Subarachnoid Hemorrhage Without Detectable Aneurysm
A Review of the Causes

Gabriel J.E. Rinkel, MD; Jan van Gijn, MD, FRCPE; Eelco F.M. Wijdicks, MD

Background: In 15% to 20% of patients with a spontaneous subarachnoid hemorrhage, no aneurysm is found on the first angiogram. This review emphasizes that this group of patients is in fact heterogeneous and describes the clinical features, pattern of hemorrhage on early computed tomographic (CT) scan, prognosis, and proposed management in the several and distinct subsets of these patients.

Summary of Review: Patients in whom no aneurysm is revealed on the initial angiogram can be subdivided mainly according to the pattern of hemorrhage on an early CT scan. In two thirds of these patients the CT scan shows a perimesencephalic pattern of hemorrhage (ie, blood confined to the cisterns around the midbrain); these patients invariably have a good prognosis, which obviates the need for a second angiogram. Patients with diffuse or anteriorly located blood on CT scan are at risk of rebleeding. In most of these patients the source of hemorrhage is an occult aneurysm, but intracranial artery dissections, dural arteriovenous malformations, mycotic aneurysms, trauma, bleeding disorders, substance abuse, or a cervical origin of the hemorrhage should also be considered. Patients with no blood revealed on an early CT scan but with xanthochromic cerebrospinal fluid are extremely rare. These patients deserve a second reading of the scan for blood in the prepontine cistern, which can be the only site of hemorrhage in perimesencephalic hemorrhage.

Conclusions: The prognosis and management of patients in whom no aneurysm is found on the initial angiogram depends on the pattern of hemorrhage on the initial CT scan. Patients should no longer be designated with the umbrella term “angiogram-negative subarachnoid hemorrhage.” (Stroke. 1993;24:1403-1409.)

KEY WORDS • aneurysm • angiography • dissection • subarachnoid hemorrhage

In 15% to 20% of patients with spontaneous subarachnoid hemorrhage, no aneurysm is found on four-vessel angiography.1 A plethora of reports has addressed the outcome in these patients.2-16 Early CT scanning, however, was often not performed in these patients; this drawback precludes the recognition of subgroups according to source and prognosis. Moreover, demonstration of blood pigments in the cerebrospinal fluid in patients without CT confirmation of the hemorrhage was required in only a few studies,2,11 and the remaining studies may have included patients with innocuous thunderclap headaches followed by a traumatic lumbar puncture.17,18 Despite the imperfections in methodology, these studies indicated that the prognosis of patients with “angiogram-negative subarachnoid hemorrhage” is better than that of patients with a detected aneurysm. However, outcome is not always favorable; rebleeding, cerebral ischemia, and acute hydrocephalus have been reported in up to 20% of these patients.8,13,14 Furthermore, 10% to 30% of patients who survive do not recover to their previous state.2-5,7-15

The small yield of aneurysms detected by repeat angiography must be weighed against the risks of cerebral angiography. In a recent study complications occurred during repeated angiography of the verteobasilar arteries in three of 16 patients in whom the initial angiogram was normal.19 At present, however, there are no safe techniques that are as reliable as angiography in the detection of aneurysms. High-resolution computed tomography correctly identifies large aneurysms but fails to detect one third of aneurysms smaller than 6 mm.20-22 Magnetic resonance (MR) angiography is a promising technique, but its value in detecting “occult” aneurysms has not yet been proved.

According to the pattern of hemorrhage on CT scan, it is now possible to identify subsets within the larger group of patients in whom the initial angiogram reveals no aneurysm.23-25 This partition has grave implications for prognosis and management of these patients and allows selection for repeated angiography of only those patients who are at risk of rebleeding. This review describes the clinical features, patterns of hemorrhage on CT scan, prognosis, and proposed management of the different causes of subarachnoid hemorrhage without detectable aneurysm.
Hemorrhage Confined to the Cisterns
Around the Midbrain

