Subarachnoid Hemorrhage: A Neurological Emergency

M. Venti*, M. Acciarresi and G. Agnelli

Stroke Unit and Department of Internal and Vascular Medicine, University of Perugia, Italy

Abstract: Subarachnoid hemorrhage (SAH) accounts for 5% of all strokes but its burden is relevant due to high mortality, high disability and remarkable incidence in the young. The rupture of an intracranial aneurysm is responsible for about 85% of SAHs; 10% are represented by non-aneurysmal conditions; 5% are represented by other medical conditions such as inflammatory or non-inflammatory lesions of cerebral artery, coagulopathy, neoplasms or drug abuse.

The clinical presentation of a subarachnoid hemorrhage can be extremely variable ranging from nearly asymptomaticity to sudden death.

Neuroimaging represent the first level instrumental investigation. In case of clinical suspect of SAH and negative neuroimaging, cerebrospinal fluid (CSF) examination is required. Following the diagnosis of SAH, determining cause and localization of bleeding is mandatory; digital catheter angiography is the gold standard.

Rebleeding is the most frequent and severe complication of SAH. The aneurysm exclusion is the most effective treatment for preventing rebleeding. Endovascular occlusion of the aneurysm with coils has been shown to be associated with better short- and long-term outcomes than surgical clipping in select patients.

Keywords: Subarachnoid hemorrhage, aneurysm.

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a neurologic emergency due to blood extravasation in the space delimitated from pia madre to arachnoid (Fig. **1**). Even if it accounts for 5% of all strokes the burden of SAH is relevant due to high mortality, high disability and remarkable incidence in the young. Early diagnosis and early treatment are essential for preventing disability.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The incidence of subarachnoid hemorrhage is about 6-7 cases out of 100,000 per year; it tends to increase with age but half of the patients are younger than 55; it prevails in female gender with a ratio of 1.6 compared to male. Mortality rate is about 50%; most deaths occur within 2 weeks; 10% of patients die before reaching the hospital [1, 2].

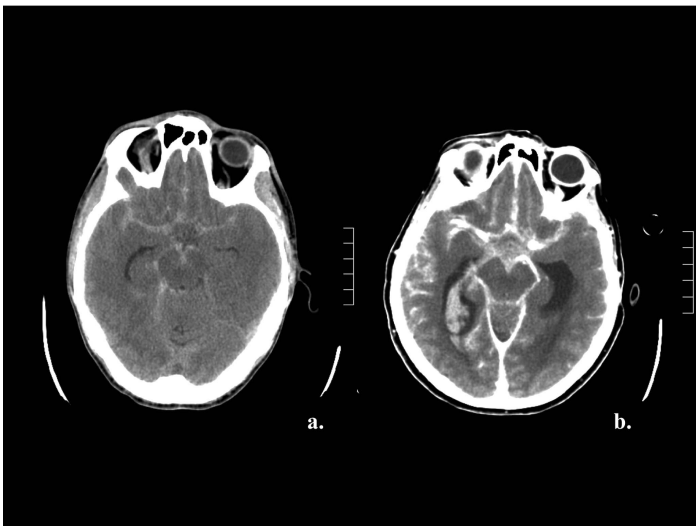

Fig. (1). Subarachnoid hemorrhage (**a**) and massive subarachnoid hemorrhage with ventricular invasion (**b**).

*Address correspondence to this author at the Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Santa Maria della Misericordia Hospital, Sant'Andrea delle Fratte, 06126 – Perugia, Italy; Tel: +39.075.5782765; Fax: +39.075.5782765;
E-mail: michele.venti@ospedale.perugia.it

The rupture of an intracranial aneurysm is responsible for about 85% of SAHs; 10% are represented by non-aneurysmal conditions; 5% are represented by other medical conditions such as inflammatory or non-inflammatory

1874-8287/11 2011 Bentham Open

lesions of cerebral artery, coagulopathy, neoplasms or drug abuse (Table **1**).

