Cognitive Functioning and Health Related Quality of Life after Treatment of Intracranial Aneurysms

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SUMMARY

Cognitive Functioning and Health Related Quality of Life after Treatment of Intracranial Aneurysms

Background: Each year between 8 and 10 per 100 000 people in Norway will suffer an aneurysmal subarachnoid hemorrhage (SAH). Cognitive dysfunction is the most common form of neurological impairment after an aneurysmal SAH with as many as 65% experiencing changes in cognitive functioning as a result of their aneurysmal SAH. In addition a large percentage of patients also experience changes in their daily functioning through reduced Health Related Quality of Life (HRQOL) and inability to return to work. A number of studies have focused on determining the medical causes of these changes in cognitive and HRQOL but so far no consensus have been reached.

Aims: The specific aims of the present study were: 1) to explore the time-course of improvement in cognitive dysfunctions the first year after an aneurysmal SAH, 2) to investigate whether an aneurysmal SAH cause a global or focal damage, with special emphasis on the effect of Anterior Communicating Artery (ACoA) aneurysms on frontal lobe functioning, 3) to evaluate the effect of surgery of unruptured intracranial aneurysms (UIAs) compared to ruptured intracranial aneurysms on cognitive function and HRQOL, 4) to explore the cognitive functioning and HRQOL in patients in clinical condition Hunt & Hess grade V after aneurysmal SAH.

Material and methods: All patients included in the studies were treated for either an aneurysmal SAH or an UIA at the Department of Neurosurgery at Rikshospitalet University Hospital from January 1st 2002 to June 30th 2007. In study I, 32 patients in clinical condition Hunt & Hess grade I-V were included. In study II, 24 patients in clinical condition Hunt & Hess grade I-III with ruptured ACoA aneurysm or 22 patients in clinical condition Hunt & Hess grade I-III with a ruptured MCA aneurysm were included. In study III, 15 patients with unruptured MCA aneurysm and 22 patients with ruptured MCA aneurysms in clinical condition Hunt & Hess grade I-III were included and finally in Study IV, 26 patients in clinical condition Hunt & Hess grad V aneurysmal SAH were included.

Data was collected on medical status using CT/MR, patient journals and clinical interviews by neurosurgeons at 3 and 12 months post aneurysmal SAH/surgery for UIAs. Patients also had a clinical psychological interview. They were tested using a comprehensive neuropsychological test battery and they answered two HRQOL questionnaires (SF-36 & GHQ-30). In Study I, patients were tested neuropsychologically at 3, 6 and12 months after SAH. In Study II, patients were tested neuropsychologically at 12 months. In study III, the UIA patients were tested neuropsychologically pre-operatively, as well as 3 and 12 months post-surgery, while the aneurysmal SAH MCA patients were tested neuropsychologically 3 and 12 months post-aneurysmal SAH. Finally, in Study IV patients were tested neuropsychologically 12 months after their aneurysmal SAH.

Statistical comparisons on medical, neuropsychological and HRQOL data were conducted using non-parametric statistical analysis (Mann-Whitney). In addition effect sizes were calculated using Cohens'D. Raw scores for each neuropsychological test were converted into scaled scores based on published norms for each test and then converted to z-scores for easier comparison.

Results: We found mild to moderate cognitive deficits in patients in a good outcome (Glasgow Outcome Scale 4-5), with the largest deficits on motor speed and memory function,

but close to normal intellectual functioning. Motor functioning seemed to improve rapidly in the first 6 months post-aneurysmal SAH while verbal memory first improved between 6 and 12 months after aneurysmal SAH. Clinical and radiological parameters reflecting the bleed and patient management could be linked to neuropsychological outcome. Our data indicated that an aneursymal SAH cause a global damage, but focal damage could be seen in some cases. For example, we suggested that ACoA patients with medial frontal damage had problems with initiation of problem solving behavior. Elective surgery of unruptured intracranial aneurysm did not cause any substantial permanent cognitive dysfunctions, but had a significant effect on the patients HRQOL. Finally, among patients in clinical condition Hunt & Hess grade V after aneurysmal SAH lower age, higher education and no hydrocephalus in the acute stages had better cognitive outcome.

Conclusions: This study showed that many patients with ruptured intracranial aneurysms have cognitive deficits and problems with HRQOL as a result of their aneurysmal SAH. The cognitive deficits improved over time although not always to the pre-morbid level. The cognitive problems were most likely caused by the bleed itself rather than the treatment of the ruptured aneurysm. A focus on cognitive and HRQOL problems in the follow-up of aneurysmal SAH patients is essential and neuropsychological testing should be an integrated part of the treatment of aneurysmal SAH patients.

LIST OF PAPERS

The thesis is based on the following papers, referred to in the text by Roman numbers.

I Haug T, Sorteberg A, Sorteberg W, Lindegaard K-F, Lundar T, Finset A. Cognitive outcome after aneurysmal subarachnoid hemorrhage: Time-course of cognitive recovery and Relationship to Clinical, Radiological and Management Parameters. Neurosurgery, 60(4), 649-657, 2007.

II Haug T, Sorteberg A, Sorteberg W, Lindegaard K-F, Lundar T, Finset A. Cognitive functioning and Health Related Quality of Life after rupture of an aneurysm on the anterior communicating artery versus middle cerebral artery. Re-submitted Br J of Neurosurg December 2008.

III Haug T, Sorteberg A, Sorteberg W, Lindegaard K-F, Lundar T, Finset A. Surgical repair of unruptured and ruptured middle cerebral artery aneurysms: Impact on cognitive functioning and Health Related Quality of Life. Neurosurgery. March 2009 In press.

IV Haug T, Sorteberg A, Sorteberg W, Lindegaard K-F, Lundar T, Finset A. Cognitive functioning and Health Related Quality of Life one year after aneurysmal subarachnoid hemorrhage in patients in preoperative clinical condition Hunt & Hess grade V. Submitted, Neurosurgery December 2008.

LIST OF ABBREVIATIONS

ABP – Arterial Blood Pressure
ACA- Anterior Cerebral Artery
AcoA – Anterior Communicating Artery
AES-C – Apathy Evaluation Scale – Clinician's version
AVM- ArterioVenous Malformations
BA - Basilar Artery
CPP- Cerebral Perfusion Pressure
CSF – CerebroSpinal Fluid
CT – Computed Tomography
CTA- Computer Tomographic Angiography
DIND – Delayed Ischemic Neurologic Deficit
ERP – Evoked Response Potential
fMRI – Functional Magnetic Resonance Imaging
GCS – Glasgow Coma Scale
GDC – Guglielmi Detachable Coils
GHQ-30- General Health Questionnaire, 30-items
GOS – Glasgow Outcome Scale
HH – Hunt & Hess score
HRQOL- Health Related Quality of Life
IA- Intracranial Aneurysms
ICA – Internal Carotid Artery
ICH- Intracerebral Haematoma
ICP- Intracranial Pressure
ISAT – International Study of Aneurysms
ISUIA – International Study of Unruptured Aneurysm
IVH- Intraventricular Haematoma
MADRS – Montgomery Aasberg Depression Evaluation Scale
MCA- Middle Cerebral Artery
MRI – Magnetic Resonance Imaging
mRS – Modified Rankin Scale
PICA – Posterior Inferior Cerebellar Artery
PcoA – Posterior Communicating Artery
SAH – Subarachnoid Hemorrhage
SF-36- Medical Outcomes Study Short Form Survey, 36 items
TCD – Transcranial Doppler Ultrasonography
TIA – Transient Ischemic Attack
UIA- Unruptured Intracranial Aneurysm
VA – Vertebral Artery

ERRATA

Paper 1:

1. p.651 Table 1 reference for Rey-Osterreith Complex figure test of visual memory should be (16).

1. INTRODUCTION

1.1 Introduction and outline of the thesis

The focus of this thesis will be the study of patients treated for intracranial aneurysms with regard to different aspects of cognitive deficits and Health Related Quality of Life (HRQOL). The level of deficits and time-course of improvement in cognitive functioning are explored, along with the impact of an aneurysm rupture and its treatment on cognitive functioning and HRQOL.

This study was composed after working with intracranial aneurysm patients at the Department of Neurosurgery Rikshospitalet University Hospital, Oslo, Norway as a clinical neuropsychologist for a few years and having seen the challenges these patients face both acutely and during the first year after their aneurysmal subarachnoid hemorrhage (SAH). It became evident that these patients experienced a wide range of problems often remaining "invisible" to the outside world, such as memory problems and lack of energy, which severely affected their functioning but were difficult to understand for both patients and their relatives. An example will illustrate this: One of the first patients I met at the Department of Neurosurgery had suffered rupture from an aneurysm on the ACoA artery. She was fully awake with some headache and nausea but without any neurological deficits after the bleed, the aneurysm was treated using endovascular coiling and she was released from the hospital in good neurological condition. However, when I met her 3 months after her aneurysmal SAH she complained of memory problems and being tired all the time. Her relatives were also worried about her possibly being depressed since she had changes from being an active and vibrant person to not seeming to care about anything any more and mainly just sitting in her chair. This patient and many similar stories raised a number of questions in our research group, for example: Do memory problems after aneurysmal SAH improve over time and if so, when would they improve? If she had been clinically more affected from the SAH, how serious would her cognitive deficits have been? If the aneurysm had been discovered and repaired before it ruptured would she have had any deficits at all? And finally could damage in the frontal lobes from the ACoA aneurysm have caused her emotional changes? Consequently, we felt there was a need for a more systematic approach to improve the understanding of the cognitive and emotional changes after aneurysmal SAH. We therefore hoped to better both the treatment of aneurysms as such and to help the patients and their families understand and, equally important, to cope better with the cognitive changes and changes in HRQOL experienced after an aneurysmal SAH.

