SUBARACHNOID HAEMORRHAGE

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INTRODUCTION

Subarachnoid haemorrhage is a relatively common and potentially devastating condition that can present in young people who have been otherwise fit and well. It has a well recognised mode of presentation, and up to half of those who are ultimately diagnosed with subarachnoid haemorrhage may present initially to primary medical services with warning symptoms. Considering the high mortality rate (10-15% patients die before reaching hospital; over 50% die within the first 2 weeks), coupled with the availability of sensitive diagnostic tests, and well-established treatment algorithms it therefore becomes an important condition to understand. Its relevance extends to all health care professionals, including General Practitioners, Casualty Staff, Radiologists (for diagnosis and intervention), Critical Care Teams, Neurologists and Neurosurgeons, Physiotherapists and Specialist Nurses. This article aims to review the basic clinical presentation and current management regimes, followed by a discussion of the major complications, which have been the focus of several large studies.

EPIDEMIOLOGY

The incidence of Subarachnoid Haemorrhage increases with age, peaking between the ages of 55-60, although a fifth occurs below the age of 45\(^1\). A minority of cases are, however, associated with systemic disease; in particular adult polycystic kidney disease, connective tissue disorders, and hereditary haemorrhagic taelangiectasia\(^2\).

AETIOLOGY

Though usually remembered as a consequence of cerebral aneurysms, trauma is in fact the most common cause of subarachnoid haemorrhage. However, where they occur spontaneously; over 75% are indeed due to

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aneurysms – the most common site being the anterior communicating artery. The majority of the remainder is made up of those with unknown aetiology, with arterio-venous malformations making a small contribution of about 5%. Rarer causes include vasculitides and bleeding from tumours.

PRESENTATION

Subarachnoid haemorrhage classically presents with a sudden onset, severe headache, which persists (and may do so for several days, even with opioid analgesia). Initial collapse (and then recovery) is not uncommon with such a sudden and severe event, but persistently depressed Glasgow Coma Scale (GCS) may herald poor outcome. In fact the GCS on presentation is used in the grading of subarachnoid haemorrhage (see box 2). Meningism too may be seen, and meningitis may be an important differential diagnosis in an obtunded patient with persistent headache, neck stiffness, photophobia, nausea and vomiting. Importantly, between 25-50% of patients experience warning symptoms prior to SAH, including ‘sentinel’ headaches, third nerve palsies (involving pupil, often from a posterior communicating artery ‘PCOMM’ aneurysm), or more rarely seizures and transient ischaemic attacks.

DIAGNOSIS

History and examination can be highly suggestive of subarachnoid haemorrhage, but further investigations should be employed for a definitive diagnosis. Computed tomography (CT) with lumbar puncture (LP) has a 100% sensitivity. A CT scan alone will demonstrate SAH in over 95% cases if it is performed within 48 hours of the bleed. A CT scan can help identify the origin of the bleed in non-traumatic subarachnoid haemorrhage (for example, inter-hemispheric blood may suggest an anterior communicating artery aneurysm, whereas blood in the sylvian fissure could be consistent with both posterior communicating and middle cerebral artery aneurysms) but this is largely based on speculations. CT Angiography (CTA) is used in many centres as a non-invasive means of identifying the vascular pathology more accurately.

Lumbar puncture can be extremely useful in diagnosing subarachnoid haemorrhage, especially where there has been a delay in presentation or CT has been equivocal. Overall, it is a sensitive means of demonstrating SAH, and may remain positive for xanthochromia for up to a month post-haemorrhage (though it becomes less sensitive). The opening pressure can be mildly elevated (normal opening pressures are <20mmCSF), the CSF will be consistently discoloured across sequential tubes from haemoglobin.
breakdown products (‘xanthochromia’ itself must be specifically assayed for, and will further differentiate true SAH from a traumatic tap); similarly the

**Box 1. Hints on CT evaluation of Subarachnoid Haemorrhage**

**Subarachnoid Haemorrhage on CT**

After confirming the patient details it is important to ascertain whether contrast has been used, as this will mimic the appearance of a SAH. Most modern CT images will have a “CONTRAST” label somewhere on the image, and if the scan was requested to look for SAH then contrast should not have been used. On an unmarked scan, attention must be focused on the blood vessels, as they appear bright if contrast has been used.