Table 1. Causes of Subarachnoid Hemorrhage

- Aneurysmal subarachnoid hemorrhage
- Non aneurysmal perimesencephalyc subarachnoid hemorrhage
- Other medical conditions:
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*
- *Cerebral dural arteriovenous fistulae*
- *Cerebral venous thrombosis*
Vascular lesions in the spinal cord
- *Saccular aneurysm of spinal artery*
- *Spinal arteriovenous fistula or malformation*
- *Cavernous angioma at spinal level*
Coagulopathies
Tumours
Drugs
- *Anticoagulant drugs*
- *Cocaine*

Cerebral aneurysms are present in 2-3% of population [3]. They are mostly located at the bifurcation of Willis polygon vessels or their branches (Fig. **2**). The risk of rupture is quite low, estimated at about 0.05% per year, but it can increase when diameter > 10 mm or if located at cerebral posterior circulation [4]. An international study has reported that the cumulative risk of rupture at 5 years is zero for aneurisms smaller than 7 mm, 2.6% for dimensions between 7 and 12 mm, 14.5% for dimensions between 13 and 24 mm and 40% for aneurysms greater than 25 mm. Those rates increase respectively at 2.5%, 14.5%, 18.4% and 50% for aneurisms located at posterior circulation [5].

Modifiable risk factors for aneurysms rupture include arterial hypertension, smoking, alcohol abuse and cocaine use. Genetic factors are determinants as demonstrated by the increased risk in first degree relatives. Connective hereditary diseases such as polycystic kidney, Ehlers Danlos (Type IV) syndrome, pseudoxantoma elasticum and fibromuscular dysplasia are conditions associated with intracranial aneurisms and SAH [6].

Perimesencephalic non-aneurysmal subarachnoid hemorrhage is characterized by blood extravasation into the cisterns around the midbrain, pons or at the level of quadrigemina cistern, without reaching the Sylvian fissure or interhemispheric fissure or ventricular system. Perimesencephalic SAH is usually not due to aneurysmal malformation and is associated with good outcome. The normality of angiographic findings supports the venous origin of the bleeding due to the rupture of a prepontine or interpeduncular vein. In these patients the perimesencephalic veins frequently drain directly into the dural sinuses instead of into the Galen Vein, predisposing to venous congestion [7].

CLINICAL FEATURES

The clinical presentation of a subarachnoid hemorrhage can be extremely variable ranging from nearly asymptomaticity to sudden death. This is believed to be responsible for a 12% of misdiagnosis with potentially severe consequences in the late treated cases [8].

Headache is the most common symptom and is the only symptom in one third of patients. Mainly it is located in the occipital-nuchal region and is of severe intensity, described often as the most intense ever experienced, typically with sudden onset. The rapidity in reaching the maximum intensity, within few seconds, is more indicative than the intensity itself. Nausea, vomiting and photophobia can be present but they are not specific as they are frequently associated with primary headaches or other secondary

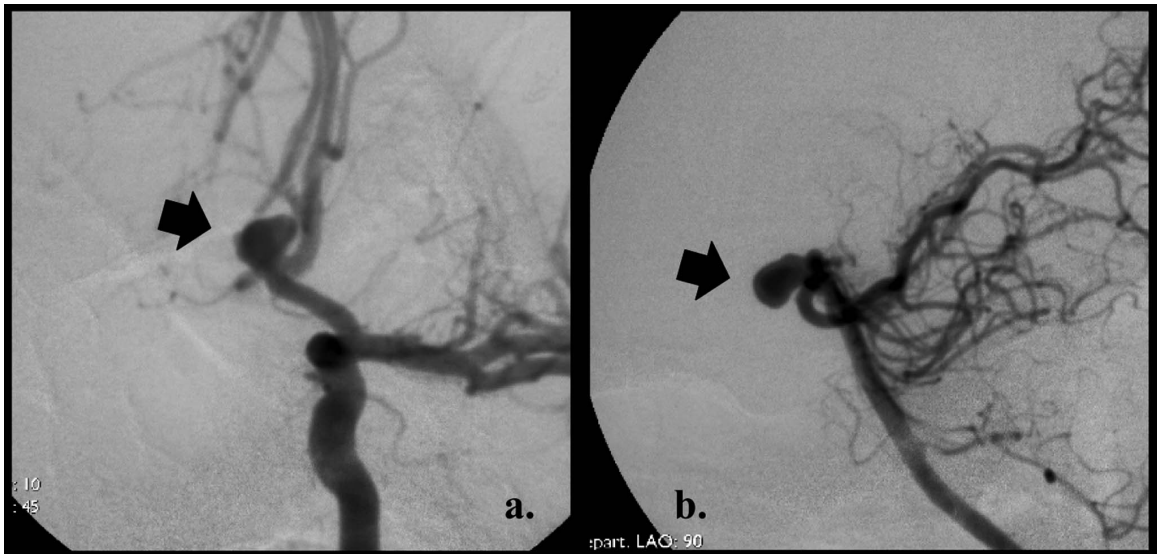

Fig. (2). Saccular aneurysm of the anterior communicating artery (**a**) and saccular aneurysm of the basilar artery (**b**).

headaches. Seventy five percent of patients with thunderclap headache have a subarachnoid hemorrhage [9].