The first part of this thesis will contain a clinical description of intracranial aneurysms and aneurysmal SAH. This section is meant to be background information for understanding the cognitive functioning and HRQOL aspects after treatment of intracranial aneurysms which will be the main focus of the thesis and will hence not be discussed further. The following two sections will describe the literature on cognitive functioning and HRQOL in relation to intracranial aneurysm and aneurysmal SAH, and consequently lead up to our research questions.

1.2 Intracranial Aneurysms and Subarachnoid Hemorrhage

1.2.1 Intracranial Aneurysms (IA)

Intracranial aneurysms (IAs) are saccular pouches on the intracranial arterial wall. If they rupture they can cause substantial morbidity and mortality (20). Intracranial aneurysms mainly form at the arterial junctions at or near the base of the brain. Why aneurysms develop is largely unknown but both individual disposition, environmental factors as well as systemic and topic hemodynamic factors are believed to be involved. It has been suggested that focal enlargements in the tunica intimae (the innermost layer of the arteries) cause increased hemodynamic stress on the more elastic areas of the arterial wall and hence cause arterial weakness leading to an aneurysm. It is also possible that the protein structure of the extracellular matrix could be different; involving some genetic or heritable factors in patients who develop aneurysms (177-178). There is also some degree of familiar predisposition, with between 5 and 20% of patients with aneurysms having a family member with an aneurysm (169, 172). Illness related factors conditions such as autosomal dominant polycysitic kidney disease, coartic aortae, fibromuscular dysplasia, Marfan's syndrome, Ehlers-Danlos syndrome type IV, and arteriovenous malformations are associated with higher incidence of aneurysms (20, 169). Life-style issues such as hypertension and cigarette smoking are also known to increase the likelihood of developing aneurysm (53, 94, 188).

Autopsy studies indicate a prevalence rate in the adult human population between 1 and 5 percent (233). Most aneurysms are small and approximately 50-80 percent of all aneurysms never rupture (29). Further, 10 to 30 percent of the individuals with intracranial aneurysms have multiple aneurysms (185). It thus follows that most intracranial aneurysms remain asymptomatic, but in the cases where unruptured intracranial aneurysms (UIAs) do cause symptoms it is due to the aneurysm exerting a mass-effect upon neural tissue, leading to cranial-nerve palsies, seizures, or brain-stem compression. UIAs have an estimated average

annual rupture risk of 1 to 2 % however larger aneurysms and aneurysms on the basilar tip or on the posterior communicating artery have higher rupture rates (20). Ruptured intracranial aneurysms are the cause of the bleed in 85% of the aneurysmal SAH cases.

The brain arteries and the localization of intracranial aneurysm

The brain receives blood from four major arteries, the right and left internal carotid artery (ICA) and the right and left vertebral artery (VA). The two ICAs supplies most of the cerebral hemispheres with blood, while the VAs supplies the brain stem, cerebellum and the two posterior brain areas. The ICA enters the brain through a canal in the base of the skull (canalis caroticus) and separates into three branches. The Opthalmic artery projects to the eye though the optic canal and does therefore normally not supply the brain itself with blood. The anterior cerebral artery (ACA) also projects medially and forward over the optic nerve and runs along the medial side of the cerebral hemisphere. The middle cerebral artery (MCA) is the largest branch of the ICA and it projects outwards in the Sylvian fissure and follows this backwards and upwards branching off in a number of smaller arteries that supply the major part of the cerebral cortex. Intracranial aneurysms occur most commonly on the anterior communicating artery (ACoA) (30%), the MCA (20%) and the posterior communicating artery (PCoA) (25%), while the remaining 25% of aneurysms are located on the pericallosal artery, the ICA, the basilarar artery (BA) or the posterior inferior artery (PICA) (20).

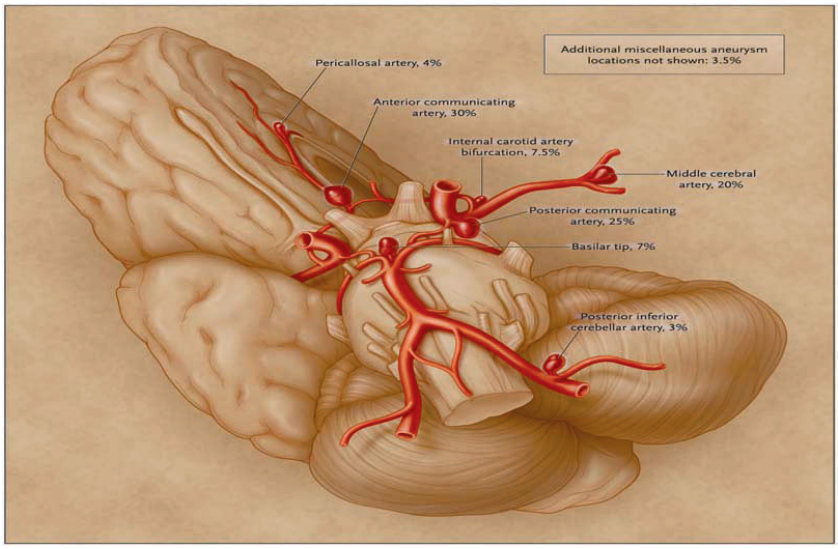

Figure 1. The large basal cerebral arteries with the most frequent locations of Intracranial Aneurysms. Percentages indicate the incidence of the various intracranial aneurysms. Copyright The Publishing Division of the Massachusetts Medical Society Ref. PS-209-163

1.2.2 Subarachnoid Hemorrhage (SAH)

A Subarachnoid Hemorrhage (SAH) occurs when there is a sudden rupture of an intracranial aneurysm (IA) caused by expansion beyond "the endurance limit of an aneurysmatically dilated wall segment of a cerebral vessel due to pressure and sharing forces, induced by blood pressure fluctuations, pulse waves or blood flow" (78). At the moment of aneurysm rupture arterial blood is suddenly released into the subarachnoid space surrounding the vessels (Subarachnoid Hemorrhage), sometimes into the cerebral parenchyma (Intracerebral hemorrhage) and occasionally the intraventricular space (Intraventricular hemorrhage) of the brain (236). When the intracranial aneurysm ruptures under arterial pressure and into the subarachnoid space there is an instant increase in the intracranial pressure (ICP). If the increased ICP is sustained over time it causes low or no blood flow to the brain over time and subsequent death. However, seconds of stop in blood flow to the brain are also seen in patients who recover after aneurysmal SAH. The premises for recovery and rehabilitation possibilities are therefore essentially determined within the first minutes after the aneurysmal SAH. The bleeding stops when ICP equals the mean arterial blood pressure (ABP), however other factors such as the blood coagulation abilities and the state of the aneurysm wall also contribute to ceasing the bleeding (139).

Demographic data

In Norway the incidence of aneurysmal SAH seems to be as in the Western world at large: 8-10 per 100 000 per year and it has seemingly not changed over the last 30 years. The average age for aneurysmal SAHs are lower compared with other stroke illnesses, with most patients suffering from an aneurysmal SAH being in the middle of their lives, with the peak age for aneurysmal rupture being in the mid 50's. The age group with the highest incidence has not changed much, but during the last two decades it has been revealed that the incidence after the age of 70 is higher than was previously known. On the other hand, aneurysmal SAH is rare before the age 20. (78). In terms of the sex distribution the ratio of females to males is estimated to be 3:1.Mortality rates from aneurysmal SAH are difficult to estimate since some patients die instantly and are never diagnosed with having an aneurysmal SAH. Among the patients who are hospitalized for treatment around 80-85% survive their first aneurysmal SAH. The overall mortality is still close to 50%, with 46% dying within the first 30 days after the initial aneurysmal SAH. About 1/3 of the survivors will become dependent on others (78).

Illness characteristics – symptoms and signs

Intracranial aneurysm bleed may follow trauma or demanding physical efforts such as lifting, bending, sexual intercourse or stress. However, most often it occurs during normal daily activities and about 33% occur during sleep (176). The primary symptoms of the aneurysmal SAH differ from patient to patient based on "the severity of the bleeding, the degree and functional relevance of the destroyed brain tissue, the enduring rise in ICP and the disruption of cerebral functioning" (78). The classical clinical picture of a full-blown aneurysmal SAH usually consists of an explosive headache (often described as "the worst headache of my life" and differs from any previous experienced headache), nausea, vomiting, and often an initial clouding of consciousness caused by the sudden release of blood and hence a sudden rise in ICP. In some instances loss of consciousness may occur without the preceding headache and is often the result of a massive aneurysmal hemorrhage. In most cases, however, consciousness will be regained within a few minutes, but in general, loss of consciousness at the beginning of an aneurysmal SAH signals a more severe prognosis in terms of chronic impairments or death (176). Some patients also experience shivering, sweating, cardiac arrhythmia and reactive hypertension as a result of the aneurysmal SAH (78). Also approximately 25% of patients experience an epileptic seizure at the time of the aneurysm rupture or hours to days later and approximately 1/3 of aneurysmal SAH patients experience warning leaks hours, days or weeks prior to the actual aneurysm rupture. The most common symptoms in association with warning leaks are headaches, stiff neck, vomiting, nausea or sensory/motor disturbances. In these cases the headache is milder than that of the actual aneurysmal SAH and often only lasts a few hours. Most patients therefore believe this headache is "only a migraine" and do not contact a medical doctor or a hospital. The headache and stiff neck may however be the result of a warning leak and could have been treated at this early stage thereby avoiding a full-blown aneurysmal SAH (176).