Idiopathic Perimesencephalic Hemorrhage

In perimesencephalic hemorrhage, the extravasated blood is confined to the cisterns around the midbrain, and the center of the bleeding is immediately anterior to the midbrain. There is no extension of blood to the lateral sylvian fissures or to the anterior interhemispheric fissure (Fig 1). Some sedimentation in the posterior horns may be seen, but frank intraventricular hemorrhage or extension into the parenchyma rules out that the patient belongs to this category.26

Perimesencephalic hemorrhage constitutes approximately 10% of all patients with subarachnoid hemorrhage and two thirds of those with a normal angiogram.24,26,27 This type of hemorrhage can occur in any patient over the age of 20, but most patients are in their sixth decade. Only few patients have a history of hypertension.28 Conspicuously absent is a history of a "warning headache," which is found in more than one third of patients with aneurysmal rupture.29

In one third of the patients, strenuous activities precede the onset of symptoms.28 The features at onset may be milder than in patients with aneurysmal rupture: the onset of the headache is gradual (minutes rather than seconds) in one fourth of the patients, loss of consciousness is exceptional, and focal abnormalities have not been observed.27,28 On admission all patients are in perfect clinical condition, apart from the headache. Typically, the early course is uneventful: rebleeds and delayed cerebral ischemia simply do not occur.28 Although 20 percent of patients have acute hydrocephalus on their admission CT scan, only few have symptoms from it, and even then an excellent outcome can be anticipated.30 The period of convalescence is short, and most patients are able to resume their previous lifestyle and work.31 Rebleeds after the hospital period have not been documented thus far, even after a long interval in a large series of patients.23

The definition of this variant of subarachnoid hemorrhage provisionally remains a descriptive one because postmortem studies have not yet been obtained. The often-mild clinical features, the limited extension of the blood on CT scan, and the normal angiograms in a large series of patients with this pattern of hemorrhage all argue against a ruptured aneurysm as the source of the hemorrhage. Rupture of a dilated vein or a venous malformation in the prefrontal or interpeduncular cistern seems a reasonable hypothesis.

The invariably good outcome and the absence of rebleeding in the long term obviate the need for repeated angiograms.

Trauma

In some patients with shearing injury, pronounced accumulation of blood can be found in the posterior part of the ambient cistern at the level of the tentorial margin.32 Blood confined to the ambient cistern has also been reported in a patient undergoing anticoagulant treatment, with a relatively mild trauma (fall in the shower).33 The blood in the ambient cistern may be part of more extensive intracranial hemorrhage, but it can be the main site of hemorrhage (Fig 2). The site of the hemorrhage excludes a ruptured saccular aneurysm as the source of the hemorrhage. The cause of the hemorrhage in these patients is probably the grazing of a vein against the tentorial edge.

Diffuse or Anteriorly Located Hemorrhage in the Basal Cisterns

The clinical features and particularly the outcome of patients with diffuse or anteriorly located blood in the basal cisterns are in stark contrast to those of patients with perimesencephalic hemorrhage. In a recent report of 36 such patients, 8 were drowsy or stuporous on admission, and 2 had a focal deficit.23 During the initial hospital period, 3 patients had a rebleed, which was fatal in 2; 5 patients had symptomatic acute hydrocephalus; and another patient deteriorated from cerebral ischemia. On long-term follow-up, an additional patient died from rebleeding. Altogether, 3 of the 36 patients died and 6 were left disabled as a result of hemorrhage.23 In two other studies in which patients with angiogram-negative subarachnoid hemorrhage were subdivided according to the pattern of hemorrhage on CT,24,25 all patients with complications and poor outcome had a nonperimesencephalic pattern of hemorrhage, whereas all patients with a perimesencephalic hemorrhage had a good outcome. In most patients with poor outcome in these studies, the
center of the bleeding was located in the anterior interhemispheric fissure.

Several causes of bleeding should be considered in patients with a normal angiogram who show a diffuse or anteriorly located hemorrhage in the basal cisterns; in this list, nonvisualized (occult) aneurysms are a large majority.

**Insufficient Examination of the Posterior Circulation**

Despite the widespread use of four-vessel angiography and the technical improvement, angiography of the posterior circulation remains a difficult procedure, and the angiogram should be reviewed for proper visualization of the branches of both vertebral arteries if no aneurysm is found.