Two thirds of patients on admission present a decreased level of consciousness; half of them are in coma. Confusion and agitation can be present [10].

Nuchal rigidity, the increased resistance to the passive flexion/extension of the neck, is a clinical sign of meningeal irritation due to the blood extravasation in the subarachnoidal space. Other signs of meningeal irritation include a positive Lasegue sign or Kernig and Brudziski signs. Meningeal signs can take from 3 to 12 hours to develop and can be completely absent in the case of coma or minimal blood extravasation. Thus, the absence of neck stiffness can not exclude the diagnosis of subarachnoid hemorrhage [11].

Seizures can be present in 7% of all patients. Young age (< 40 y), entity of the bleeding, presence of hydrocephalus and early rebleeding are the main risk factors for early seizures while vasospasms with cortical ischemia, intraparenchymal bleeding and neurosurgery instead of endovascular treatment are risk factors for late onset seizures [12].

About 14% of patients can present intraocular hemorrhage: the sudden increase in intracranial pressure can lead to a central retinal vein occlusion with subsequent pre-retinal (subhyaloidal) blood extravasation. In the case of severe bleeding an emovitreous can occur (Terson Syndrome) [13].

Focal neurological deficits are not typical findings in the acute phase of subaracnhoid hemorrhage but they may occur in case of intraparenchymal extension of bleeding, compression of cranial nerves or ischemic lesions due to early vasospasm [14].

Cardiovascular changes, mainly hypertension and tachycardia due to the adrenergic tone, can be present in the acute phase; a sudden cardiac arrest can occur at the onset in 3% of cases [15].

DIAGNOSTIC STUDIES

Brain computed tomography (CT) scan is the first level instrumental investigation if a SAH is suspected. This examination can show the hyperdensity of the extravased blood in the subarachnoidal space with a sensitivity depending on the amount of bleeding and the interval after symptom onset. CT scan will be positive in 97% of the cases if carried out within 12 hours; this percentage decreases to 93% at 24 hours and is 50% one week after symptom onset [16]. Moreover, CT scan can evidence intaparenchymal or intraventricular extension of bleeding, hydrocephalus, cerebral oedema or ischemic lesions due to vasospasm [17].

Magnetic resonance imaging (MRI) with proton density, FLAIR and gradient echo images, is as sensitive as CT in the acute phase whilst it becomes more sensitive than CT after the initial days [18]. MRI can permit a preliminary cerebral blood vessel evaluation without contrast medium with magnetic resonance angiography (MRA) whereas with diffusion images it allows for the detection of ischemic lesions. In contrast MRI takes longer to acquire images and needs patient collaboration; this limits a widespread application in the acute phase.

In case of clinical suspect of SAH and negative neuroimaging, cerebrospinal fluid (CSF) examination is required. In the past, the three tube test was performed with the aim of evidencing blood in the CSF and ruling out that the same blood could be the consequence of a traumatic lumbar puncture. But this test can no longer be considered adequately sensitive and specific. The most informative CSF test is obtained 6-12 hours after symptom onset and should be focused on the presence of bilirubin, haemoglobin catabolite, that provides CSF with the characteristic xanthochromia. Spectrophotometry can allow for a more sensitive determination [19].

Following the diagnosis of SAH, determining cause and localization of bleeding is mandatory. The pattern of blood extravasation can suggest the site of aneurysm rupture particularly for aneurysms of the anterior communicating artery, which have bleeding in the interhemispheric fissure or aneurysms of the middle cerebral artery, which have bleeding in the Sylvian fissure; while the posterior circulation aneurysms have no common pattern.

Isolated extravased blood on the anterior part of the brainstem permits the diagnosis of perimesencephalic SAH with a more favourable outcome even if in the 5% of cases a vertebrobasilar aneurysm can be present.

CT angiography has a 95% sensitivity to detect ruptured aneurisms [20]. Magnetic resonance angiography (MRA) reproduces the same results but, as it requires patient collaboration, it is not suitable for critical patients [18].