Diagnosing aneurysmal SAH

The first diagnostic intervention for a patient with a possible aneurysmal SAH is a computer tomographic (CT) scan of the brain. The CT scan will in the majority of cases detect the presence of blood in the Subarachnoid space and often also blood in the ventricular system when present. CT scanning will, if conducted within the first 24 hours, therefore positively identify the bleeding in a large percentage of the patients. The CT will, further also show the anatomical distribution and extent of the aneurysmal SAH. It thus documents if the blood has spread to the basal cisterns, the Sylvian fissures, the intrahemispheric fissures, over the

cerebral convexities or into the parenchyma in the cases of an intracerebral haematoma. To verify the presence of the aneurysm and plan further treatment a cerebral CT angiography (CTA) is performed. An angiography assesses the individual vascular anatomy, possible single or multiple aneurysms and accompanying angiomas (78).

If aneurysmal SAH is not found using a CT or a lumbar puncture, the bleeding may be identified using a magnetic resonance imaging (MRI). MRI can pinpoint the exact location of the bleed and also has the ability to identify other causes of aneurysmal SAH, such as AVMs (78). Finally, a fourth diagnostic tool that can be used to identify alterations in blood flow velocities in the basal cerebral arteries is the Transcranial Doppler sonography (TCD). TCD, may identify location and degree of arterial narrowing, and thus point out cerebral vasospasms (78).

Treatment of aneurysmal SAH

When an intracranial aneurysm has been identified as the cause of an aneurysmal SAH, there are two major treatment goals: 1) to prevent or minimize the primary and secondary complications of the bleed and 2) to prevent aneurysm re-bleed.

During the first hours after aneurysmal SAH maintaining adequate ABP and ICP, and thus the cerebral perfusion pressure (CPP) is vital. Surgery may be needed to control ICP by means of draining cerebrospinal fluid (CSF) or by evacuation of a haematoma. The aneurysm should be repaired urgently, the timing of repair determined by the clinical condition of the patient and findings on the CT scan.

<u>Surgical aneurysm repair (clipping)</u>

The first successful surgical clipping of an intracranial aneurysm was reported by Walter Dandy in 1938 (33). The first microsurgical technique for securing an aneurysm was presented in 1962 (88) and further refined by Yasargil (239). At Rikshospitalet University Hospital Nornes performed the first microsurgical clipping of an aneurysm in 1969 (140). The surgical technique for aneurysm clipping consists of finding the vessel where the aneurysm is located and excluding the aneurysm from the cerebral circulation by placing a clip across its neck (see figure 2) (236). Possible complications from surgical aneurysm repair include aneurysm rupture under dissection, damage to the brain tissue and cranial nerves during surgery, unintentional closing of brain vessels, post-operative haematoma and cerebral infections.

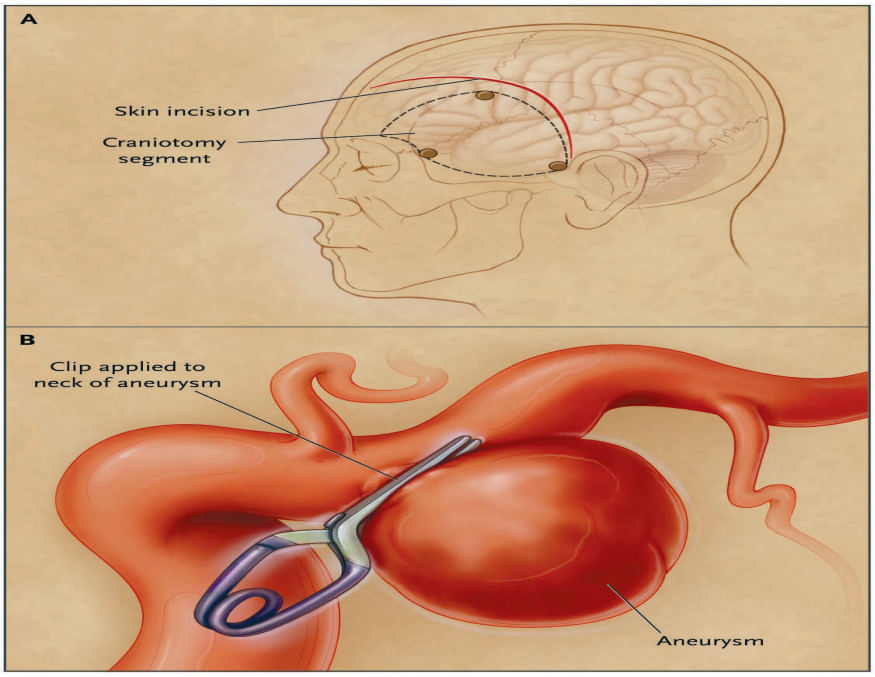

Figure 2. Microsurgical Clipping of an Aneurysm of the Posterior Communicating Artery. Panel A shows a typical skin incision (unbroken curved line) and craniotomy (dashed lines) needed to access an aneurysm through the Sylvian fissure. Panel B shows the application of the clip blade to the neck of the aneurysm. Copyright The Publishing Division of the Massachusetts Medical Society Ref. PS-209-1631

Endovascular aneurysm repair (coiling)

In 1974 Serbinenko presented the first endovascular aneurysm repair method with detachable balloons inserted into the aneurysm (190). Guglielmi and Viñuela (67) introduced the coil system used today with metal treads inserted into the aneurysm. These devices have subsequently been known as GDC's (Guglielmi Detachable Coils). The coiling procedure uses special microcatheters which under fluoroscopic vision are guided into the aneurysm sac, where after Guglielmi Detachable Coils are placed into the aneurysm (see figure 3) (12). Professor Per Nakstad, Rikshospitalet University Hospital conducted the first coil procedure in 1994 (235). The mode of action of coils is based on stagnation of flow within the aneurysm and thereby excluding it from the cerebral circulation. The later years, a variety of different coiling materials have been developed, like for instance coils with surface active substances (growth factor, radioactivity) or hydrogel expanding coils.

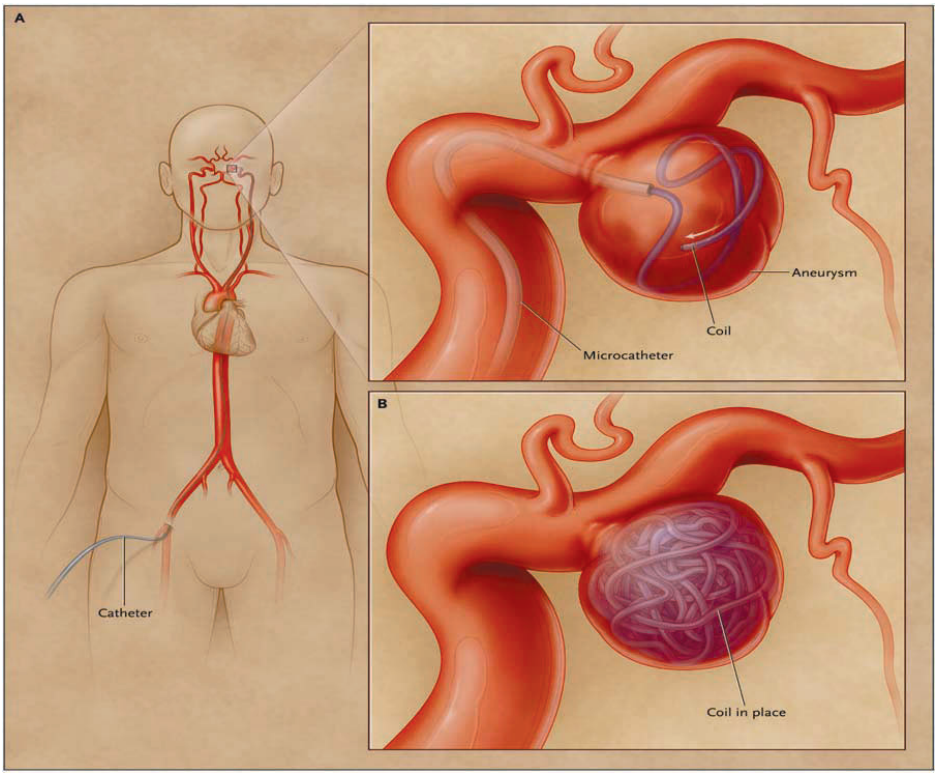

Figure 3. Endovascular Occlusion of an Aneurysm of the Posterior Communicating Artery with Guglielmi Detachable Coils. Panel A and inset show the route of the microcatheter into the aneurysm through the right femoral artery, aorta, and left carotid artery and the beginning of the coil deployment. Panel B shows the final occlusion of the aneurysm with coils. Copyright The Publishing Division of the Massachusetts Medical Society Ref. PS-209-1631

Medical therapy

Medical therapy includes the administration of transexamic acid from the diagnosis of aneurysmal SAH until (early) aneurysm repair (72) and administration of nimodipin the first three weeks after the bleed. In patients with angiographically or TCD diagnosed cerebral vasospasms or those developing delayed ischemic neurological deficits (DINID) triple-H therapy is used (hypertension, hypervolemia and hemodilution) is used. Medical therapy is also used to obtain adequate values ABP, ICP and CPP (196). Artificial ventilation on a respirator may then be necessary to ensure adequate supply of oxygen.