Fresh subarachnoid blood will appear bright on CT and is typically seen in the basal cisterns, giving the pointed star appearance shown. One slice in particular can be very helpful in identifying small bleeds: that of the interpeduncular fossa. Sometimes, especially where there are simultaneous bleeds elsewhere (a subdural haematoma, for example) it can be easy to miss the subarachnoid blood, but it should be remembered that the subarachnoid space is closely related to the brain surface topography, and thus the blood in this space will take the form of the surface sulci and gyri, whereas subdural and extradural blood will not.

red cell count should be persistently raised in all tubes. The presence of red cells may also lower the glucose (as the surviving cells metabolise it) and raise the protein content.

**INITIAL MANAGEMENT**

Like any other life threatening presentation the core of initial management is resuscitative, centring on airway patency (in the context of reduced consciousness), fluid replacement, analgesia (though many will continue to have headaches even with strong opioids) and antiemetics. Prompt neurosurgical referral is usually indicated. Interim advice is likely to advocate four hourly nimodipine (see below), with sensible fluid resuscitation to a level roughly normal for that patient (slight hypotension will reduce the risk of rebleeding, but at the expense of promoting vasospasm). Invasive monitoring can be valuable in high grade subarachnoid haemorrhage, but the principal aim will be transfer to a neurosurgical unit.
NEUROSURGICAL SERVICES

On reaching a Neurosurgical Unit, the aim of further management will be:

1. Reassessment: noting in particular any fall in GCS or new neurology

Box 2: Grading Subarachnoid Haemorrhage

**Grading Subarachnoid Haemorrhage**

A number of radiological and clinical grading systems are in use, each giving useful prognostic information, as well as helping to quantify the severity of the bleed and communicating information clearly between distant sites. The World Federation of Neurosurgeons Grading System\(^5\) is a robust and easy to use system:

**Grade I**: GCS 15

**Grade II**: GCS 13-14, no focal deficit (specifically aphasia, hemiparesis, and hemiplegia)

**Grade III**: GCS 13-14, with focal deficit

**Grade IV**: GCS 7-12 irrespective of focal deficit

**Grade V**: GCS 3-6 irrespective of focal deficit

Other commonly used systems are the Hunt and Hess Grade (Clinical) and the Fisher Grade (Radiological).

that might suggest rebleed, vasospasm, or hydrocephalus – the three major complications of subarachnoid haemorrhage (see below).

2. Continued medical management and (neuro) observation.

3. Evaluation of an underlying cause: by CTA, Angiography, more rarely by MRA/MRI.

4. Treatment of any underlying cause. For aneurysmal SAH, by endovascular coiling, though the role of microsurgical clipping by craniotomy is under evaluation (see below). Arteriovenous malformations may be ‘glued’ by an endovascular technique. In case this is not possible or has failed, surgical resection may be indicated.

5. Continued observation until risks are minimised. In most units Nimodipine will be continued for 21 days, thereafter the risk of vasospasm reduces. ‘Triple H’ (HHH - Hypertensive- Hypervolaemic- Haemodilution) therapy is implemented after stabilisation of an aneurysm, and has been shown to be beneficial in reducing the vasospasm\(^6\).

6. Arrangement of regular follow-ups, usually at a multi-disciplinary team meeting with interventional radiologists, vascular nurse specialists, and
the neurosurgical team. Typically a check-angiogram is performed at six
months, 1 year, and thereafter at a frequency individual to the patient.

COMPLICATIONS

The three major much quoted complications of subarachnoid haemorrhage
are hydrocephalus, cerebral vasospasm, and re-bleeding. Sodium
abnormalities which occur quite frequently can also be added to this list and
are prevalent amongst neurosurgical patients, which can in themselves lead to
impaired conscious levels, systemic disturbance and seizures.

1. Hydrocephalus

Hydrocephalus is an abnormal accumulation of CSF within the ventricles
and may be classified in a number of ways: non-communicating (where there
is a physical obstruction to the normal CSF flow, leading to ventricular
enlargement proximal to the obstruction) or communicating (where there is
defective resorption, or rarely increased production, of CSF and a more global
ventricular enlargement is seen). Alternatively, it may be acute or chronic.

