FUNCTIONAL OUTCOME OF MICROSURGICAL CLIPPING COMPARED TO ENDOVASCULAR COILING

BY

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Introduction: Nontraumatic subarachnoid hemorrhage is the second most frequent cause of hemorrhagic stroke and accounts for 3 – 5% of all strokes. In more than 85% of cases, it is caused by a ruptured intracranial aneurysm with incidence of at 6–8 cases per 100,000 population. The treatment options available for ruptured aneurysms includes microsurgical and endovascular means. In recent years endovascular coiling has been used increasingly as an alternative to microsurgical clipping for treating subarachnoid hemorrhage secondary to aneurysm rupture.

Objectives: The purpose of this study was to compare functional outcomes in terms of modified rankin scale, morbidity and mortality at 6 months after treatment of post-subarachnoid hemorrhage secondary to cerebral aneurysm rupture in subjects who were either microsurgically clipped or endovascularly coiled. In addition, the present study aims to identify the predictors in the clinical course of primary subarachnoid hemorrhage.

Patients and methods: A retrospective case review on the treatment methods of aneurysm rupture in Hospital Kuala Lumpur over the period of five years (2005-2009). A total of 268 patients who fulfilled the inclusion criteria were included in this study. These patients were broadly categorized into two groups based on their treatment mode for ruptured aneurysm. The case notes, CT brain films reports and angiography reports were analyzed with respect to their clinical, radiological, surgical clipping or endovascular coiling treatments and outcome data. Statistical analysis was determined using Chi-Square tests to study these associations.

Results:

There was a female predominance with male-to-female ratio 1:1.4. The mean age was 50.9 years old in this series. 50 patients were less than 40 years (18.7%) and 218 patients were more than 40 years(81.3%). 37 patients(74%) in age group less than 40 years had significant good outcome as compared to125(57.3%) patients above 40 years old.($p=0.03$). One hundred and eighty one patients (67.5%) presented with Good WFNS (WFNS1-2) and 87 patients (32.5%) presented with Poor WFNS (WFNS 3-5) prior to intervention. One hundred and sixty two patients (60.4%) had good functional outcome (mRS grade 0-2) as compared to 106 patients(39.6%) who had poor mRS outcome(MRS 3-6) while 50 patients died(18.7%) during our follow up at 6 months . When we analyzed the WFNS group with functional outcome (mRS), there was significant association ($p<0.01$). In good WFNS, 143(79%) had good outcome and in poor WFNS, 68 patients (78.2%) had poor mRS outcome. There were 204 (76.1%) patients in clipping group and 64 (23.9%) patients in coiling group. Patients who underwent coiling, initially showed a better

mRS outcome with 47patients (73.4%) than, 115 patients (56.4%) in clipping. Further comparison showed that 89(43.6%) patients in clipping group had poor functional (MRS) outcome as compared to17 patients (26.6%) coiling, which was significant (p=0.015). However when we controlled the WFNS grade of presentation in the treatment groups, we obtained a different result. In good WFNS group, it was noted that 98 patients (76%) out of 129 patients in clipping group had a good MRS outcome while, 45 patients (86.5%) out of 52 patients in coiling group had good mRS outcome (p=0.114). In poor WFNS presentation, it was noted that in clipping group, 58 patients (77.3%) out of 75 had poor mRS outcome. Similarly with poor WFNS presentation, 10 (83.3%) out of 12 patient in coiling group had poor outcome. (p=1.00). Hence when we control the WFNS group, there was no significant association between treatment group (clipping and coiling) and mRS outcome at 6 months. Further we noted that age less than 40 and Fisher grade of 1-2 have better outcome while patients with EVD, CSF infection and pneumonia have poorer outcome. Using multiple logistic regression analysis we have determined that good mRS outcome is associated with good WFNS and absence of EVD

Conclusion: Clinical severity of the SAH (WFNS grade) was the most significant predictor of functional outcome (mRS) at 6 months. Therefore the decision regarding treatment option needs to be individualized based on the presentation of the patient.

Mr. (Dr) Ramesh Narenthiranathan : Supervisor

Associate Professor Dr. Hillol Kanti Pol : Co-supervisor

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IV. ABBREVIATIONS

ACOM aneurysm : Anterior Communicating Artery Aneurysm

BA aneurysm : Basilar Artery Aneurysm

CT : Computed Tomography

DACA aneurysm : Distal Anterior Cerebral artery Aneurysm

EVD : Extraventricular Drain

HKL : Hospital Kuala Lumpur

ICA : Internal Carotid Artery

ISAT : International Subarachnoid Trial

ISUA : International Study of Unruptured Intracranial Aneurysm

MCA aneurysm : Middle Cerebral Artery Aneurysm

mRS : modified Rankin Scale

PCA aneurysm : Posterior Cerebral Artery Aneurysm

PCOM aneurysm : Posterior Communicating Artery Aneurysm

SAH : Subarachnoid Hemorrhage

VA aneurysm : Vertebral artery Aneurysm

VP Shunt : Ventriculo-peritoneal Shunt

WFNS grade : World Federation of Neurosurgeon grade

V. ABSTRAK

OBJEKTIF: Kaedah endovaskular melingkar semakin telah digunakan sebagai alternatif untuk kliping bedah saraf untuk mengubati pendarahan subaraknoid sekunder berikutan kepecahan aneurisma. Tujuan utama kajian ini adalah untuk membandingkan hasil fungsional pada enam bulan selepas pendarahan subaraknoid sekunder berikutan kepecahan aneurisma otak pada subjek yang dirawat dengan kaedah endovaskular melingkar atau kliping bedah saraf. Selain itu, kajian ini juga bertujuan untuk mengenal pasti prediktor dalam jangkamasa rawatan klinikal pendarahan subaraknoid primer.