A ruptured aneurysm of the posterior circulation can often be suspected from the distribution of the blood on an early CT scan. Up to 85% of these patients show marked intraventricular bleeding that is found predominantly in the fourth (and to a lesser extent in the third and lateral) ventricle. In one fourth of patients with posterior circulation aneurysms, intraventricular hemorrhage is the only finding. Subarachnoid blood, if evident on the CT scan, is usually centered around the midbrain; in addition, it symmetrically extends to the anteriorly located basal cisterns. In patients with such a pattern of hemorrhage, repeated angiography should certainly be performed, with specific attention to the branches of the vertebral arteries.

**Occult Aneurysm**

Although it has been argued that repeating the angiogram is useless, combined data of seven studies on patients with angiogram-negative subarachnoid hemorrhage reveal that 135 repeated angiograms demonstrated no less than 22 aneurysms. If one takes into account that patients with perimesencephalic hemorrhage were not excluded from these series, the yield of follow-up angiograms in patients with diffuse or anteriorly located hemorrhage on CT scan must be even higher.

A hidden aneurysm should be suspected in particular in patients with extensive extravasation of blood in the anterior interhemispheric fissure or the sylvian fissure. In a recent report of patients with an initially normal angiogram, a repeated study revealed an aneurysm in 7 of 10 patients with blood predominantly in the anterior interhemispheric fissure and in 1 of 3 patients with blood predominantly in the sylvian fissure. In such patients even a second normal angiogram does not definitively exclude an aneurysm (Fig 3). A third angiogram seems indicated in such patients, although this strategy has never been consistently evaluated.

**Vertebral Artery Dissection**

The proportion of all patients with subarachnoid hemorrhage in whom this is caused by vertebral artery dissection is unknown, but in a recent autopsy series a dissection was found in 5 of 110 patients who died from subarachnoid hemorrhage. Most patients are middle-aged, and approximately one third are being treated for hypertension.

A vertebral artery dissection should be suspected in patients with a recent history of uncommon neck movements (with painting the ceiling, for instance) or of minor trauma such as chiropractic neck manipulation, although dissection can also occur without precipitating trauma. Another clue to the diagnosis may be the presence of lower cranial nerve palsies, Horner's syndrome, or more extensive lateral medullary syndromes. In dissection with subarachnoid hemorrhage, CT scans show blood throughout the basal cisterns and often intraventricular blood as well, particularly in the fourth and third ventricles. Angiographically the diagnosis rests on the demonstration of narrowing of the artery with signs of intimal flap, a pseudoaneurysm, or a double lumen; however, these features may be absent on an initial angiogram. In a series of 14 patients with a vertebral artery dissection, the first angiogram was normal in 2 and showed only nonspecific arterial narrowing in 2 others; in these 4 patients only the second angiogram revealed the characteristic abnormalities. A second angiogram is not always diagnostic because dissecting aneurysms may resolve spontaneously. CT or MR imaging may detect a thrombus within the false lumen of the dissection, a finding that also confirms the diagnosis.

Rebleeds occur in 30 percent of patients, sometimes within hours of the initial hemorrhage but in other cases after several weeks; these are fatal in half the patients. Approximately half the reported patients have a good outcome.

**Carotid Artery Dissection**

Very few patients with subarachnoid hemorrhage from carotid artery dissection have been described. The presenting features are the same as in aneurysmal rupture: a severe headache of sudden onset that may be accompanied by focal deficits, a depressed level of consciousness, or both. The patterns of hemorrhage on the CT scans of patients with carotid artery dissection are indistinguishable from those of patients with ruptured saccular aneurysms. CT-documented rebleeds have been reported; these may occur within a few hours of the initial hemorrhage.

The diagnosis should be considered in patients in whom the angiogram shows localized nonspecific nar-
rowing of the carotid artery. Repeated angiograms may disclose the true cause of the hemorrhage in these patients.49

Dural Arteriovenous Malformation

Dural arteriovenous malformations (AVMs) of the tentorium can give rise to a basal hemorrhage that is indistinguishable on CT scan from aneurysmal hemorrhage.51 The anomaly is rare and can be found from adolescence up to old age.

