than in the general population,¹³³ suggesting that familial intracranial aneurysms have a higher risk of rupture or that the rate of development of new aneurysms is more rapid. Yet the aim of screening is not so much to detect or to treat an aneurysm, but to increase the number of quality years of life. Before any intracranial vessels are imaged, the risks and benefits of screening should be weighed against the considerable psychosocial effects, both positive and negative.¹³⁴ No clinical trials have been done on screening for aneurysms in patients at increased risk; presumably they will not be done in the near future either, because the follow-up needs to be 20 years or longer. Therefore, decisions about screening must be made from calculations and assumptions.

In individuals with only a single affected first-degree relative, screening is not efficient or effective. To prevent a single episode of fatal subarachnoid haemorrhage, 300 at-risk people must be screened and, in treated (in this case operated) patients, the expected gain in life expectancy is outweighed by the complications of treatment.¹³⁵ Exceptions can be made for siblings with one affected relative who are younger than 40 years and so anxious that their quality of life is already impaired. Screening should be considered in individuals with two or more affected first-degree relatives, and in patients with autosomal dominant polycystic kidney disease, at least after age 20 years, and provided the life expectancy is not too short. If a first screen is negative, repeated screening—say every 5 years—should be discussed, because the risk of finding an aneurysm 5 years after the initial screening is about 7%.¹³⁶ Screening should also be considered in identical twins if subarachnoid haemorrhage has occurred in one of the pair.¹³⁷

Screening for new aneurysms after subarachnoid haemorrhage

Although patients who have survived a sporadic episode of subarachnoid haemorrhage are at increased risk of a new episode from a new aneurysm or from recurrence of the treated aneurysm, screening of these patients in general cannot be recommended, according to a Markov decision model (Wermer M and colleagues, for the

ASTRA study group, personal communication). In this model, screening of individuals with previous subarachnoid haemorrhage prevented almost half the recurrent episodes, with slightly increased life-expectancy, but reduced quality of life and increased costs. Only if risks of aneurysm formation and aneurysm rupture were at least 4–5 times above baseline, screening reduced costs and increased quality of life. Unfortunately, at present identification of patients with a sufficiently high formation and rupture risk to benefit from screening is not possible. We are therefore reluctant to offer screening to patients after an episode of subarachnoid haemorrhage, except in those (especially women) with an initial episode at very young age and multiple aneurysms at time of the initial subarachnoid haemorrhage. Finally, even repeated screening and subsequent preventive treatment cannot prevent all episodes of subarachnoid haemorrhage, since aneurysms can develop and rupture within the regular screening interval of 5 years.¹³⁸

Contributors

J v Gijn wrote the first and subsequent drafts of the manuscript. G J E Rinkel participated in the writing of this manuscript. R S Kerr participated in critical revision of the paper. All authors have seen and approved the final version.

Conflict of interest statement

JvG has received payment for travel and accommodation from Sanofi-Aventis in the past 5 years; this company does not produce proprietary drugs discussed in this Seminar. RSK is co-principal investigator of ISAT, and therefore holds a UK Medical Research Council grant. GJER has several grants from the Netherlands Heart Foundation and ZonMw—the Netherlands Organisation for Health Research and Development.

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