TATACARA: Hasil analisis retrospektif terhadap kaedah rawatan kepecahan aneurisma telah dilakukan di Hospital Kuala Lumpur selama tempoh 5 tahun (2005-2009). Seramai 268 pesakit yang memenuhi criteria inklusi direkrut untuk kajian ini. Pesakit tersebut dikategorikan kepada dua kumpulan berdasarkan kaedah rawatan mereka untuk kebocoran aneurisma. Nota kes pesakit, laporan filem CT otak dan laporan angiografi dianalisis berkaitan dengan aspek klinikal, data radiologi, pembedahan atau rawatan melingkar endovaskular dan data hasil. Analisis statistik ditentukan dengan menggunakan ujian Chi-Square untuk mengkaji hubungkait antara kedua-dua kaedah rawatan yang dikaji dan hasil rawatan.

KEPUTUSAN: Hasil daripada kajian menunjukkan terdapat lebih ramai subjek perempuan berbanding dengan lelaki dalam populasi kajian (lelaki:perempuan ialah 1:1.4). Purata umur

subjek adalah 50.9 tahun. Didapati 50 pesakit berumur kurang dari 40 tahun (18.7%) manakala 218 pesakit berumur lebih dari 40 tahun (81.3%). 37 pesakit (74%) dari kelompok usia kurang dari 40 tahun telah menunjukkan hasil baik yang signifikan berbanding dengan 125 (57.3%) pesakit di atas 40 tahun (p = 0.03). 181 pesakit (67.5%) menunjukkan gred WFNS baik (WFNS1-2) manakala 87 pesakit (32.5%) menunjukkan gred WFNS yang tidak baik (WFNS 3-5) sebelum intervensi. Seratus enam puluh dua pesakit (60.4%) mempunyai hasil fungsional yang baik (gred mRS 0-2) dibandingkan dengan 106 pesakit (39.6%) yang mempunyai hasil mRS yang tidak baik iaitu gred mRS 3-6, malah 50 pesakit meninggal dunia (18.7%) pada waktu kajian susulan pada 6 bulan. Hasil daripada analisis kumpulan WFNS dengan hasil fungsional (mRS) menunjukkan terdapat hubungan yang signifikan (p<0.01). Dalam golongan pesakit dengan gred WFNS yang baik, 143 (79%) mempunyai keputusan yang baik dan dalam golongan pesakit dengan gred WFNS yang tidak baik, 68 pesakit (78.2%) mempunyai hasil mRS yang tidak baik. Terdapat 204 (76.1%) pesakit dalam kumpulan kliping dan 64 (23.9%) pesakit dalam kumpulan endovaskular melingkar. Pesakit yang menjalani kaedah endovaskular melingkar, pada awalnya menunjukkan hasil mRS yang lebih baik; iaitu 47 pesakit (73.4%) berbanding dengan 115 pesakit (56.4%) di kumpulan kliping. Perbandingan yang lebih lanjut menunjukkan bahawa 89 (43.6%) pesakit dalam kumpulan kliping mempunyai hasil fungsional (mRS) yang tidak baik berbanding dengan 17 pesakit (26.6%) dalam kumpulan endovaskular melingkar di mana perbandingan ini didapati signifikan (p <0.05). Namun, apabila kelas WFNS dijadikan kumpulan kawalan bagi kedua-dua kaedah yang dianalisakan, hasil yang berbeza diperolehi. Dalam kumpulan gred WFNS yang baik, dicatatkan bahawa 98 pesakit (76%) dari 129 pesakit dalam kumpulan kliping mempunyai hasil mRS yang baik, sementara, 45 pesakit (86.5%) dari 52 pesakit dalam kumpulan endovaskular melingkar mempunyai keputusan mRS yang baik (p = 0.114). Dalam kategori gred WFNS yang tidak baik, diperhatikan bahawa dalam kumpulan kliping,

58 pesakit (77.3%) dari 75 mempunyai hasil mRS yang tidak baik. Demikian pula dengan kategori gred WFNS yang tidak baik, 10 (83.3%) daripada 12 pesakit dalam kumpulan endovascular melingkar mempunyai keputusan yang tidak baik (p = 1.00). Oleh kerana itu, apabila kelas WFNS dijadikan kumpulan kawalan, didapati tiada hubungan yang signifikan antara kedua-dua kaedah kliping dan melingkar dan juga hasil mRS pada 6 bulan.Selain dari ini kami juga mendapati bahawa keputusan yang baik bagi pesakit di bawah usia 40 tahun and gred Fisher 1-2, sementara pesakit yang memerlukan EVD, jangkitan CSF and radang paru-paru mempunyai keputusan yang tidak baik. Kami menggunakan analisis multiple logistic regression dan dapat menetapkan bahawa mRS yang baik berkaitan dengan WFNS yang baik dan ketiadaan EVD.

KONKLUSI: Keparahan klinikal pendarahan subaraknoid (gred WFNS) adalah prediktor yang paling signifikan untuk hasil fungsional (mRS) pada 6 bulan. Oleh kerana itu, keputusan tentang pilihan kaedah rawatan bagi seseorang individu perlu di ambil kira berdasarkan kepada keadaan pesakit tersebut.

VI. ABSTRACT

Objective: Endovascular coiling has been used increasingly as an alternative to neurosurgical clipping for treating subarachnoid hemorrhage secondary to aneurysm rupture. The purpose of this study was to compare functional outcomes at 6 months post-subarachnoid hemorrhage secondary to cerebral aneurysm rupture in subjects who were either surgically clipped or endovascularly coiled. In addition, the present study aims to identify the predictors in the clinical course of aneurysmal subarachnoid hemorrhage.