A history of a head injury with a skull fracture should raise the suspicion of a dural shunt, since healing of a skull fracture may be accompanied by the development of a dural AVM.52 In patients in whom CT scanning suggests a tentorial origin of the hemorrhage and in whom the angiogram seems normal, the angiogram should be reviewed again, with the possibility of a tentorial AVM in mind. If once again no lesion is found, repeat angiography is indicated, including visualization of the external carotid artery because branches of this artery can be the main or the sole feeders.53 Rebleeding may occur in patients with dural AVMs; in a series of 28 patients, 5 presented with subarachnoid hemorrhage, and 3 of these 5 had one or more rebleeds.54

Spinal Arteriovenous Malformation

Subarachnoid hemorrhage is the mode of presentation in approximately 10% of patients with a spinal AVM; in more than half these patients, the first hemorrhage occurs before the age of 20.55,56 If the malformation is located high in the cervical region, the symptoms at onset may be indistinguishable from those with an intracranial source of subarachnoid hemorrhage,56 and CT may show blood throughout the basal cisterns and ventricles.57 Specific attention should be given to a history of severe pain in the lower part of the neck or pain radiating to the shoulders or arms.57 If even these clues are absent, the true origin of the hemorrhage emerges only when spinal cord dysfunction develops after a delay that may be as short as a few hours or as long as a few years.56,58 Vertebral or spinal angiography can demonstrate the lesion, but this procedure is not always diagnostic;56,58 it is impractical without localizing signs or symptoms, and it carries a greater than 5% risk that persisting neurological deficit will ensue.59 At present, MR imaging in the sagittal plane seems to be the first line of investigation. Rebleeds occur in half the patients who survive the initial bleed,60 and eventually less than 10% of patients who have bled once remain asymptomatic thereafter.61

Trauma

In most patients with trauma, the subarachnoid hemorrhage is located in the superficial cortical sulci, adjacent to a fracture or intracerebral contusion. Particularly in patients with basal frontal contusions, the pattern of hemorrhage can resemble rupture of an anterior communicating artery aneurysm. In patients with direct trauma to the neck or with head injury that provokes vigorous neck movement, the trauma can immediately be followed by a massive basal hemorrhage that results from a tear or even a complete rupture of one of the arteries of the vertebrobasilar circulation.62,63 These lesions are often rapidly fatal.62,63

Mycotic Aneurysms

The most frequent causes of mycotic aneurysms are infective endocarditis and aspergillosis. In patients with infective endocarditis, most aneurysms are located on distal branches of the middle cerebral artery, but approximately 10% of the aneurysms are more proximally located.64 Rupture of a mycotic aneurysm gives rise to an intracerebral hematoma in most patients, but some patients have a pattern of hemorrhage indistinguishable on CT from that of a ruptured saccular aneurysm.65 CT-documented rebleeds have been reported.65 Most patients present with valve endocarditis before subarachnoid hemorrhage occurs, but rupture of a mycotic aneurysm can be the initial manifestation of infective endocarditis.66,67 In older series, 10% of mycotic aneurysms were missed by angiography,68 but even now the initial angiogram may be normal. The aneurysms in these patients can be found on repeated angiograms69; however, if angiography is repeated after too long an interval, it may be truly normal because mycotic aneurysms can resolve after antibiotic therapy.64

Mycotic aneurysm in patients with aspergillosis are usually located on the proximal part of the vertebrobasilar or carotid artery.69 Rupture of such an aneurysm causes a massive subarachnoid hemorrhage in the basal cisterns, indistinguishable from that associated with a saccular aneurysm.70 In some cases the initial angiogram is normal and only repetition of the study reveals the aneurysm.70 Rupture of a mycotic aneurysm in patients with aspergillosis is often fatal.69