In its early stages, hydrocephalus may be asymptomatic and difficult to
define precisely as there is considerable anatomical variation in the ventricular
size. It is often useful to look for the enlarged temporal horns of the lateral
ventricles as these are not normally visible. However, owing to the difficulty
in defining early hydrocephalus there is a wide range in the reported rate of
hydrocephalus seen in subarachnoid haemorrhage on presentation, from 9-
67%7. A smaller percentage (<5%) develop hydrocephalus subsequently,
within one week of admission7.

Hydrocephalus in subarachnoid haemorrhage is generally a
communicating hydrocephalus, as the subarachnoid blood interferes with CSF
reabsorption at the arachnoid granulations. However, in the context of trauma
or a bleeding tumour, it may be non-communicating.

2. Vasospasm

Cerebral vasospasm leading to cerebral ischaemia is currently the most
important cause of morbidity and mortality following a subarachnoid
haemorrhage due to an aneurysm10. Several studies show that it accounts for
twice the number of poor outcomes as rebleeding11, but to a certain extent
may be predicted by the blood load within the basal cisterns seen on CT\textsuperscript{2,12}, and the clinical grade on presentation.

*Types of Vasospasm*

Vasospasm may be radiological or clinical; these do not always occur together. The former is commonly seen after angiography, where luminal

**Box 3: Management of Hydrocephalus and CSF drainage**

**Management of Hydrocephalus**

A study has shown that approximately half of the patients with symptomatic hydrocephalus recover spontaneously\textsuperscript{7}. Hydrocephalus after subarachnoid haemorrhage with reducing GCS is usually managed by CSF diversion i.e. placement of an external ventricular drain, EVD. Alternatives such as ventriculostomy exist, but these may be associated with an increased rate of rebleeding\textsuperscript{7,8} and is technically more difficult to perform. Placement of an EVD has the advantage of being easily reversible, with only half of those requiring one needing permanent CSF diversion, in the form of a ventriculoperitoneal (VP) shunt\textsuperscript{9}.

**External Ventricular Drain-**

These are catheters inserted via a Burr Hole through the brain parenchyma into the ventricles. The catheter empties into a drain by gravity. The drain height may be adjusted (relative to the foramen of Monro, estimated by the external auditory meatus) so that it will only drain at a given pressure setting (in cmCSF). Thus a ‘normal’ CSF pressure can be maintained by placing the drain at a ‘height’ <20cmCSF. It is important to adjust the drain height if the patient’s position is changed since this will naturally change the relative pressure setting. The drain may also be used to measure the Intracranial Pressure (the height in cmCSF at which the drain just stops draining), to obtain CSF samples, and to give intrathecal medication. The patency of an EVD may be easily assessed by observing oscillation of the CSF in the tubing, arising from brain and arterial pulsation. On recovery, the patient can be ‘challenged’ by progressively raising the drain (so that it will only drain at higher pressures) and monitoring for neurological deterioration and/or radiological worsening of hydrocephalus. In such a case, the patient may be deemed ‘shunt dependent’, and have a more permanent ventriculo-peritoneal shunt inserted which is a small catheter, tunnelled beneath the skin, from the head to the abdominal peritoneal cavity. Various types exist, including those with programmable valves that allow the resistance to drainage to be changed.
narrowing may accompany impaired flow of contrast. It is seen as a complication of the procedure probably due to the physical manipulation of those vessels. However, as many as 70% of the subarachnoid haemorrhage patients show angiographic vasospasm without any clinical manifestations. Clinical vasospasm can present with more generalised symptoms of increasing headache, fall in conscious level, or focal neurological signs much like a thrombo-embolic stroke. In fact neurological deterioration, or onset of new neurological signs, is the most reliable indicator of vasospasm.

Management

A number of important studies have shown that the incidence of vasospasm is greatest 5 to 12 days after the initial bleed, rare within the first 3 days, and may occur for up to 21 days. This is important in the prophylactic management of vasospasm by nimodipine, which is usually continued for 21 days (at a dose of 60mg every 4 hours). Nimodipine is lipid soluble and able to cross the blood-brain barrier. It has been shown to reduce the incidence of vasospasm and improve long-term outcome when used prophylactically. Once the risk of rebleeding has been minimised by endovascular coiling or surgical clipping, Hypertensive- Hypervolaemic- Haemodilution (‘triple H’) therapy can then be used to increase cerebral perfusion pressure, and thereby reduce the cerebral ischaemia. Induced hypertension may also necessitate the use of inotropes particularly since nimodipine is given in conjunction.