Materials and methods: A retrospective case review on the treatment methods of aneurysm rupture in Hospital Kuala Lumpur over the period of five years (2005-2009). A total of 268 patients who fulfilled the inclusion criteria were recruited for this study. These patients were broadly categorized into two groups based on their treatment mode for ruptured aneurysm. The case notes, CT brain films reports and angiography reports were analyzed with respect to their clinical, radiological, surgical clipping or endovascular coiling treatments and outcome data. Statistical analysis was determined using Chi-Square tests to study these associations.

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There was a female predominance with male-to-female ratio 1:1.4. The mean age was 50.9 years old in this series. 50 patients were less than 40 years (18.7%) and 218 patients were more than 40 years(81.3%). 37 patients(74%) in age group less than 40 years had significant good outcome as compared to125(57.3%) patients above 40 years old.(p=0.03). One hundred and eighty one patients (67.5%) presented with Good WFNS (WFNS1-2) and 87 patients (32.5%) presented with Poor WFNS (WFNS 3-5) prior to intervention. One hundred and

sixty two patients (60.4%) had good functional outcome (mRS grade 0- 2) as compared to 106 patients(39.6%) who had poor mRS outcome(MRS 3-6) while 50 patients died(18.7%) during our follow up at 6 months . When we analyzed the WFNS group with functional outcome (mRS), there was significant association ($p<0.01$). In good WFNS, 143(79%) had good outcome and in poor WFNS, 68 patients (78.2%) had poor mRS outcome. There were 204 (76.1%) patients in clipping group and 64 (23.9%) patients in coiling group. Patients who underwent coiling, initially showed a better mRS outcome with 47patients (73.4%) than, 115 patients (56.4%) in clipping. Further comparison showed that 89(43.6%) patients in clipping group had poor functional (MRS) outcome as compared to17 patients (26.6%) coiling, which was significant ($p=0.015$). However when we controlled the WFNS grade of presentation in the treatment groups, we obtained a different result. In good WFNS group, it was noted that 98 patients (76%) out of 129 patients in clipping group had a good MRS outcome while, 45 patients (86.5%) out of 52 patients in coiling group had good mRS outcome ($p=0.114$). In poor WFNS presentation, it was noted that in clipping group, 58 patients (77.3%) out of 75 had poor mRS outcome. Similarly with poor WFNS presentation, 10 (83.3%) out of 12 patient in coiling group had poor outcome. ($p=1.00$). Hence when we control the WFNS group, there was no significant association between treatment group (clipping and coiling) and mRS outcome at 6 months. Further we noted that age less than 40 and Fisher grade of 1-2 have better outcome while patients with EVD, CSF infection and pneumonia have poorer outcome. Using multiple logistic regression analysis we have determined that good mRS outcome is associated with good WFNS and absence of EVD

Conclusion: Clinical severity of the SAH (WFNS grade) was the most significant predictor of functional outcome (mRS) at 6 months. Therefore the decision regarding treatment option needs to be individualized based on the presentation of the patient.

1. INTRODUCTION

Nontraumatic subarachnoid hemorrhage which accounts for 3 – 5% of all strokes, is the second most frequent cause of hemorrhagic stroke, and in more than 85% of cases is caused by a ruptured intracerebral aneurysm. The incidence is at 6–8 cases per 100,000 population (Varelas, 2006). There are various treatment options available for ruptured aneurysms including surgical and endovascular means. Class I evidence for the relative merits of one treatment option over the other is scanty. (Gnanalingham, 2006).

From the era of Dandy until recently, clipping was the most popular treatment. This procedure, which requires craniotomy, aims to prevent rebleeding of the aneurysm by placing a clip across its neck. As such the aneurysm will be excluded from the circulation. Surgical clipping involves the exclusion of re-rupture with a certainty of approximately 98% (Frazer, 2007). In the past decade, endovascular coiling has grown in popularity as an alternative to clipping. This procedure aims to obstruct the aneurysmal lumen with a detachable coil, with the intent to provoke secondary thrombosis of the aneurysm.

This new mode of treatment for intracranial aneurysms has been compared to open surgery in multiple studies. The most recent of these studies, international subarachnoid aneurysm trial (ISAT) was a multicentre randomised trial, which compared neurosurgical clipping with coiling for ruptured anterior circulation aneurysms that were considered suitable for either treatment. Analysis of the outcome at 1-year follow-up revealed a 6.9% absolute risk reduction in dependency or death for the endovascular group in comparison with patients allocated to surgery (Molyneux, 2005). However, a 5 year review of the study noted that the proportion of survivors at 5 years who are independent did not differ between

the two groups; endovascular 83% (626 of 755) and neurosurgical 82% (584 of 713) (Molyneux, 2009).

The definite method of treatment remains debated with conflicting views being constantly published. In addition there is a growing body of evidence suggesting that the most important causal factor for the neuropsychological sequelae of aneurysmal SAH is the hemorrhage itself and associated secondary brain damage, rather than the location of the aneurysm or treatment methods (Frazer, 2007). As such we reviewed the outcome of aneurysm treatment in our centre as both methods of treatment are being practiced here.