Digital catheter angiography is the gold standard. Furthermore, it can give information about the morphological features of the aneurysms and its relations with other arteries thereby permitting a better treatment planning. The angiographic study must be extended to all the cerebral arteries as in the 15% of cases multiple intracranial aneurysms can be present. In 1-2% of cases angiography can be complicated by aneurism rupture and in 1.8% of cases by neurological complication with possible permanent sequelae [21].

CLINICAL COMPLICATIONS

Rebleeding is the most frequent and severe complication of SAH. It can occur in the first 24 hours in about 15% of patients with a cumulative risk of 40% in the first month and an incidence of 3% per year after six months. Rebleeding is associated with a poor outcome: mortality and disability can reach 80% [22].

Cerebral ischemic lesions can occur in the acute phase as a consequence of the sudden increase in intracranial pressure with the secondary decrease in cerebral perfusion pressure. More frequently ischemic complications develop later, with a peak between 4 and 14 days from symptom onset, due to vasospasm. Usually, the focal neurological deficits show a less acute onset with respect to atherothrombotic or cardioembolic ischemic stroke and frequently more arterial territories are involved [23].

The presence of blood in the ventricular system can cause alterations in CSF circulation leading to an acute

hydrocephalus. The clinical presentation is usually represented by a progressive decrease in consciousness with possible associated focal neurological deficits [24].

Cardiovascular complications are represented by drug resistant hyper- or hypotension, arrhythmias or heart failure. Other possible complications are hydro-electrolyte disorders with hypo- or hypernatremia and hypomagnesemia; hyperglycemia and fever can occur [25].

Long term complications are mainly represented by cognitive deficit and psychosocial dysfunction. Cognitive domains in which patients with a SAH show frequent impairment include memory, executive function, and language; the prevalence is ranging from 14% to 61%, depending on the different standardized tests [26]. Up to 60% of the patients reported changes in personality, most commonly increased irritability or emotionality [27].

TREATMENT

Subarachnoid hemorrhage is a clinical emergency with high mortality from onset. First of all, the stability of respiratory and cardiovascular functions needs to be evaluated and treated if required. After the vital functions are stabilized the second step is to prevent rebleeding and other possible complications that can compromise patient prognosis.

Hypertension must be treated promptly with endovenous anti-hypertensive drugs such as labetalol or urapidil if needed. Recommended systolic blood pressure values are between 140 and 90 mmHg [28]; after the exclusion of the aneurysm the blood pressure treatment can be less intensive. Considering the risk of hypoperfusion, hypotension should be avoided even if definite target values are not established.

Headache could require medical treatment. Non-steroidal anti-inflammatory drugs (NSAID) should be avoided as they increase rebleeding risk and opioids should be avoided as they can interfere with the level of consciousness. First choice drug is paracetamol per os or intravenous. Hyperpyrexia should be treated (recommended body temperature $\leq$ 37.2°C) and hyperglycemia should be corrected (recommended blood glucose level 80-120 mg/dl) as they are predictive of poor outcome [28]. Proton pump inhibitors are indicated to prevent stress peptic ulcers. Deep vein thrombosis prophylaxis with low molecular weight heparin can be used after the treatment of the aneurysm.

Nimodipine 60 mg orally every 4 hours for 21 days can reduce the risk of delayed cerebral ischemia due to vasospasm. A Cochrane revision has reported a relative risk reduction of 18% with an absolute risk reduction of 5.1% [29].

Magnesium sulphate has been studied in vasospasm prevention given that hypomagnesemia is present in the 50% of patients with SAH and is significantly associated with delayed cerebral ischemia. A phase II study has produced positive results but the phase III trial results do not support a clinical benefit of intravenous magnesium sulfate infusion over placebo in patients with acute aneurysmal subarachnoid hemorrhage [30, 31].

Antifibrinolytic agents can reduce the rate of rebleeding even if they increase the risk of cerebral ischemia or systemic thrombosis. Tranexanic acid reduces the rebleeding rate from 11 to 2.4% but this benefit is offset by ischemic complications [32].

The aneurysm exclusion is the most effective treatment for preventing rebleeding. Over the last decades, endovascular coiling has become the first choice treatment with respect to the neurosurgical clipping. Endovascular coiling consists in reaching the neck of the aneurysm with a superselective catheterism and compacting platinum detachable coils of adequate lengths and diameter into the aneurysm sac (Fig. **3**). After that, the blood clots forming around the coils block the flow of blood into the bulge and keep the vessel from rupturing or leaking.