Prior to coiling or clipping, maintaining a normo-tensive or even slightly hypotensive state has shown to reduce the risk of rebleeding. However, stabilising an unruptured aneurysm by coiling or clipping is in itself recognised as an important early step in the prevention of not only a re-bleed but also clinical vasospasm.

3. Rebleeding

Rebleeding represents a significant early complication that contributes to the high mortality after subarachnoid haemorrhage. For unruptured aneurysms, the precise natural history remains elusive, though a number of large retrospective and prospective studies have helped in this regard. Of note, the International Study of Unruptured Intracranial Aneurysms (ISUIA) is currently in its third phase. The first phase combined a retrospective analysis of approximately 1,500 cases where no intervention had been
received and a prospective study of roughly 4,000 patients over a 4 year period\textsuperscript{19}. The second phase was organised to investigate the result that unruptured aneurysms appeared to have a lower rate of rupture than previously considered, and that surgical treatment offered similarly higher rates of complication. This study of over 5,000 patients took place over seven-and-a-half years, and divided its prospective cohort into 1, 700 patients who were conservatively managed, 1,900 who had surgical treatment, and 450 who underwent endovascular treatment\textsuperscript{20,21}. These were further subdivided into two groups: one with and the second without a previous history of aneurysmal subarachnoid haemorrhage. The study reported an increasing rate of rupture with aneurysm size (from 0\% 5yr rupture rate in 3-7mm aneurysms, versus 40\% 5yr rupture rate in aneurysms $>25$mm), which did not differ significantly if there had been a previous subarachnoid haemorrhage. The complication rate for surgical clipping and endovascular coiling was lower than the first phase had suggested, but still higher than other smaller studies had shown\textsuperscript{19}. The study, however, has been criticised for an apparent selection bias (only $\sim$10\% subarachnoid haemorrhage presentations were recruited), and gross differences between the cohort populations: the former having significantly higher levels of cardiovascular disease, alcohol users and smokers, and lower proportions of cranial nerve deficits, seizures and larger aneurysms\textsuperscript{19}.

A number of other studies have looked specifically at the rate of rebleeding subsequent to subarachnoid haemorrhage. This appears to be maximal on the first day after a bleed, but with a cumulative risk of 1.5\% per day for the next thirteen days; up to a fifth will rebleed within two weeks, and a half will rebleed after six months\textsuperscript{2}. The risk then falls to $<5$\% per year. Several factors have been associated with higher rates of rebleeding: poor clinical grade, increasing age, hypertension and female gender\textsuperscript{22}.

In view of these risks, management strategies have favoured early identification of unruptured aneurysms after a subarachnoid haemorrhage, followed by early endovascular coiling or surgical clipping, with strict blood pressure control prior to stabilisation.

**COILING AND CLIPPING**

The relative merits of clipping versus coiling remain, to some extent, controversial, but the well-known International Subarachnoid Aneurysm Trial (ISAT) has helped in this regard\textsuperscript{23}. This was a prospective study of 2143 patients randomised to either clipping or coiling, which was halted at the first annual interim analysis due to the significantly improved outcome with
coiling (absolute risk reduction with coiling 6.9%, p =0.0019)\textsuperscript{24}. However, there have been limitations much quoted for the ISAT trial: there was a higher representation of small (<10mm) carotid circulation aneurysms, with far fewer vertebrobasilar and MCA aneurysms\textsuperscript{24}; the levels of training of the respective surgical and endovascular groups was not given\textsuperscript{24}; only 20% of patients presenting with subarachnoid haemorrhage were randomised – those in whom it was not clear who would benefit from either treatment\textsuperscript{2}; 80% patients were of a low clinical grade\textsuperscript{2}. Despite these criticisms, further studies have shown largely similar results. A Cochrane review concluded that: “For patients in good clinical condition with ruptured aneurysms of either the anterior or posterior circulation we have firm evidence that, if the aneurysm is considered suitable for both surgical clipping and endovascular treatment, coiling is associated with a better outcome.”\textsuperscript{25}. It must however be noted that these refer to cases where it is unclear whether coiling or clipping will provide the better outcome. In the ISAT trial, of the 80% patients not randomised a majority underwent surgical clipping, felt to be the better course of action by the treating physicians. Furthermore, there is evidence to suggest that certain aneurysms may be better treated by clipping rather than coiling – MCA aneurysms in particular\textsuperscript{26}. The debate continues, with several competing trials aiming to decide more definitively which one is a better option of the two.