We performed a retrospective cohort review on the treatment methods of aneurysm rupture in Hospital Kuala Lumpur over the period of five years (2005-2009). The purpose of this study was to evaluate the outcome of patients with rupture aneurysm who had been treated surgically with clipping or endovascularly with coiling. A total of 268 patients who fulfilled the inclusion criteria were recruited for this study. Their case notes, radiology reports and films were studied specifically on methods of treatment, clinical presentation (WFNS grade) prior treatment, CT Fisher Grade of SAH, angiographic site of aneurysm, clinical vasospasm, requirement of EVD and shunt, pneumonia, CSF infection and subsequent recovery to independence, morbidity and mortality. Apart from that, demographic data including age, gender, ethnicity and duration of illness were also recorded. Statistical analysis (Chi-square and Fisher's exact test) was then performed to determine the association between treatment methods and good functional outcome, morbidity and mortality.

2. LITERATURE REVIEW

2.1 HISTORICAL PERSPECTIVE

Intracranial aneurysms as probable cause of subarachnoid hemorrhage were postulated in the 17th century by Morgagni. He was the first to report the presence of incidental “dilatations” of both posterior cerebral arteries in 1725. Francesco Biumi in 1765 on the other hand was the first to have documented account of an unruptured intracranial aneurysm. In 1814, the first verified account of aneurysmal rupture was reported by Blackall (Greenblatt, 1997).

Most of the reports during this period were based on postmortem findings. There were no treatment options available. However in late 19th century, the concept of carotid artery ligation for intracranial vascular pathology was adopted based on Hunters success in proximal femoral artery ligation for popliteal aneurysm (Prestigiacomo, 2006).

Cooper in 1808 was the first to successfully ligated the carotid artery for an aneurysm of the left cervical carotid artery. In fact even a century later, ligation of cervical artery was still in practice with more sophisticated method and materials. An example will be Neff‘s clamp that was invented to allow for the development of collateral circulation while occluding and dividing the vessel (Prestigiacomo, 2006; Richling, 2006).

There are many difficulties encountered with the indirect approaches of cervical carotid ligation including thrombotic, embolic phenomenon, infections and poor success rate of aneurysm occlusion. Therefore, more direct, intracranial approaches were sought. The limitation of technology in the 1930s made securing an aneurysm at the neck hazardous, as

only ligatures and silver clips were available for use at that time. Zeller's patient who died from hemorrhage after avulsion of ligated artery by his assistant is an example. (Prestigiacomo, 2006)

Norman McComish Dott was the first surgeon to attempt direct attack on an intracranial aneurysm and introduce wrapping of aneurysm (Choudari, 2004). In 1932, Dott secured bleeding during the exposure of aneurysm of the ICA by placing harvested muscle from patient's thigh on the exposed aneurysm dome. The patient was reported to have made an excellent recovery. The next advance in aneurysm treatment was aneurysm trapping, which was initially described by Walter Dandy in 1936. He performed cervical internal carotid ligation and clipping of the supraclinoid carotid artery for a cavernous aneurysm. (Prestigiacomo, 2006)

The first description of clipping on neck of aneurysm was by Dandy, who placed a silver clip across neck of posterior communicating artery aneurysm and cauterized its dome (Greenblatt, 1997; Bulters, 2010). The next important step in the development of the aneurysm clip was the development of an adjustable clip that could be reopened and repositioned. This was followed by the development of fenestrated clip. Using the fenestrated clip, neck of an aneurysm could be safely clipped without displacing and compromising other vessels in the field.

Currently, modifications to the aneurysm clip are based on metallurgy and different design configurations. Concurrent with the development of the aneurysm clip came many other developments in techniques and parallel technologies like microsurgical techniques which improved the treatment strategy.

There were many attempts to treat aneurysms from the “endovascular side” as early as 1936 when Gardner opened and packed a giant ICA aneurysm with 5 cotton sponges. The patient was well until 2 years later when it became infected (Prestigiacomo, 2006). Mullan in 1965 stereotactically placed wire electrodes into exposed aneurysms and subjected them to an electric current with only partial success (Berenstein, 2006). Gallagher in 1965 described the injection of a horse hair into a surgically exposed aneurysm (pilojection) with only partial thrombosis in most patients (Kamble, 2008)

Despite many approaches at endosaccular occlusion of aneurysms as described earlier, true catheter-based endovascular approaches to vascular diseases of the central nervous system did not take place until 1960. During this period, Luessenhop and Spence were able to cannulate the internal carotid artery and deposited silastic spheres to treat an arteriovenous malformation in the operating room (Guglielmi, 2000 ; Kerber, 2006). Two years later, Rothenberg introduced the concept of using balloons in the treatment of intracranial aneurysms.

In 1971, Serbinenko used balloons for temporary occlusion of brain vessels and carotid cavernous sinus fistulae. By 1974, Serbinenko used detachable balloons filled with a liquid silicone for the treatment of saccular aneurysms of the cerebral arteries (Greenblatt 1997; Guglielmi, 2000). Important milestone was achieved when he reported the successful detachment of balloons within a basilar tip aneurysm and supraclinoid carotid aneurysm (Randall T. Higashida, 2000). In 1985, Braun et al. reported the first intracranial aneurysm treated with coil embolization. In 1988 platinum coils with Dacron fiber were introduced to induce thrombosis for the treatment of vascular malformations and aneurysms (Linxia Gu, 2005).

Guido Guglielmi developed techniques that combined these concepts. He developed the first generation of electrolytically detachable coil. In 1990, the first coil was introduced in a patient for a traumatic carotid cavernous fistula who failed balloon occlusion (Strother, 2001). Since that time, the tremendous advancement in endovascular technology and techniques has challenged the role of microsurgery in the treatment of aneurysms

2.2. EPIDEMIOLOGY OF SAH AND ANEURYSM

SAH represents 2 to 5 percent of all new strokes and affects 21000 to 33000 people each year in the Unites states. Approximately 10,000 per year suffer from SAH in Germany (Bulters 2010).Worldwide incidence is about 10.5 cases per 100,000 person-years. The leading cause of spontaneous (non traumatic) SAH is rupture of aneurysms which account for 85% of all spontaneous SAH, followed by perimesencephalic hemorrhage (10%) and other causes account for the remaining 5%.