Complications

Patients surviving the initial aneurysmal SAH may have some major complications. About 25% of the patients do not recover from the immediate damage caused by the bleed. Among the patients that do improve after the first aneurysm bleed a substantial proportion (25-50%) deteriorate again within two weeks of the bleed as a result of aneurysmal re-bleed. A further 11-34% die or become disabled by cerebral vasospasm (78). The term "cerebral vasospasm" here refers both to the clinical picture of DIND (symptomatic vasospasms) and the narrowing of cerebral vessels without clinical symptoms (arterial vasospasm) (10) documented by angiography or TCD. Approximately 40% to 70% of aneurysmal SAH patients have arterial narrowing after the aneurysmal SAH whereas only 20% to 30% develop clinical vasospasm, typically starting 3 or 4 days after aneurysm rupture and with frequency of incidence and severity peaking at 7-10 days (78). Young females on oral contraceptives, individuals with a history of arterial hypertension, smokers and those with much subarachnoid blood on CT have the greatest risk of developing cerebral vasospasms (77). If a patient does develop vasospasms, he or she may become increasingly confused or there may be a decrease in the level of consciousness. If untreated, cerebral vasospasms may lead to more severe neurological and cognitive deficits and also brain infarction, coma and eventually death. In less severe cases neurological recovery will usually occur as soon as the arterial narrowing has been resolved either spontaneously or through treatment.

Aneurysm size may also have effect in terms of functional outcome. The majority of aneurysms range in size between 4 and 15mm, but in rare cases they may be 25mm in diameter or more (78). Additionally, in about 20% of the cases there are two or more aneurysms (78, 176). Consequently, the larger and the more numerous the aneurysms are, the larger is the possibility of complications.

Intracranial cerebral hemorrhage (ICH) can also be a serious consequence of an aneurysmal SAH. An ICH can be caused by aneurysms on any location it is however most commonly the result of a MCA aneurysm bleed (78). Blood may reach the cerebral ventricles thorough several different routes. Firstly, an aneurysm may rupture into brain tissue causing ICH that again may rupture into the ventricles. This appears most often in aneurysms on the anterior communicating artery, where the parenchymal layer between the aneurysm wall and the anterior horn of the lateral ventricle is thin. Secondly, blood may also enter the ventricular system through a retrograde flow of blood from the basal cisterns through the fourth ventricle at the base of the brain or thirdly it can enter directly into the ventricles, which will cause numerous brain functions to be affected as the blood spread though out the ventricles (77).

Brain edema can also be a dangerous complication of an aneurysmal SAH, and is present when the basal cisterns and the cortex's sulci and gyris' are completely or nearly completely compromised or when the grey and white substances are no longer separate.

Lastly, aneurysmal SAH may cause systemic complication such as heart failure, trombo-emblic episodes disturbances in the body's electrolyte or fluid balance.

1.2.3 Unruptured Intracranial Aneurysms (UIA)

Unruptured Intracranial Aneurysms (UIAs) are aneurysms without histological or clinical evidence of a breach through the arterial wall (230). An UIA can come to clinical attention in several ways, including an unexpected finding when undergoing neurological investigations for symptoms such as headaches, seizures, Transient Ischemic Attack (TIA) or if causing focal neurological signs and symptoms (e.g. III nerve palsy). An UIA may also be discovered when treating a subject for a ruptured aneurysm (149).

The decision to treat an UIA depends upon the relative risk of subsequent spontaneous rupture of the aneurysm versus the risk of prophylactic aneurysm repair. Detailed knowledge of the natural history of a given intracranial aneurysm is still lacking. However an annual rupture rate of 1% is well accepted. Juvela and colleagues (94) followed the natural history of UIAs treated conservatively even further and found the cumulative rates of bleeding to be 10% after 10 years, 26% after 20 years and 32% after 30 years. With regard to aneurysm size, the International Study of Unruptured Aneurysms (ISUIA) found a very low risk of rupture among patients without any history of aneurysmal SAH and an UIA smaller than 10mm (212). The ISUIA study also showed that the size and aneurysm location were both independent predictors of rupture; larger aneurysms and those of the VA, BA bifurcation, posterior cerebral artery (PCA) or the PCoA were most likely to rupture (212). Clarke (27) did a meta-analysis of 11 studies following 30204 patients with UIAs and reported an annual rupture rate of 1.8% in the posterior cerebral (vertebrobasilar) circulation and only 0.49% in the cerebral circulation.

Aneurysm size is also a major predicting factor for clinical outcome in surgery of UIAs (149). Solomon (193) found that aneurysm <10mm in size can be surgically treated with a risk of 1% morbidity, whereas aneurysms between 10 and 25mm carry a 5% risk of major morbidity and whereas UIAs >25mm have a 20% risk of major morbidity after surgical treatment.

Risk factors associated with aneurysms rupture include age, aneurysm size, arterial hypertension, smoking habits, alcohol intake and mental stress (214). The crucial question is therefore whether a patient is be better off if the aneurysm is left untreated, with regular radiological control and minimizing the risk factors or if the aneurysm is repaired using prophylactic aneurysm surgery with its calculated risks. Surgical risk factors include the manipulation of the brain during surgery and aneurysm dissection and clipping. Endovascular treatments with aneurysm coiling carry a risk of the aneurysm not being fully excluded from the circulation. There is also a calculated risk of aneurysm rupture associated with both treatment options.

1.3 Cognitive dysfunction and improvement in cognitive functioning after aneurysmal SAH

Cognitive dysfunction is the most common form of neurological impairment after aneurysmal SAH (130). Studies have thus found cognitive impairments in as much as 65% of patients after an aneurysmal SAH (212). The majority of studies agree that good outcome aneurysmal SAH patients (Glasgow Outcome Scale (GOS) 4-5) mainly have mild-to-moderate cognitive deficits (164). However, other studies have suggested that rather than all patients having mild-to moderate impairments it might be that a subset of patients has more severe deficits (105).

The most common cognitive deficits after aneurysmal SAH are verbal memory problems (40, 87, 105, 156, 164, 179, 221) and visual memory problems (80, 144, 179, 221), as well as problems with information processing (54, 80). The results for executive functioning are somewhat varying with some studies reporting problems with cognitive flexibility (221) verbal fluency (15, 129, 164, 213, 221) and concept formation (213) while others studies fail to find any impairments in executive functioning (41). Further impaired concentration and motor speed functioning are also common after an aneurysmal SAH (105), while intellectual functioning remains relatively unaffected (78).

1.3.1 What is the rate of recovery in cognitive functioning after aneurysmal SAH?

Early research on the improvement in cognitive functioning after aneurysmal SAH suggested that deficits which lasted more than one or two months following surgery were likely to remain. The general view was hence that most of the improvement in cognitive functioning occurred in the immediate post-operative period (8, 82). Further, a study by Richardsson (166) failed to find any significant improvements in cognitive functioning over

time. Since then, studies (144, 200) have found that improvement in cognitive functioning continues for many months (144, 180) or even years (164) after an aneurysmal SAH. Ogden (144) suggested that this discrepancy in the rate of improvement in cognitive functioning were associated with underlying impairment in concentration and the ability to process information, possibly as a consequence of acute encephalopathy that may resolve in some individuals but not in others.

Although there seem to be a general agreement in the literature that patients in a good outcome (GOS 4-5) aneurysmal SAH have a mild to moderate cognitive deficits there are still some variability in the results regarding which cognitive functions that are mostly affected. Furthermore, studies on the rate of improvement in these cognitive functions are sparse. At the time when we were planning our studies there were few studies that had evaluated cognitive functioning in the same individuals at more than two points in time. Therefore, to better understand the degree of dysfunction and rate of improvement of cognitive deficits after aneurysmal SAH we followed a group of patient in good clinical outcome (GOS 4-5) patients at 3, 6 and 12 months post aneurysmal SAH (see paper I).

1.3.2 Are the cognitive deficits seen after an aneurysmal SAH caused by a diffuse cerebral damage or a focal damage at the aneurysm site?

Due to the diversity of neurological insults that may occur at the time of the ictus, during aneurysm repair, or post-operatively relatively little is known about the precise cause of cognitive deficits after aneurysmal SAH. However, two different hypotheses regarding the basis for cognitive impairments after aneurysmal SAH have emerged. One hypothesis propose that an aneurysmal SAH cause focal damage at the aneurysm site (2, 96, 141, 147, 189), while the other suggest that an aneurysmal SAH cause diffuse cerebral damage (38, 42, 77, 79, 82-84, 105, 107, 121, 141, 167, 212, 220, 224).