**Hyponatraemia**

Hyponatraemia is a well-recognised complication of subarachnoid haemorrhage occurring in up to 30% cases of subarachnoid haemorrhage\textsuperscript{27}. Plasma sodium should be carefully monitored as it can mimic other complications, producing reduced conscious levels and seizures. Two mechanisms have been postulated. These should give very different clinical pictures but in practice they can be difficult to distinguish. The first is through a Syndrome of Inappropriate ADH secretion (SIADH) with consequential water retention and hypervolaemia. This was formerly considered to be the principal cause of hyponatraemia after subarachnoid haemorrhage\textsuperscript{2,27,28,29} but newer evidence suggests that Cerebral Salt Wasting is a more likely mechanism\textsuperscript{30,31,32,33}. Cerebral salt wasting is thought to arise due to secretion of Brain Natriuretic Peptide (BNP) leading to sodium loss with water depletion. These two views offer very different prospects for management, with SIADH being treated essentially by fluid restriction but the latter requiring fluid replacement. Implementation of the wrong regime would worsen the condition, which in practice is often clouded by aggressive fluid resuscitation, HHH therapy, and pre-admission medications (like diuretics).
FUTURE TRENDS IN SUBARACHNOID HAEMORRHAGE

Emerging trends in subarachnoid haemorrhage research have focused on almost every aspect of the condition, from delineating its natural history to its prevention and management.

The natural history of the condition, particularly in aneurysmal subarachnoid haemorrhage remains poorly understood. As mentioned earlier in this review, the International Study of Unruptured Intracranial Aneurysms (ISUIA) is now in its third phase and it may further our understanding of factors which lead to aneurysmal rupture, as well as evaluate the relative risks of intervention (endovascular or microsurgical) particularly in small aneurysms which appear to have a very low rate of spontaneous rupture\(^{20,21}\). Added to this, the specific question of coiling versus microsurgical clipping is the subject of several competing clinical trials, following on from the somewhat controversial findings of the ISAT trial.

Secondary prevention through medical therapy is also under investigation. Of note, the STASH trial (SimvaSTatin in Aneurysmal Subarachnoid Haemorrhage) is a clinical phase III randomised double-blinded placebo controlled trial across 30 neurosurgical units in the UK, Europe, Asia and North America. It aims to investigate the effects of a short course of Simvastatin on the outcomes of 800 patients with confirmed subarachnoid haemorrhage. It is based on previous findings that statins can reduce vasospasm, and may have antiinflammatory effects\(^{34,35}\).

The management of vasospasm has been the subject of intense study since it is currently the most important cause of morbidity and mortality in SAH patients. Vasospasm is thought to be related to the liberation of oxygen free radicals into the subarachnoid space following the breakdown of erythrocytes\(^{3,6}\). The use of oxygen free radical scavengers could therefore reduce vasospasm. One such candidate is the 21-aminosteroid tirilazad mesylate, an inhibitor of lipid peroxidation\(^{10}\). So far there have been mixed reports about its efficacy, some even suggesting no effect at all\(^{6}\). However, a large randomised, double-blind vehicle controlled trial supported its use\(^{36}\), though more recent randomised, double-blind clinical trials have had mixed results\(^{37,38}\). An alternative view, however, is that vasospasm is underpinned by failures within the nitric oxide system, leading to a failure of relaxation of arterial smooth muscle\(^{39}\). Currently, early trials in animal models suggest
nitric oxide potentiators may reduce vasospasm, \textsuperscript{40,41} but there are difficulties transferring this benefit to patients which include the hypotensive effects of nitrates \textsuperscript{12} and cyanide toxicity. \textsuperscript{39,42}

References


34. The STASH Trial: SimvaSTatin in Aneurysmal Subarachnoid Haemorrhage; http://stashtrial.com/home