Cocaine Abuse

In half the patients with subarachnoid hemorrhage related to the use of the alkaloid form of cocaine, no aneurysm is demonstrated by angiography.71 The pattern of hemorrhage revealed on CT scan is indistinguishable from that of a ruptured saccular aneurysm,72 and the diagnosis rests on a confirmatory history or the results of toxicological tests. Rebleeds do occur, even in patients with a normal angiogram.73 Outcome seems poor for these patients: four of five recently reported patients had died after the cocaine-related subarachnoid hemorrhage.73 The source of the hemorrhage in patients without an aneurysm is unknown. Although biopsy-proven vasculitis has been found in patients with cocaine abuse,74 angiograms of patients with subarachnoid hemorrhage related to cocaine abuse do not show changes suggestive of vasculitis.73,75

Sickle Cell Disease

Subarachnoid hemorrhage is a rare complication of sickle cell disease.76 Thirty percent of patients with sickle cell disease and subarachnoid hemorrhage are children.77 CT scans performed in these children show blood in the superficial cortical sulci; angiograms reveal no aneurysm but often show multiple distal branch occlusions and leptomeningeal collateral circulation.77 The subarachnoid hemorrhage is attributed to rupture of these collaterals. The outcome is poor: only three of the 11 recently reviewed children had a good outcome.77

Most adult patients with sickle cell disease–related subarachnoid hemorrhage have an aneurysm. The hemorrhage is located diffusely in the basal cisterns,78 and
Subdivision and Proposed Management of Patients With Subarachnoid Hemorrhage and a Normal Angiogram According to Hemorrhage Pattern on an Early* CT Scan

<table>
<thead>
<tr>
<th>Cause of Hemorrhage</th>
<th>Suggestive Feature</th>
<th>Diagnostic Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood confined to cisterns around the midbrain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic perimesencephalic hemorrhage</td>
<td>Typical pattern of hemorrhage on CT</td>
<td>First normal angiogram</td>
</tr>
<tr>
<td>Trauma</td>
<td>Typical pattern of hemorrhage on CT</td>
<td>History</td>
</tr>
<tr>
<td>Diffuse or anteriorly located hemorrhage in the basal cisterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occult aneurysm</td>
<td></td>
<td>Repeat angiography</td>
</tr>
<tr>
<td>Intracranial artery dissection</td>
<td>Recent trauma</td>
<td>Review angiogram; repeated angiography; intraluminal thrombus on CT or MRI</td>
</tr>
<tr>
<td>Dural AVM</td>
<td>Old skull fracture</td>
<td>Review angiogram; repeat angiography</td>
</tr>
<tr>
<td>Cervical AVM</td>
<td>Radiating pain to shoulders or arms; young age</td>
<td>MRI; vertebral or spinal angiography</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td>History</td>
</tr>
<tr>
<td>Myotic aneurysm</td>
<td>History</td>
<td>Repeat angiography</td>
</tr>
<tr>
<td>Cocaine abuse</td>
<td>History</td>
<td>Toxicological tests</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>History; young age</td>
<td>Multiple distal branch occlusions</td>
</tr>
<tr>
<td>Coagulation disorders</td>
<td>History; systemic bleeding</td>
<td>Appropriate laboratory tests</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>Poor or double vision</td>
<td>CT or MRI</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; AVM, arteriovenous malformation; and MRI, magnetic resonance imaging.

*Within 72 hours of ictus.

the outcome is comparable to that of patients with ruptured saccular aneurysms.77

Coagulation Disorders

Anticoagulation-related subarachnoid hemorrhage seems rare. In a series of 116 patients with anticoagulant treatment and intracranial extracerebral hemorrhage, 7 had only subarachnoid hemorrhage. In two of these 7 patients the hemorrhage was associated with trauma, and in two other patients an aneurysm was found by angiography.79 Thus, in only three of these patients no other cause for the hemorrhage than anticoagulation was found.