Early studies on focal damage at the aneurysm site as a factor for cognitive deficits came in the 1960s mainly from studies on ACoA aneurysms. Brion (19) and Tallan (208) found that an AcoA aneurysm rupture caused amnesia as a result of damage to the medial frontal lobe (especially anterior cinguli and posterior gyrus rectus). Sengupta (189) added further support to the idea that an aneurysmal SAH cause a focal damage at the aneurysm site when he showed that patients with AcoA aneurysms projecting posteriorly were less likely to return to work. Moreover patients that had the perforating vessels arising from the AcoA compromised by direct trauma or by clip positioning showed poorer cognitive performance. Likewise, both Bornestein (17) and De Luca (38) found that patients with ruptured AcoA

aneurysms were more impaired on tests of delayed verbal recall and confabulated more compared to patients with ruptured aneurysms at other locations. One study also investigated the effect of aneurysm location at sites other than AcoA on cognitive functioning and found a poorer functioning among patients with ruptured MCA aneurysms (171), however this study did not include comprehensive neuropsychological testing. Kreiter (105) recently observed that patients with ruptured aneurysms on the posterior cerebral circulation showed better cognitive performances than those on the anterior cerebral circulation. They therefore concluded that rupture on posterior circulation aneurysms generally resulted in less blood coming in contact with the cortical surfaces of the brain and that this may result in less disruption of brain regions involved in cognition. Bjeljac (16) also found that localization of the aneurysm significantly correlated with cognitive measures. Interestingly, unlike other ACoA studies (17, 38, 105, etc) they found the best cognitive outcome among patients with ruptured ACoA aneurysms, followed by those with ruptured PCoA aneurysms and right-sided ICA aneurysms. Overall there is therefore evidence supporting the idea of focal damage from SAH at the aneurysm site. However, the evidence varies according to location and in different studies, no general consensus has been made.

The other main line of research (13, 38, 42, 77, 79, 82-84, 107, 144, 166, 173, 180, 182, 194-195, 222) has failed to find any differences in cognitive functioning among patients with ruptured aneurysm at various sites and therefore suggested that an aneurysmal SAH cause a diffuse cerebral damage. The reasoning for this hypothesis was summarized by Satzger (182) who concluded that it is theoretically very unlikely to detect connections between aneurysm location and specific cognitive deficits since 1) the various aneurysms are located close together at the base of the brain and 2) the sensitivity of neuropsychological tests used to identify defects in the basal brain cerebral areas are low. Further support for this hypothesis also came from studies comparing patients with aneurysm at different sites. De Santis (42), Ljunggren (120) and Richardsson (166) found that there were no differences between patients with aneurysm rupture on different sites, hence concluding that the pattern of neuropsychological deficits were consistent with a diffuse aneurysmal SAH induced encephalopathy. Likewise, support for an aneurysmal SAH causing a diffuse also comes from studies (83, 144, 195) failing to find differences between patients who underwent surgery for a known aneurysm and those with aneurysm rupture from an unknown aneurysm. Finally, support for the hypothesis about a global cerebral damage after an aneurysmal SAH also comes from looking at the pattern of cognitive deficits (i.e. mainly problems with memory

and attention, but normal intellectual capacity) which strongly resembles the one seen in mild traumatic head injury patients (84, 204).

Studies have also looked at right- versus left-sided aneurysms and failed to find any differences (7, 46, 164, 213). This gives further support to the hypothesis that an aneurysmal SAH cause a diffuse cerebral damage. On the other hand, studies done by Barbaretto (13), Logue (121), Vilkki (221) found differences between right and left sided aneurysms suggesting aneurysm location being an important predictor for cognitive functioning after an aneurysmal SAH. Logue (121) found that although there were no differences in intellectual functioning between patients with aneurysm rupture on right- and left-side and overall the IQ tests were close to the population mean for both groups, memory was significantly poorer compared to mean and left sided aneurysm patients did have an increased rate of forgetting. In an attempt to explain this difference they proposed that memory deficits was related to the close proximity of the aneurysm to the base of the 3rd ventricle, a site where lesions may affect new learning, whilst leaving other aspects of IQ unimpaired. Later, Vilkki (221) used CT scans to look at the association with deficits in cognitive functioning and found that although patients with left lateral infarctions had poorer performance on verbal tests and patients with right lateral infarctions were poorer on visuospatial tasks, these deficits were still only pronounced when lateral infarctions were associated with diffuse brain damage. Finally, Barbaretto (13) found that MCA patients showed a wide spectrum of neuropsychological disorders, which was in good agreement with the pattern predicted by the side of the lesion. Left sided MCA aneurysms showed impaired visual naming and verbal fluency and verbal memory while visual memory was impaired among right sided MCA (13).

Overall, research so far seems to support the hypothesis that cognitive deficits are the result of a more diffuse cerebral damage. There is however also results suggesting that aneurysms in the posterior circulation have a somewhat better prognosis and hence supporting the hypothesis that cerebral damage at the aneurysm location might cause specific cognitive changes (105). Both theories might therefore be correct since the very nature of an aneurysmal SAH with both disruption of a wide range of brain cortices at the time of the hemorrhage and more localized disruptions though ischemia and vasospasms, naturally cause a wide range of both focal and global cognitive impairments across patients.

Our first study (see paper I) did not give a definite answer to the question regarding the effect of aneurysm location on cognitive functioning since the patient group was relatively small and contained a wide range of aneurysm locations. Based on a discussion between neurosurgeons and neuropsychologists we therefore decided to further investigate the local

versus focal damage after aneurysmal SAH hypothesis by comparing a group of ACoA and MCA patients (See paper II). The decision on using ACoA and MCA patients was two-fold: first, these are the most common aneurysm sites and therefore would give us the greatest likelihood of assembling a large enough sample sizes. Secondly, and perhaps more important, these two aneurysm localizations are interesting from a neuropsychological standpoint since rupture on the ACoA might affect sensitive structures in the frontal lobes while rupture on the MCA structures in the parietal/temporal lobes. A comparison of these two groups would therefore give us the best possibility to delineate any differences in cognitive functioning between the two groups.

1.3.3 Are there differences in cognitive functioning after rupture of MCA and ACoA aneurysms?

As described above there is a discrepancy in the literature between those studies (13, 38, 42, 77, 79, 82-84, 107, 144, 166, 194-195, 173, 180, 182, 222) arguing that the severity and quality of cognitive deficits after aneurysmal SAH are unrelated to the location of the ruptured aneurysm and those arguing that an aneurysmal SAH cause focal damage at the site of the aneurysm rupture (2, 96, 141, 147, 189). Further, among the studies suggesting a focal damage at the site of the aneurysm rupture there are conflicting results that suggest that the rupture and repair of ACoA and MCA aneurysms might cause more severe cognitive functioning and HRQOL than aneurysm sites at other sites (17, 76).

MCA aneurysms

Although MCA is the second most common place for aneurysm rupture, relatively few studies have looked specifically at outcome after MCA rupture. A study by Rinne (171) on MCA aneurysm found significantly poorer outcome among these patients despite good surgical results. Patients with MCA aneurysms in their study had more epilepsy, as well as severer hemiparesis and visual field deficits. Giant aneurysms were also more common among MCA aneurysm and in addition they also had more intracerebral haematoma compared to patients with aneurysm at other sites. Unfortunately no neuropsychological testing was conducted as part of this study so little is known in regard to MCA patients cognitive functioning. Some studies (153-154, 205-206) have also described MCA aneurysm but with somewhat conflicting results. Paztor (153) and Suzuki (206) showed patients with MCA aneurysms having a good recovery, but Sundt (205) found poorer outcome in MCA patients. None of these studies did however include neuropsychological testing. One of the few studies on

neuropsychological functioning among MCA patients were done by Barbaretto (13) who found that MCA patients showed neuropsychological deficits in good agreement with the pattern predicted by the side of the lesion (i.e. left sided MCA aneurysms showed impaired visual naming, verbal fluency and verbal memory while visual memory was more impaired among right sided MCA).

ACoA aneurysm

The majority of studies on the focal effect of intracranial cerebral aneurysm rupture on cognitive functioning have focused on ACoA aneurysm because of its influence on the frontal lobes (25, 107). Damage to these areas has previously shown to result in memory problems, executive problems and changes in personality/behavior (58, 197). Patients with ACoA aneurysm rupture was thus often described as having Korsakoff syndrome (2, 30, 118, 211) and later the term ACoA syndrome were applied to describe the same set of symptoms (38, 107, 200).

The most frequently studied problem after ACoA aneurysm rupture has been the memory problems observed in these patients. The literature on memory problems after an ACoA aneurysm also divides itself into two dominant lines of research. Damasio (34), Eslinger (51), Gade (60), Morris (136), Philips (155) and Volpe (224) suggested a focal lesion hypothesis (i.e. amnesia is associated with infarct of the basal forebrain, an area whose blood is supplied by perforating branches of the ACoA), while DeSantis (42), Ljunggren (120), Vilkki (220) suggested a diffuse cerebral injury hypothesis (i.e. the memory deficits after ACoA aneurysm were consistent with a diffuse subarachnoid hemorrhage induced encephalopathy).

Although frontal lobe damage usually does not cause classic amnesia, it may disrupt various aspects of learning and memory, such as loss of source memory (89, 92), disturbed memory for temporal order (23) and other complex aspects of memory often considered as metamemory or the use of memories (138). Likewise, the memory problems associated with ACoA aneurysm have often been described as a confabulation problem rather than a classical amnesic problem (2, 11, 22, 32, 34-35, 41, 56, 96, 102, 137, 199, 203, 220). It is believed that these confabulation problems are due to ACoAs distribution to the basal forebrain, anterior cingulate, anterior hypothalamus, anterior columns of the fornix, septal nucleus, anterior commissure and corpus callosum (unlike the anterior cerebral artery which distribute blood to the prefrontal areas and hence do not include either the midline diencephalic structures implicated in Korsakoff syndrome or those structures in the medial temporal lobe implicated

in amnesia following for example temporal lobe excision) (3, 34, 39, 166, 232). Further support for this hypothesis was also found by Volpe (224) who showed two amnesic ACoA patients with medial temporal lobe abnormalities using PET and Vilkki (220, 222) who found that memory deficits after ACoA aneurysm rupture were typical for patients with frontomedial infarctions often caused by arterial spasms. Finally, Alexander (3) also found that patients with lesions either on the left posterior dorsolateral frontal region or the posterior medial frontal region had overall impaired learning and recall on the California Verbal Learning Test-II (CVLT-II).