Most aneurysms are found in patients aged 40 to 70 years. The incidence increases with age, with a mean age at presentation of 55 years. The prevalence of aneurysm is noted twice as high in oldest age group (75-84 years) as compared to lower age groups. However the incidence of intracerebral hemorrhage due to rupture of these aneurysms is most frequent in the age group of 40 to 60 years.

The relationship between age and risk of rupture is undetermined. An autopsy study by Inagawa fails to demonstrate a relationship between the patient's age and the thickness of the aneurysmal walls (Inagawa, 2009) .Therefore it is likely those factors associated with aging, such hypertension, smoking, and atherosclerotic vessel degeneration, might affect the risk of aneurysm rupture.

While in patients below the age of 40, aneurysms are more common in men, the majority of aneurysm which occurs above the age of 40 predominates in women .The risk for women to develop aneurysm is 1.6 times that of men. The exact etiology is unknown but it

was proposed that the hormonal factors especially after menopause may have a role in the pathogenesis of aneurysmal rupture

The average mortality rate for subarachnoid hemorrhage is 51 percent, with approximately one third of survivors requiring lifelong care. Most mortality occurs within two weeks after the ictus, with 10 percent occurring at home or on transit to hospital and 25 percent within 24 hours. About 46 percent of survivors of subarachnoid hemorrhage may have long-term cognitive impairment, with an effect on functional status and quality of life. The disorder has direct impact on health care resources, most of which are related to hospitalization. (Suarez, 2006)

2.3 PATHOLOGY

The pathogenesis of spontaneous aneurysms are only partially understood Almost all of the aneurysms are located above the carotid siphon on the circle of Willis The most common causes for the development of an aneurysm are hemodynamically induced vascular injuries, atherosclerosis, underlying vasculopathy and high flow states.

Endogenous factors like elevated arterial blood pressure (Inci, 2000), special anatomical relationships given by the Circle of Willis, altered flow conditions, and exogenous factors like cigarette smoking, heavy alcohol and coffee consumption and use of anticoagulant or contraceptive medications have all been found to be associated with the occurrence of cerebral aneurysms (Juvela, 2001; Isaksen, 2002)

Intracranial aneurysms may be classified based on morphology, size, and location and etiology. However commonly intracranial aneurysms are divided into three basic types: saccular, fusiform and dissecting. According to their size, saccular aneurysms can be grouped into three types: small (<10 mm), large (10– 25 mm), giant (>25 mm). According to the neck width they are further classified into small neck (<4 mm) and large neck (>4 mm) (Gasparotti, 2005). They mostly develop spontaneously as solitary (70%–75%) or multiple (25%–30%) vascular lesions located at the Circle of Willis.

Saccular aneurysm

Saccular aneurysms had been described as berry-like vessel outpouchings arising from arterial bifurcations. They account for 66%–98% of intracranial aneurysms (Yong-

Zhong, 1990) in adults and rare in children. The majority of aneurysms (85%) are located in the anterior circulation and only 15% are located in the posterior circulation (Kassell, 1983).

In adults the role of acquired changes in the arterial wall is likely the cause because of exposure to general risk factors responsible for the development of aneurysms like hypertension, smoking and alcohol abuse. These factors might contribute to general thickening of the intimal layer in the arterial wall, distal and proximal to branching sites. Within these "intimal pads" the intimal layer is inelastic and therefore causes increased strain of the more elastic portions of the vessel wall. Further abnormalities in structural proteins of the extracellular matrix contribute to aneurysm formation (Chyatte, 1990; Mizutani, 2000). In addition to above, aneurysms are acquired due to hemodynamic stress on the relatively unsupported bifurcations of cerebral arteries.

Other pathological factors which are associated with formation of aneurysms include increased density of vasa vasorum in proximal segments of atherosclerotic intracranial arteries which has angiogenesis potential. This is augmented by presence of 5-lipoxygenase pathway. 5-lipoxygenase pathway generates LTD4 which binds to endothelial and leads to inflammation of media and subsequently results in aneurysm formation.

The previous theory of a congenital defect in the tunica media through which the inner layer of the arterial wall would bulge was popular in past. These defects are located on the distal carina at the point of branching, at the apex of bifurcation and may also occur at the lateral angles. However the theory is now disputed as media defects noted to occur in the cerebral arteries in many more places than the sites of aneurysms formation. Similar defects have also been observed in the extracranial arteries. It was also noted that if aneurysm has

formed, any defect in the muscle layer is not located at the neck as expected, but somewhere in the aneurysmal wall of the sac (Stehbens, 1989)

Dissecting aneurysms

Dissecting aneurysms are usually aneurysms consisting of a false lumen within an injured arterial wall. An intimal tear is followed by an intramural hemorrhage between the media and adventitia. The prevalence of intracranial dissections is unknown but dissecting aneurysms accounts for 4.5% of the autopsy cases of SAH (Sasaki, 1991). Dissecting aneurysms occur much more often in the vertebrobasilar system and more often in male (Yamaura, 2000; Yonekawa, 2008). Dissecting aneurysms of the extracranial carotid and vertebral arteries are often traumatic in origin but they may also be caused by fibromuscular dysplasia, atherosclerosis, infection, arthritis and heritable connective tissue disorders.