Severe coagulopathy other than by anticoagulant is also a rare cause of hemorrhage confined to the subarachnoid space. In a recent series of 13 patients with intracranial hemorrhage after liver transplantation, three had a subarachnoid hemorrhage on CT.80 In all patients but one in this series, the intracranial hemorrhage was associated with systemic bleeding.80

Pituitary Apoplexy

Pituitary apoplexy has been proposed as one of the causes of subarachnoid hemorrhage of unknown cause.81 The initial features consist of a sudden and severe headache, followed by nausea, vomiting, neck stiffness, and sometimes a depressed level of consciousness.82 The hallmark of pituitary apoplexy is that most patients suffer a decrease in visual acuity or double vision. In one series of 15 patients, only 2 had normal visual acuity; 9 had an oculomotor nerve palsy, 6 an abducens nerve palsy, and 3 a trochlear nerve palsy.83 CT and MR scanning indicate the pituitary fossa as the source of the hemorrhage; in most instances the adenoma itself is also visible.83,84

Miscellaneous Causes

Other (exceedingly rare) lesions that can give rise to subarachnoid hemorrhage in the basal cisterns and a normal angiogram are a cervical tumor, such as a meningioma,85 and rupture of a small circumferential artery in the pontine cistern.86

Patients With Normal CT Scan and Normal Angiogram

Patients with clinical features of spontaneous subarachnoid hemorrhage and xanthochromia in the cerebrospinal fluid (demonstrated by spectrophotometry) in whom no blood is found on a CT scan performed within 3 days of onset of hemorrhage deserve a second reading of the scan. Particular attention should be paid to the prepontine cistern because in some patients with a "perimesencephalic" hemorrhage this cistern is actually the only one in which subarachnoid blood is seen.28 We found only three normal CT scans in a personal series of 116 patients with subarachnoid hemorrhage and a normal angiogram.87 The CT scans of these patients were made on the first or second day after the hemorrhage. All three had a good outcome after a median period follow-up of 55 months.

Conclusions

The pattern of hemorrhage on an early CT scan is an invaluable guide to the management of patients with subarachnoid hemorrhage in whom no aneurysm is found on the initial angiogram (Table). The potential risks of angiography debar injudicious repeat studies.

Patients with perimesencephalic hemorrhage (blood confined to the cisterns around the midbrain, perhaps with some extension to the suprasellar cisterns but not to the anterior interhemispheric fissure, lateral sylvian fissure, or the ventricles) run an uncomplicated course
and invariably have an excellent outcome, also in the long term. A ruptured vein is the most probable cause, although this has not yet been confirmed. Follow-up angiography is not indicated in these patients.

Patients with a pattern of hemorrhage in the basal cisterns that is more extensive than that of the perimesencephalic type are at risk of a fatal rebleed from an occult aneurysm; we therefore urge follow-up angiograms in this group unless review of the initial angiogram reveals signs of vertebral artery dissection or a dural AVM. An occult aneurysm should be suspected particularly in patients with thick, localized clots in the anterior interhemispheric or sylvian fissure, and even a second normal angiogram does not definitively exclude an aneurysm in these patients.

Other, but rare causes of extensive hemorrhage in the basal cisterns without a detectable aneurysm are trauma, mycotic aneurysm, bleeding disorders, cocaine abuse, or a spinal AVM. The diagnosis of trauma and mycotic aneurysm is usually straightforward from the history. Cocaine abuse should specifically be queried and can be confirmed by results of toxicological tests. Bleeding disorders can be inferred from systemic bleeding, history, and appropriate laboratory tests. Pain radiating to the shoulders or to the arms suggests a cervical origin of the hemorrhage.

Patients with true subarachnoid hemorrhage (xanthochromic cerebrospinal fluid) in whom no blood is found on an early CT are extremely rare. If there are no features suggestive of a spinal AVM, repeat angiography is warranted; this is especially true in patients with focal deficits or loss of consciousness because these features are incompatible with an idiopathic perimesencephalic hemorrhage.

The term “angiogram-negative subarachnoid hemorrhage” is meaningless in both individual patients and follow-up studies if no specification of the pattern of hemorrhage on CT is given. Physicians, researchers, and editors should abandon this blanket term.

Acknowledgments

We thank Drs H.G.J. Krouwer and L.J. Kappelle for their critical review of the manuscript and helpful suggestions and Drs L.M.P. Ramos and A. van Die for their help in preparing the photographs.

References


Subarachnoid hemorrhage without detectable aneurysm. A review of the causes.
G J Rinkel, J van Gijn and E F Wijdicks

*Stroke*. 1993;24:1403-1409
doi: 10.1161/01.STR.24.9.1403

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/24/9/1403