More detailed analysis of the results on the memory tests such as the CVLT-II has also been used to understand ACoA patient's memory problem. Diamond (45), O'Connor (143) and Ravnik (164) all found that ACoA patients showed retrograde memory problems but they were less severe than those seen in patients with temporal amnesia. They also found that cuing and recognition probes significantly enhanced the performance suggesting problems with recall rather than storage. As a result they concluded that patients with frontal damage mainly seemed to have insufficient learning due to poor implementation of a strategy of subjective organization (3). Further, DeLuca (40) and Turner (216) found that ACoA patients had more intrusive errors on CVLT-II than non-amnesic patients and suggested that intrusions might reflect a failure to inhibit inappropriate responses and have therefore been linked to confabulation. Stefanova (198) looked at serial position effects in patients with ACoA aneurysm rupture and found ACoA patients maintained the primacy-recency effect more than controls and neither primacy nor recency effects were found in the delayed recall trial for the ACoA patients possibly due to minimal recall of anything on the lest (i.e. ACoA seem to be fixed to the starting serial position effect pattern with no change across trials). Eslinger (50) also found poorer subjective organization caused alterations in the serial position learning in patients with dorsolateral frontal lesions. All of these studies therefore point towards patients with ruptured ACoA aneurysms not having a classical amnesia, but rather a confabulation problem.

In terms of executive functions the orbitofrontal and ventromedial aspects of the frontal lobes which are supplied by ACoA and its perforating branches would be expected to be predominately affected by any ischemic damage subsequent to aneurysm rupture and hence influence executive functions. It has been shown that confabulation is often associated with poor performance on executive tests (11, 31, 96, 103, 126, 199, 202-203) and as a result executive function deficits are common in association with memory problems after ACoA aneurysm rupture. Rousseaux (175) found that patients with prefrontal mediobasal and

cingulate lesions were significantly slower than control on Trail Making Test and Tower of London. In addition initiation time was also increased on Tower of London. On the other hand, Mavaddat (128), Eslinger (49) and Shallice (191) all showed that executive tests failed to show any deficits in chronic ACoA patients. Shallice (192) suggested that the results failing to find any executive dysfunction in these patients are influenced by frontal lobe tests operating as typical psychometric tests in that they have a test administrator who is closely involved and task material which also directs the attention of the subject. Thus, tests designed to investigate specifically ventromedial prefrontal functions (i.e. decision making/gambling /sorting tests) are essential.

The final of the three symptoms compromising the "ACoA syndrome" is associated with personality and behavioral changes. These changes are often seen at clinical follow-up as well as observed by the ACoA patients themselves or family members and are often described as a feeling of apathy or depression. However, the majority of these patients do not classify as having a depression according measurements such as the Montgomery and Aasberg Depression Rating Scale (MADRS) (135) or apathy as defined by the Apathy Evaluation Scale (AES) (124). Levy (117) separated apathy (a quantitative reduction of voluntary, goal-directed behavior) into three subtypes, emotional-affective associated with lesions in the orbito-medial prefrontal cortex, cognitive-processing associated with dorsolateral lesions and auto-activation associated with bilateral associative and limbic areas of the internal portion of the globus pallidus. It is therefore believed that damage from an ACoA aneurysm could result in reduction in the medial frontal cortex's' ability to select, initiate, maintain and shift behavior. Medial frontal lobe has also been connected to reduction on mood and motivation by Paradisio (151) who found that patients with lateral lesions in medial frontal lobes showed greater reduction of emotion and motivation (apathy), and therefore concluded that lateral prefrontal damage may disrupt mood regulation and drive while leaving intact the ability to experience emotions. Further support for this medial frontal lobe hypothesis comes from both neuropsychological and behavioral studies. Ridderinkhof (168) found that posterior medial prefrontal cortex and lateral prefrontal cortex are important contributors to a cognitive control system for selecting contextually relevant information and for organizing and optimizing information processing, which further is essential in flexible goal-directed behavior. Likewise, Luu (123), Seitz(187) and Szatkowska (207) found that medial frontal cortex is important in response inhibition, action monitoring, self-regulation and stimulus-based switching of attention, which are important in goal-directed behavior and is involved in cognitive processes such as overcoming habitual responses or suppressing goal-irrelevant information. Using

neuropsychological tests Sonnesson (194) found that patients with ACoA aneurysms had larger decrease in tempo and perceptual vigilance and therefore suggested that the subfrontal midline structures are particularly involved in process demanding flexibility, attention and capacity to adapt to novel demands in a perceptual situation. More specifically, one of the most promising areas affected by an ACoA rupture which might explain the apathic behavior is the anterior cingulate which play a crucial role in initiation, motivation and goal-directed behavior (44).

Finally, it is essential to note that that since not all ACoA patients present with the same symptoms due to differences in the distribution of neural damage reference to a single syndrome such as Korsakoff does not adequately describe the variety on neurobehavioral impairments observed after an ACoA aneurysm rupture (18, 87). A few studies (79, 220) have also failed to find that ACoA patients had poorer neuropsychological outcome than other aneurysmal SAH patients.

The literature on ACoA and MCA aneurysms has a few short comings. First of all, numerous of the studies were done many years ago and during the last few decades there have been major changes in the treatment of aneurysms (for example the introduction of endovascular coiling) which may have affected the outcome in these patients. Secondly, older neuropsychological tests of executive functions and memory do not seem to be able to capture subtle differences in function among good outcome patients. As mentioned earlier we designed a study in which we compared a group of endovascularly coiled ACoA patients and a group of surgically clipped MCA patients to look specifically at the effect of aneurysm on cognitive functioning. Further based on knowledge the frontal lobe functioning we focused on memory, executive function and behavioral changes. Finally, to achieve the best possible measurements of these functions we used newer neuropsychological tests (i.e. subtests from the D-KEFS battery and CVLT-II) which include more detailed scoring measures enabling us to look for these more subtle cognitive changes in memory and executive functions.

1.3.4 Does elective treatment of Unruptured Intracranial Aneurysms affect cognitive functioning?

Many complex issues associated with treatment of unruptured intracranial aneurysms (UIAs) make the decision to treat controversial. However, taking into account the fact that up to 50% of patients suffering from a ruptured intracranial aneurysm die or become long-term disabled, an increasing number of patients choose to have their UIA treated despite a surgical morbidity rate between 3 and 37% (65, 162, 212, 214, 233).

The majority of outcome studies of UIAs have only looked at mortality and neurological morbidity. The International Study of Unruptured Intracranial Aneurysm (ISUIA) thus study found a mortality rate of 1.8% after 30 days and 3.6% after 1 year (212). However, when evaluating cognitive outcome the ISUIA study found that mental status added substantially to morbidity both at 30 days (6.3%) and 1 year (6.1%) after surgery (212). The literature has therefore increasingly called for detailed neuropsychological testing in association with elective surgery of UIAs, predicting that such testing will be the way of the future in helping both the patients and the surgeons make the decision on whether or not to operate (9).

Limited psychological research has been looked at UIAs and the studies that are published vary considerably in terms of measurements used, time-intervals, group sizes etc. They are therefore difficult to compare (71, 150, 215). In addition, the degree of cognitive impairments reported in UIA patients varies greatly between studies. Some studies report mild or moderate cognitive deficits similar to those seen in aneurysmal SAH patients (71) while others report no reduction in cognitive functioning (150, 215). The most common cognitive deficits reported after UIA surgery have been verbal fluency, immediate and delayed recall and executive tests (71). It has therefore been suggested that the long-term cognitive sequels after both aneurysmal SAH and UIA surgery may be the effect of the neurosurgery per se, rather than the hemorrhage. On the other hand, Tuffiash (215) found no evidence of subtle cognitive deficits resulting from the aneurysm clipping alone in their patients and therefore suggested that the common impairments found after surgery for ruptured aneurysm are due to the aneurysmal SAH itself (i.e. the impairments are due to complications such as vasospasms or hydrocephalus, or preoperative strokes). They did however also find that craniotomy for the repair of UIAs was associated with a 4% incidence (1 out of 25) of cognitive deficits. Overall, the consensus from the few studies that have investigated cognitive dysfunction after UIAs is therefore that some cognitive deficits will be evident soon after treatment, although many of these may resolve with time (214).

As mentioned there is limited and conflicting evidence regarding UIAs. Also many of the studies have lacked control-groups, lacked pre-operative evaluation or only followed the patients at the most 6 months post-aneurysmal SAH. We therefore compared a group of patients with MCA UIAs and a group of patients with ruptured MCA aneurysm to evaluate any differences in cognitive functioning and HRQOL. To get a longer time perspective we tested our patients with a comprehensive neuropsychological test battery both pre-operatively as well as 3 and 12 months post-operatively (see paper III).