Randomized clinical trials including 2,272 patients have compared endovascular treatment versus traditional neurosurgery. Endovascular coiling has shown a 24%

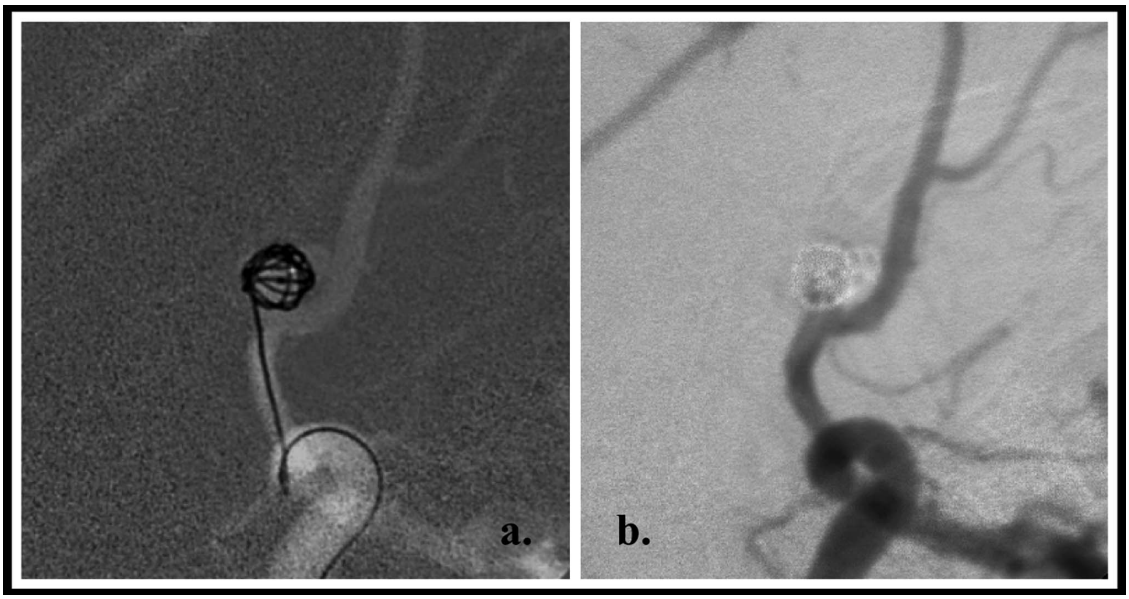

Fig. (3). Aneurysm embolization with platinum coils (**a**) and final control (**b**).

relative risk reduction in unfavourable outcome with an absolute risk reduction of 7% [33,34]. Nevertheless, this technique is not suitable for all aneurysms: wide neck and close relations with vessel branches require a neurosurgical approach. Regarding the timing of procedure, while in the past it was chosen to avoid the period in which vasospasm has its greatest risk – from the 4th to the 15th day – considering also a delayed treatment, evidence suggests that an early treatment best prevents rebleeding [28].

In conclusion, the subarachnoid hemorrhage must be considered a clinical emergency even in the presence of mild symptoms. A complete diagnostic process is highly recommended even in the presence of weak clinical features. An urgent execution of medical and interventional treatment reduces mortality and disability.

REFERENCES

[1] Zacharia BE, Hickman ZL, Grobelny BT, *et al.* Epidemiology of aneurysmal subarachnoid hemorrhage. Neurosurg Clin N Am 2010; 21(2):221-33.

[2] Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology 1998; 50: 1413-18.

[3] Brisman JL, Song JK, Newell DW. Cerebral Aneurysms. N Engl J Med 2006; 355: 928-39.

[4] Rinkel GJE, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998; 29: 251-56.

[5] Wiebers DO, Whisnant JP, Huston J III, *et al*. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003; 362: 103-10.

[6] Qureshi AI, Suri MF, Yahia AM, *et al*. Risk factors for subarachnoid hemorrhage. Neurosurgery 2001; 49: 607-12.

[7] van der Schaaf I, Velthuis BK, Gouw A, Rinkel GJE. Venous drainage in perimesencephalic hemorrhage. Stroke 2004; 35: 1614-18

[8] Linn FHH, Rinkel GJE, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. J Neurol Neurosurg Psychiatry 1998; 65: 791-93.

[9] Jan van Gijn, Richard S Kerr, Gabriel J E Rinkel. Subarachnoid haemorrhage. Lancet 2007; 369: 306-18

[10] Vermeulen M, van Gijn J. The diagnosis of subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 1990; 53: 365-72.