Fusiform aneurysms

Fusiform aneurysms are dilated, tortuous and elongated arterial segments. These aneurysms are uncommon (Atalay, 2007). Fusiform aneurysms are characterized by the absence of a defined neck, circumferential involvement of the parent artery and a long course. The aneurysm can be partially thrombosed.

Fusiform aneurysms can occur in any location but more frequently in the distal vertebral artery, basilar artery, PI segment of the posterior cerebral artery and the supraclinoid internal carotid artery. The usual presentations are with symptoms mainly due to mass effect and distal embolization. Hemorrhage from these aneurysms is unusual.

Familial aneurysms

"Familial aneurysms" is defined when more than 2 first-degree relatives are affected. First degree relatives but not second degree relatives of SAH patients have an increased risk of SAH (Ferro, 2008). Estimates of the frequency of familial intracranial aneurysms range from 7 to 20%. The inheritance pattern is unclear. However, the greatest evidence of linkage was found on chromosomes 4 (Foroud, 2008). A search for intracranial aneurysm susceptibility gene in Finnish families , detected two regions of suggestive linkage, one on chromosome 19 and the other on the X chromosome (Olson, 2002). Familial aneurysms are more likely to be multiple than sporadic aneurysms and tend to bleed at a significantly younger age compared to patients with sporadic aneurysms.

Various hereditary connective tissue disorders have been associated with formation of aneurysms. They occur most likely as a result of the weakening of the vessel wall. Intracranial aneurysms may develop in 10%–15% of patients with polycystic kidney disease. Other associated connective disorders are Ehlers–Danlos Syndrome Type IV and a1-antitrypsin deficiency. Coarctation of the aorta, fibromuscular dysplasia and pheochromocytoma are associated with intracranial aneurysms, most likely because of the elevated blood pressure that occurs in these conditions.

2.4 CLINICAL PRESENTATION AND NATURAL HISTORY

Clinical Presentation

A sudden onset of severe headache (frequently described as the "worst ever") is present in 97% of cases. The headache may be associated, with nausea, vomiting, neck pain, photophobia and loss of consciousness. Headache may be the only presenting symptom in up to 40 percent of patients and may abate completely within minutes or hours. These are called sentinel or thunderclap headaches or "warning leaks." In such patients a CT scan or lumbar puncture may reveal bleed. However warning headaches may occur without SAH and this are due to aneurysm enlargement or bleed confined to aneuysmal wall.

Physical examination may reveal retinal hemorrhages, meningismus, a diminished level of consciousness, and localizing neurologic signs. The latter finding usually includes third-nerve palsy (posterior communicating aneurysm), sixth-nerve palsy (increased intracranial pressure), bilateral lower-extremity weakness or abulia (anterior communicating aneurysm) (DeLuca, 1993) and the combination of hemiparesis and aphasia or visuospatial neglect (middle cerebral artery aneurysm).

There are three types of ocular haemorrhage associated with SAH. Subhyaloid (preretinal) haemorrhage is seen in 11-33% of cases as bright blood near the optic disc. Retinal hemorrhages on the other hand are seen surrounding fovea, while vitreous humor haemorrhage (known as Terson's syndrome) seen in 4-27 % of cases (Ferro, 2008) which indicates an abrupt increase in intracranial pressure.

If the classical signs and symptoms are absent, it is possible to misdiagnose SAH. The frequency of misdiagnosis may be up to 50 percent in patients presenting for their first visit to a doctor. The common incorrect diagnoses are migraine and tension-type headaches. Inability to obtain the appropriate imaging study accounts for 73 percent of cases of misdiagnosis, and failure to perform or correctly interpret the results of a lumbar puncture accounts for 23 percent.

Misdiagnosed patients tend to be less ill and have a normal neurologic examination. However, in such cases, neurologic complications which occur later in as many as 50 percent of patients tend to be associated with higher risk of death and disability.

Natural history

One of the feared complications is rebleed, which peaks in the first few days after the first bleeding. Rebleeding carries a poor outcome and is more frequent in patients with poor clinical condition and in those with large aneurysms. If an aneurysm is not treated, the risk of rebleeding within 4 weeks is estimated to be of 35–40%. After the first month the risk decreases gradually from 1–2%/day to 3%/year (Ferro, 2008)

Prevalence of intracranial aneurysms in the general population is estimated at about 0.65–5% of the population, with an estimated yearly rate of rupture of 1–2% (Winn, 2002). The International Study of Unruptured Intracranial Aneurysms (ISUIA) is an international, multicenter study that evaluated the natural history of unruptured intracranial aneurysms both retrospectively and prospectively and the risk associated with their repair, including endovascular and surgical treatment. The primary end points of the study included SAH,

intracranial hemorrhage and death. Patients were eligible for the study if they had at least one unruptured aneurysm.

The retrospective ISUIA were analyzed in separate groups based on if they had no history of SAH (Group 1) versus if they had a history of SAH (Group 2). The predictors of rupture in Group 1 included size and location. There was an increased relative risk of rupture in aneurysms 10 to 24 mm in diameter and further increased relative risk with those greater than 25 mm. Similarly increased risk rupture is noted in posterior circulation. In Group 2, only those with basilar tip aneurysm had a higher risk of rupture. In both groups the risk of rupture increases with the size of aneurysm (Wiebers, 2003)

In the prospective arm of ISUIA2, 41.7% patients did not have endovascular or surgical treatment and were observed. Of the patients in the conservative arm, 51 patients (3%) had confirmed aneurysmal rupture during follow-up. In those patients without a history of SAH, only two of the 41 ruptures were in patients with aneurysms less than 7 mm in diameter. These data indicate that rupture risk of aneurysms is dependent on aneurysm size, location, and history of SAH.