1.3.5 How does SAH in clinical condition Hunt & Hess grade V after aneurysmal SAH affect cognitive functioning?

Patients in clinical condition Hunt & Hess grade V after an aneurysmal SAH comprise 4-24% of all an aneurysmal SAH individuals (74-75, 98, 122). Despite of consistently improving management of aneurysmal SAH patients, prognosis of the Hunt and Hess grade V subjects has remained poor (24, 115). Many of them have thus been treated conservatively and eventually deceasing. However, several studies reporting on the results from aggressive early intervention of poor grade an aneurysmal SAH individuals have shown favorable outcome in a fraction of them (26, 46, 75, 108-109, 113-114, 142, 186, 230, 240). Further, it has been difficult to identify, on an individual basis, preoperative markers that accurately predict survivorship and outcome after high grade an aneurysmal SAH bleed (114, 160). It has therefore been a dilemma regarding management of a Hunt and Hess grade V subject where, on one hand, outcome may be extremely poor despite of enormous treatment efforts, but on the other hand, a more passive attitude to aggressive treatment may withhold a potentially good outcome.

Few studies have looked at the neuropsychological sequelae in patients with clinical condition Hunt & Hess V after aneurysmal SAH. Mocco (133) found that poor-grade aneurysmal SAH is strongly predicted by the patient's age, worse pre-operative Hunt & Hess grade and size of the aneurysm. Using Telephone Interview for Cognitive Status (TICS), a telephone version of the Minimal Mental Status Examination at discharge, 3 and 12 months after aneurysmal SAH, Mocco (133) also found that a substantial portion of Hunt and Hess grade IV and V subjects recover cognitively over time.

However, such a screening of cognitive functioning does not give an accurate evaluation of cognitive functioning so the level of cognitive deficits among these patients is still uncertain

At the Department of Neurosurgery, Rikshospitalet University Hospital, Hunt and Hess grade V subjects after an aneurysmal SAH are managed aggressively with urgent aneurysm repair and maximum medical therapy. As a result a significant survival rate has been observed among these patients and a need to assess their level of cognitive functioning and HRQOL arose. We therefore examined our cohort of an aneurysmal SAH clinical grade Hunt and Hess grade V patients from a 5 ½ years time period using a comprehensive neuropsychological battery and HRQOL questionnaires one year after the aneurysmal SAH. We also related neuropsychological findings to the commonly used outcome evaluations in an aneurysmal SAH as well as with Rankin score, GOS and employment status one year after the aneurysmal SAH (see paper IV).

1.3.6 What is the effect of medical and radiological parameters on cognitive functioning?

The precise mechanisms behind the cognitive deficits after an aneurysmal SAH are still to a large degree unknown. Numerous studies (for example 14, 42-43, 84, 105, 213, 223) have therefore looked at a wide range of medical and radiological parameters to try to decipher the possible medical causes behind the cognitive deficits.

Intracerebral Haematoma (ICH), Intraventricular Haematoma (IVH) and amount of subarachnoid blood

Hütter (77) concluded that neither focal brain damage associated with the aneurysm site nor surgery but the hemorrhage itself and related events were regarded as the most important factors for the late results after aneurysmal SAH. Following this reasoning some studies have looked at the effect of ICH (47, 111, 144) and IVH (111, 144) on cognitive functioning but the results have been conflicting.

The presence of blood in the subarachnoid space induces a global brain dysfunction by starting a complex pathophysiological process, which results in focal and generalized disturbances in brain function (66). It might also cause a substantial lasting effect on cognitive functioning due to the diffuse cortical damage immediately after the hemorrhage through a neurotoxic effect of the subarachnoid blood (77, 85, 144). Some studies have as a result looked at correlations between the amount of Blood (Fisher score) and cognitive functioning, however, the results of these studies have been conflicting. Berry (15), Germano (62), Ogden (144), Orbo (148), Ravnik(164) and Romner (173) did not find any association between the amount of subarachnoid blood and cognitive deficits. One the other hand, Hütter (76, 80, 84) found associations between subarachnoid blood and cognitive functioning (esp. executive functioning) and Larsson (111) found some associations with verbal memory and amount of blood. Hütter (82) also showed the relationship between mean blood flow velocity (TCD) and cognitive functioning, but found no substantial effects on cognitive functioning. Likewise Odgen (143-144) found that the location of blood on the admission CT scan did not prove to be a useful predictor of specific types of cognitive impairments. However in their study intracerebral blood was only present in 19% of their patients at 10 weeks and was only associated with verbal memory impairment. Likewise at 12 months only 27% of the patients had visible blood on their CT scan and poor word recognition scores. Kreiter (105) further largely found no association between amount of blood and cognitive functioning.

The perhaps strongest association between cognitive functioning and medical variables is found in relation to cerebral edema which has shown to greatly affect cognitive functioning (105). This association is explained by suggesting that global edema may be a manifestation of transient global ischemia related to elevated intracranial pressure at the time of the bleeding, resulting in microvascular injury, impaired autoregulation and rebound hyperemia. In the study by Kreiter (105) they found that cerebral infarcts in the left hemisphere caused more severe cognitive dysfunctions. On the other hand, Romner (173) found that absence of pathological findings on MRI scans did not exclude cognitive problems and visa versa. Further support for the importance of cognitive deficits and CT documented infarctions have also been found in other studies such as Ogden (144), Hillis (71) and Vilkki (220) but more research is needed to confirm this hypothesis.

Temporary vessel occlusion during surgery

Only one study (1) has looked the effect of temporary vessel occlusion during surgery. By looking at a group of 40 ACoA patients that either had temporary vessel occlusion during surgery or not they found that vessel occlusion had a negative long-term effect on cognitive functioning, but due to the limited research on this phenomena more research is needed to confirm their hypothesis .

Hydrocephalus & Cerebrospinal fluid (CSF)

The effect of hydrocephalus on cognitive functioning is also conflicting. Ogden (144) and Larsson (111) reported finding an association between hydrocephalus and cognitive functioning, while others such as Dombovy (47) and DeSantis (42) were unable to find such an association. One study (217) also looked at the effect on the neuropeptide concentration in CFS on cognitive functioning and found that patients with cognitive impairments after aneurysmal SAH had higher CSF concentrations of endorphins, corticotropin-releasing factor and delta sleep-inducing peptide than those with normal cognitive capacities, but these finding have not been explored further and no definite conclusion has been reached.

Cerebral vasospasm

Some studies have looked at the effect of vasospasms on cognitive functioning and although early studies found an association (112, 166-167, 200) the improved treatment of vasospasms using nimodipine and HHT have led to numerous studies not finding any associations (15, 71, 80, 104, 144). Unfortunately it is not yet clear what effect the vasospasm has on the cognitive

functions, because vasospasms can occur at any arterial position in the brain and hence affect any number of brain functions (10).

Clips versus Coil

Traditionally the efficacy and safety of neurosurgical or endovascular techniques have been evaluated by comparing neurological morbidity and mortality rates associated with the different treatments (21, 134). Recently quite a few studies (14, 69, 101, 157, 179) have also looked differences in cognitive functioning as a result of clipping and coiling. The international subarachnoid aneurysm trial (ISAT) found lower rates of mortality and morbidity among endovascular treated patients, with 24% of coiled patients being dependent or dead versus 31% of the surgically clipped patients being dependent or dead after one year (134). Some studies have also supported these findings (14, 69, 101). Bellebaum (14) found that clipped patients were slightly more impaired than coiled patients, but more on measurement of affect and self-assessed measure of executive function rather than neuropsychological tests. However, both groups showed decreased verbal and visual memory, which they ascribed to the aneurysmal SAH itself. Hadjicassiolou (69) and Chan (25) reported more severe deficits in visual memory and executive functions among clipped patients one-year after aneurysmal SAH. On the other hand, Koivisto (101) did not find any differences at either 3 or 12 months between clipped and coiled patients. Studies by Kähärä (95), Preiss (157), Santiao-Ramajo (179) and Fontanella (58) supported the findings of Koivisto (101) and found no differences between the two types of aneurysm treatment. One recent study by DeSantis (43) found that surgical patients seemed to achieve better outcome than coiled patient using a new assessment scale (DeSantis-CESE assessment tool) for measuring outcome after surgical or endovascular treatment for aneurysms. The overall consensus regarding surgical clipping versus endovascular coiling's effect on cognitive function seem to be that there are minimal differences in the long-term cognitive outcome (59).

Re-bleeding

There are limited studies looking at the effect of aneurysm re-bleed but Tidswell (213) argued that cognitive outcome was most strongly predicted by post-operative neurological events, with the exception of executive problems which were most influenced by pre-operative re-bleeding. However, they failed to find that measures of overall severity of the initial aneurysmal SAH (unconsciousness, Fisher, clinical grade) were good predictors of later cognitive damage. Due to the difficulty of separating the effect of the re-bleeding from all the

other medical complications associated with an aneurysmal SAH no definite conclusions regarding the effect of re-bleeding on cognitive functioning have been made.