[11] Edlow JA, Malek AM, Ogilvy CS. Aneurysmal subarachnoid hemorrhage: update for emergency physicians. J Emerg Med 2008; 34(3): 237-51.

[12] Pinto AN, Canhao P, Ferro JM. Seizures at the onset of subarachnoid haemorrhage. J Neurol 1996; 243: 161-64.

[13] Stiebel-Kalish H, Turtel LS, Kupersmith MJ. The natural history of nontraumatic subarachnoid hemorrhage-related intraocular hemorrhages. Retina 2004; 24: 36-40.

[14] Vermeulen M, van Gijn J. The diagnosis of subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 1990; 53: 365-72.

[15] Khechinashvili G, Asplund K. Electrocardiographic changes in patients with acute stroke: a systematic review. Cerebrovasc Dis 2002; 14: 67-76.

[16] Boesiger BM, Shiber JR. Subarachnoid hemorrhage diagnosis by computed tomography and lumbar puncture: are fi fth generation CT scanners better at identifying subarachnoid hemorrhage? J Emerg Med 2005; 29: 23–27.

[17] Provenzale JM, Hacein-Bey L. CT evaluation of subarachnoid hemorrhage: a practical review for the radiologist interpreting emergency room studies. Emerg Radiol 2009; 16(6): 441-51.

[18] Mitchell P, Wilkinson ID, Hoggard N, *et al*. Detection of subarachnoid haemorrhage with magnetic resonance imaging. J Neurol Neurosurg Psychiatry 2001; 70: 205-11.

[19] Beetham R. Recommendations for CSF analysis in subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2004; 75: 528.

[20] Chappell ET, Moure FC, Good MC. Comparison of computed tomographic angiography with digital subtraction angiography in the diagnosis of cerebral aneurysms: a meta-analysis. Neurosurgery 2003; 52: 624-30.

[21] Villablanca JP, Hooshi P, Martin N, *et al*. Three-dimensional helical computerized tomography angiography in the diagnosis, characterization, and management of middle cerebral artery aneurysms: comparison with conventional angiography and intraoperative findings. J Neurosurg 2002; 97: 1322-32.

[22] Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. Stroke 2001; 32: 1176-80.

[23] Rabinstein AA, Weigand S, Atkinson JL, Wijdicks EFM. Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke 2005; 36: 992-97.

[24] van Gijn J, Hijdra A, Wijdicks EFM, Vermeulen M, van Crevel H. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. J Neurosurg 1985; 63: 355–62.

[25] Jose I. Suarez, Robert W. Tarr, Warren R. Selman. Aneurysmal Subarachnoid Hemorrhage. N Engl J Med 2006; 354: 387-96.

[26] Timour Al-Khindi; R. Loch Macdonald,; Tom A. Schweizer. Cognitive and Functional Outcome After Aneurysmal Subarachnoid Hemorrhage. Stroke 2010; 41: e519-e536.

[27] Wermer MJH, Kool H, Albrecht KW, Rinkel GJE. Aneurysm Screening after Treatment for Ruptured Aneurysms Study Group. Subarachnoid hemorrhage treated with clipping: long-term effects on employment, relationships, personality, and mood. Neurosurgery 2007 60: 91-98.

[28] Bederson JB, Connolly ES Jr, Batjer HH, *et al*. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association. Stroke 2009; 40; 994-1025.

[29] Dorhout Mees S, Rinkel GJE, Feigin VL, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD000277. DOI: 10.1002/14651858.CD000 277.pub3

[30] Veyna RS, Seyfried D, Burke DG, *et al*. Magnesium sulfate therapy after aneurysmal subarachnoid hemorrhage. J Neurosurg 2002; 96: 510-14.

[31] Wong GK, Poon WS, Chan MT, *et al.* IMASH Investigators. Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial. Stroke. 2010; 41(5): 921-6.

[32] Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. J Neurosurg 2002; 97: 771-78.

[33] Molyneux A, Kerr R, Stratton I, *et al*. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002; 360: 1267-74.

[34] van der Schaaf I, Algra A, Wermer M, Molyneux A, Clarke MJ, van Gijn J, Rinkel GJE. Endovascular coiling versus neurosurgical clipping for patients with aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev 2005, Issue 4. Art. No. CD003085. DOI: 10.1002/14651858. CD003085.pub2.

Received: May 19, 2010 Revised: March 27, 2011 Accepted: April 15, 2011