However the results of the ISUIA have been controversial because the low rates of rupture do not seem to match actual practice. The prevalence of unruptured intracranial aneurysms is about 2% with average annual rate of rupture of only 0.1%. This does not not correspond to 21,000–33,000 cases of aneurysmal SAH that occur in the US each year (Bulters, 2010). The average size of ruptured aneurysms is 6–7 mm, well within the range estimated by ISUIA to have a benign natural history (Joo, 2009; Jeong, 2009). It is possible that in ISUIA, patients who were already at lower risk of rupture may have been selected to

be managed without intervention and modifications of lifestyle to reduce risk factors for rupture were done.

Cerebral vasospasm

Cerebral vasospasm (marked narrowing of conducting arteries and parenchymal arterioles) following subarachnoid hemorrhage remains a major cause of morbidity and mortality (Komotar, 2009). Vasospasm may account for up to one-third of infarctions or deaths following a cerebral bleed which is estimated to affect up to 1.2 million patients worldwide per annum (Pyne-Geithman, 2009).

The exact cause of vasospasm has yet to be determined. Most reviews determined vasospasm following SAH to be a problem of the cerebral vasculature. Blood in the subarachnoid space bathing cerebral vessels have been implicated to cause vasoconstriction. Various mediators of constriction have been implicated including irritation from hemoglobin or breakdown products of hemoglobin, bilirubin oxidation products, binding of nitric oxide by hemoglobin, production of endothelin-1 by damaged endothelium, generation of 20-hydroxyeicosatetraeonic acid from arachidonic acid, infiltration of the vessel wall by inflammatory cells resulting in vessel narrowing and manipulation of cerebral vessels during surgical intervention to clip the ruptured aneurysm. (Ko, 2008; Thampatty, 2011)

Mutch et al puts forward a new theory that blood in the subarachnoid space generates multiple Spreading Depression waves noted by rapidly increasing extracellular potassium resulting in EEG silence. It is postulated that Spreading Depression waves cause glial cell dysfunction following glutamate accumulation with hemichannel disruption. This leads to

smooth muscle contraction in the cerebral vessel, which causes vasoconstriction and neuronal ischemic damage.(Mutch, 2010)

Cerebral vasospasm is seen angiographically in 70% and clinically in 20 to 30% of patients with aneurysmal subarachnoid hemorrhage (Hoh, 2004). Despite maximal therapy, nearly 50% of patients with symptomatic vasospasm will develop stroke. Vasospasm leads to delayed cerebral ischemia with 2 major patterns: single cortical infarction, usually near the site of a ruptured aneurysm, and multiple widespread lesions that are often not related to the site of the ruptured aneurysm (Rabinstein, 2005). Onset of vasospasm rarely occurs prior to day 3 after SAH. Vasospasm is maximal at days 6–8, and is significantly reduced or disappears in most patients within 2 weeks. Fewer than 4% of cases occur after day 12 after SAH.

Symptomatic vasospasm typically presents as confusion and a decline in the level of consciousness. Focal neurological deficits may appear as well. The onset of symptoms may be sudden or insidious. Neurological change is the best indicator of symptomatic vasospasm, and therefore frequent neurological exams are essential in patients with SAH (Lee, 2006).

<u>Radiographic evaluation of vasospasm</u>:

(a) Catheter angiography:

It is considered as gold standard for diagnosis of cerebral vasospasm. Significant vasospasm is indicated by a reduction in arterial caliber by 25–50% or more.

(b) CTA:

CTA is relatively accurate hemodynamically significant vasospasm affecting large intracranial vessels. It is less accurate for evaluating distal vessels and for detecting mild or moderate vasospasm.

(c) CT perfusion:

CT perfusion can detect reductions in regional CBF indicative of symptomatic vasospasm. CT perfusion using the deconvolution technique has significant drawbacks including the necessity of selecting a reference artery and a dependence on hemispheric asymmetry to identify ischemia.

(d) Transcranial Doppler (TCD) ultrasonography:

Flow velocity within a vessel is directly proportional to the volume of blood flow and inversely proportional to the square of the diameter of the vessel. Therefore, TCD velocity changes can be nonspecific and can reflect either vasospasm or an *increase* in CBF. The MCA is the most reliable vessel to assess, and mean flow velocities >200 cm s^{-1} are highly suggestive of significant vasospasm, whereas velocities <100 $cm\,s^{-1}$ are not. Lindegaard ratio was introduced to correct for changes in CBF by calculating the ratio between the MCA velocity and the ICA velocity. A ratio of <3 is normal and a ratio >6 is highly suggestive of vasospasm.

Other techniques which are still on development include continuous electroencephalographic monitoring, single-photon emission computed tomography and near-infrared spectroscopy, which has the potential to be a safe, noninvasive technique that could be performed at the bedside.

Prior to the onset of vasospasm, all patients should receive prophylaxis with nimodipine within 12 hours after SAH is diagnosed (Manno, 2004). The oral dose is 60 mg every 4 hours by mouth or nasogastric tube, and it should be continued for 21 days. The addition of simvastatin before or after SAH may also prove to be a potential treatment for reducing cerebral vasospasm.

The core of medical treatment once aneurysm secured, is hyperdynamic therapy, also called “triple-H therapy.” Triple-H therapy consists of hypervolemia, induced arterial hypertension, and hemodilution with aggressive hemodynamic monitoring of central venous pressures or pulmonary artery pressures with a Swan-Ganz catheter (Manno, 2004; Lee, 2006).

In cases refractory to triple-H therapy, intra-arterial infusions of antispasmodics such as nicardipine, verapamil, or papaverine as well as angioplasty have been used. Early (< 24 hr after onset) transluminal balloon angioplasty is preferred to the antispasmodic infusions and leads to significant clinical improvement, with moderate to dramatic improvement in approximately 70% of cases.

2.5 DIAGNOSTIC STUDIES

CT brain

CT brain should be the first to be performed for diagnosis of SAH. Extravasated blood is hyperdense, localized in the subarachnoid spaces of the basal and slyvian cisterns. It distribution depends on the location of ruptured aneurysm .Focally thick blood layers; present near the ruptured aneurysm can localize the ruptured vessel. This is useful when multiple aneurysms are discovered on arteriograms.

Plain CT brain obtained within 24–48 h show blood density in approximately 95% of ruptured aneurysms. A good quality CT brain with thin slices will reveal subarachnoid hemorrhage in 100 percent of cases within 12 hours and in more than 93 percent of cases within 24 hours. Delayed CT brain may have negative finding despite a suggestive history because of rapid clearance of blood. The sensitivity can drop to 50 percent at seven days.

Fisher investigated the relationship of the amount and distribution of subarachnoid blood detected by CT to the later development of cerebral vasospasm in 47 cases of ruptured saccular aneurysm. He concluded that blood localized in the subarachnoid space in sufficient amount at specific sites is the only important etiological factor in vasospasm and thus the formation of Fisher Grade. (Fisher, 1980) Other authors have found direct unfavorable outcome association with increased thickness of SAH, intraventricular hemorrhage and intracerebral hematoma. Axel had determined that on multivariable analysis of patients with complete data using the binary GOS, some of the factors that associated with unfavorable

outcome were greater SAH thickness on admission CT scan, intraventricular hemorrhage and intracerebral hematoma (Rosengart, 2007).

Lumbar puncture

Lumbar puncture should be performed in any patient with suspected subarachnoid hemorrhage and negative CT brain finding. Cerebrospinal fluid should be collected in four consecutive tubes, with the red cell count determined in tubes 1 and 4. Findings consistent with subarachnoid hemorrhage include an elevated opening pressure, an elevated red-cell count that does not diminish from tube 1 to tube 4, and xanthochromia (owing to red cell breakdown detected by spectrophotometry), which may require more than 12 hours to develop.

Conventional cerebral angiography

Conventional cerebral angiography is still the gold standard for the detection of a cerebral aneurysm. An early angiogram is crucial for any therapeutic decision. Cerebral angiography can localize the lesion, reveal aneurysm shape and size, determine the presence of multiple aneurysms, define vascular anatomy and collateral situation, and assess the presence and degree of vasospasm.

Four-vessel angiography is necessary with anteroposterior, lateral, and oblique views to rule out presence of multiple aneurysms. However, in the case of a space occupying hematoma angiography of the most likely affected vessel should be done.

CT angiography

CT angiography has become more popular and is frequently used due to its noninvasiveness. The sensitivity and specificity of CT angiography is comparable to that of cerebral angiography.

Patients with a negative imaging study should have a repeated study 7 to 14 days after the initial presentation. If the second evaluation does not reveal an aneurysm, magnetic resonance imaging should be performed to uncover a possible vascular malformation.

2.6 TREATMENT

2.6.1 Treatment: Surgical clipping

Microsurgery was the established standard of treatment of intracranial aneurysms. The main strength of surgical treatment is that a successful surgery effectively excludes the aneurysm from the circulation. The recurrence with clipping is uncommon. Postoperative catheter angiography is necessary to check for residual aneurysm and to ensure that the parent vessels are preserved.

In recent years this established practice has been challenged by development of endovascular treatment which was further reinforced by release of ISAT studies. ISAT was a landmark study that validated the technique of endovascular coiling. However, many aneurysms are not equally suitable for either microsurgical clipping or endovascular coiling. In individual cases, analysis of several factors such as the patient's age, medical condition and the aneurysm's location, morphology, and relationship to adjacent vessels are required before applying appropriate treatment. Despite major technical advances in imaging and in endovascular treatment of cerebral aneurysms, surgical clipping still remains mainstay treatment in certain aneurysms (Regli, 2002; Ryttlefors, 2008).

There are drawbacks of surgical method. Of these, accessibility remains the most important factor and it varies considerably with aneurysm location. Aneurysms in the posterior circulation tend to be less accessible than those in the anterior circulation, requiring cranial base surgical approaches that are highly invasive. Even in the anterior circulation,

similar difficulties arise along the carotid artery from the petrous segment to the clinoidal segment.

Neck calcification is more difficult to appreciate on magnetic resonance images and best appreciated on CT scans. However it can be obscured by surrounding subarachnoid blood. A high index of suspicion and a preoperative CT scan is needed prior to clipping in older patients with atherosclerosis elsewhere.

Medical co-morbidities seem to have a greater impact on surgical risk than on endovascular risk. Most often it is related to hemodynamic and cardiac parameters which are influenced by length of surgery, blood loss, brain manipulation, and coagulation abnormalities.

Unexpected intraoperative difficulties when occur are usually related to inadequate exposure, incomplete proximal and distal control of the aneurysm, catastrophic rupture, or aberrant anatomy (e.g., fusiform morphology or unusual branch arteries at the base of the aneurysm) that was not appreciated on preoperative imaging studies. The availability of three-dimensional CT imaging has provided neurosurgeons with a better appreciation of the anatomy preoperatively and may minimize these failures.

2.6.2 Treatment: Endovascular approach

Endovascular treatment of aneurysms has been available as an alternative to surgical therapy for the past 15 years. Coils are made of platinum and are attached to a delivery wire.