Early versus late surgery and Surgical complications

Some studies (42, 166, 182, 194) looked at the effect of surgical complications on cognitive deficits and found that since patients with known aneurysm and patients with aneurysmal SAH from aneurysm of unknown origin have the same cognitive deficits the surgery itself does not cause major damage beyond the damage caused by the aneurysmal SAH itself (84). This view has been challenged in later research especially on patients with unruptured aneurysm and on research looking at the difference between patients operated on shortly after ictus and those with later surgery. Richardson (166), Sonesson (194) and Satzger (182) failed to find any differences between early and late surgery and concluded that the cognitive disturbances seen after an aneurysmal SAH were the result of the initial hemorrhage itself and not the surgery. Other studies have also supported this view for example, two studies found that mild hypothermia during surgery did not have a significant effect on cognitive function (4, 180). Further, Ravnik (164) also failed to find any effect of the time from onset of aneurysmal SAH to the operation on cognitive functioning. On the other hand, DeSantis (42) found that late surgery correlated with poor prognosis and in a new study by Pasternak (152) with patients at risk for ischemic brain injury found that patients with intraoperative hyperglycemia (i.e. elevated intraoperative glucose concentrations) have long-term changes in cognitive and neurological functioning but these results needs further research to be confirmed.

Demographic variables

Demographic variables such as age, education and race have been shown to greatly influence neuropsychological tests (105). However, there is no general consensus as to how much such variables influences the results. Tidswell (213) failed to find any age effect (i.e. older patients did not fare worse), but De Santis (42), Lanzino (110), Ogden (144) and Säveland (183) found a clear age effect. Race has also been shown to have an effect on neuropsychological tests (5, 57, 159, 174) but no studies have looked especially on race in relation to cognitive functioning and aneurysmal SAH. The effect of education on cognitive recovery is well known, with higher intellect being associated with better health and longevity and less vulnerability to the impact of disease (5, 42, 165, 181).

Outcome scales

Many studies have addressed the association between outcome scales scores such as GOS and cognitive functioning (17, 42, 52, 77, 80, 84, 120, 127, 132, 144, 164, 180, 194, 199, 202, 217, 222) and the majority of these studies have failed to find any significant correlations between the GOS and cognitive outcome (4, 164). It is therefore largely excepted that despite good outcome (according to GOS) cognitive deficits are still evident in aneurysmal SAH patients. There are however two exceptions to these results. Odgen (144) and Vilkki (222) both found that poor GOS at discharge was a strong predictor of cognitive functioning at later stages. Further, mRS has shown somewhat better promise than GOS with Towgood (214) finding mRS to be the best predictor of functional outcome in their patients. A possible explanation for the differences between outcome scales and cognitive functioning might be caused by the observer variability that can occur when grading the neurological status of aneurysmal SAH patients which is not the case during neuropsychological testing (119). Overall there is therefore a general consensus that a considerable percentage of patients who survive an aneurysmal SAH without persisting neurological deficits as reflected by GOS or mRS nevertheless can suffer from cognitive impairments.

Summary on medical and radiological parameters

Since the relative importance of these types of injuries still are largely unknown, a clearer identification of preoperative, perioperative and postoperative risk factors for later cognitive disabilities is necessary to understand the functional outcome of aneurysmal SAH patients. The consensus today does however seem to be that the mild-to-moderate dysfunction across multiple cognitive domains reflect a diffuse injury caused by ictal temporary cerebral circulatory arrest and exposure of the brain to subarachnoid blood (105). As a result interventions aimed at reducing neurological injury from brain swelling, ischemia and clot-related hemotoxity hold the best promise for improving cognitive outcome after aneurysmal SAH (105).

To further the understanding of the interaction between medical variables and cognitive functioning after an aneurysmal SAH, all our studies have looked at the effect of some of the previously mentioned medical variables on cognitive functioning both in good outcome patients, in patients operated on for unruptured aneurysms and in poor-grade patients(see papers I-IV).

1.4 Health Related Quality of Life (HRQOL)

Health Related Quality of Life (HRQOL) is defined as a subjective experience of well-being affected by a health condition (i.e. dimensions related to quality of life or subjective well-being that are independent of, or not directly associated with health, are not comprised by HRQOL) (93). Assessment of HRQOL therefore represents an attempt to determine how variables within the dimension of health (e.g., a disease or its treatment) relate to particular dimensions of life that have been determined to be important to people in general (generic HRQOL) or to people who have a specific disease (condition-specific HRQOL). Most conceptualizations of HRQOL emphasize the effects of disease on physical, social/role, psychological/emotional, and cognitive functioning. Symptoms, health perceptions, and overall quality of life are often included in the concept domain of HRQOL (227).

1.4.1 HRQOL and aneurysmal SAH

It is well known that lack of initiative, reduced energy levels and emotional changes often accompany aneurysmal SAH, but the reasons for these changes remain unclear (68, 73, 84, 86, 100, 156, 219). Only two studies have failed to find any reduction in HRQOL among aneurysmal SAH patients (54, 234). The emotional and behavioral changes after aneurysmal SAH may be a direct consequence of brain damage caused by the aneurysmal SAH or the subjective experience of changes after an aneurysmal SAH without any permanent brain lesion. Since aneurysmal SAH is an illness that strikes instantly, the patient will in some cases require psychological both in the acute stage to manage stress of the illness trauma and subsequent follow-ups (84). Anxiety and depression are commonly reported in aneurysmal SAH patients (84, 199, 222, 225) Further, it is not uncommon for aneurysmal SAH patients to experience symptoms such as fatigue, lack of motivation, and reduced concentration (84, 120, 145, 213).

Patients that experience emotional and behavioral changes associated with the cognitive dysfunctions after an aneurysmal SAH are often those that are hardest to classify because they often seem to be normal in the eyes of society, but in reality they are significantly different from their “normal self” especially in the eyes of their relatives. To show this Hütter (84) did a retrospective study on 58 patients with either a good or fair outcome after an aneurysmal SAH and found marked reduction in a wide range of aspects of HRQOL in the majority of the patients.

Although there seem to be a general agreement that HRQOL is affected after an aneurysmal SAH in a large percentage of patients, the degree and long-term effect of the

problems are still debatable. A with the cognitive problems it is believed that the emotional problems are relatively mild (78), with about 25% of the aneurysmal SAH patients experiencing some form of emotional problems after an aneurysmal SAH (120). The impact on the patient's life can however, still be substantial and hence hard to treat since the emotional changes after an aneurysmal SAH are most likely to be "the consequence of multifactorial events in which the extent of organic and cognitive impairments with their psychosocial and economic sequelae, damage to relevant brain structures, psychic traumatization, individual illness coping and an increased strain through chronic headache acts together in a so far unexplained way" (78). Therefore, to further understand the emotional and personal problems the aneurysmal SAH patients experience, researchers (e.g. 84, 120, 222) have looked closer at the discrepancy between the prevalence of emotional and personality disorders, and the seemingly milder levels of neurological problems and concluded that the "disorder of psychological adjustment in patients cannot be explained alone as a simple psychological reaction to persisting deficits" (76). However, although such a conclusion put the effect of an aneurysmal SAH into the complexity of everyday life, it also raises the question about what the underlying causes of emotional changes found after aneurysmal SAH really are.

Hütter (76) argued that there are four natural hypotheses that might answer this question. First, the patients might have some sort of maladjustment before the bleeding. There is however no evidence that suggest that the aneurysmal SAH patient's differ from the normal population in terms of psychological functioning and hence the use of the age and education related norms that have been developed for the test and questionnaires must be regarded as reliable. An alternative could of course be to do a prospective epidemiologic study, but this would be extremely time consuming and costly due to the immense amount of subject one would have to include in order to assure that some in fact end up with an aneurysmal SAH at some point in time. Secondly, a catastrophic event such as an aneurysmal SAH could lead to post-traumatic stress disorder (PTSD). In a study by Stegen and Freckmann (199) over 50% of the patients had such concerns. Third, since aneurysmal SAH patients seem to have certain common features, in addition to the cognitive deficits, such as lack of motivation and increased emotional problem. It has been suggested that certain structures in the brain are affected to such an extent that it causes such problems. For example blood in the basal cisterns may cause damage to medial frontobasal or brain stem structures causing the emotional and motivational problems. Fourth, it is possible that aspects of the aneurysmal SAH such as "the clinical state at admission, the severity of the

vasospasm, a distributed circulation of cerebrospinal fluid, and psychological factors such as illness coping and social support contribute to the psychological maladjustment after aneurysmal SAH" (76). At the present time it is still not known which of these hypotheses that truly explains the underlying causes of the problems seen after an aneurysmal SAH.

Another important factor correlating with HRQOL is the ability to return to work. It does however seem clear that not one factor is responsible for patients not returning to work. Most often a combination of factors such as of ongoing excessive fatigue, depressed mood and subtle cognitive impairments seems the most likely explanation for lowered work status (144). Katati (99) found that over half of the patients answered that the state of their physical health interferes with their work and other daily tasks (Role Physical on SF-36). Vilkki (222) also found that failure to return to work and impaired social relations were related to poor performance on cognitive tests. Therefore, the studies that have evaluated the patients' ability to return to work seem to agree that despite a good recovery, with 20-60% of patients with aneurysmal SAH not being able to return to their pre-aneurysmal SAH level of employment even after a year or more has passed (78, 145). Return to work is important in maintaining a good HRQOL, however many patients seem to compensate their reduced work-capacity by decreasing their social life and hobbies to keep up with their work (146). Ogden (146) further suggested that the severity of the aneurysmal SAH was associated with impairments working capacity and social activities rather than with specific cognitive deficits. They also suggested that diffuse brain damage tended to reduce work capacity rather than result in specific cognitive deficits which were more clearly associated with left and bilateral infarction. Gomez-Tortosa (64) found that some patients experience the cognitive deficits more significantly because they had more demanding jobs and greater expectations they had to live up to and "as a result the patient's preoperative level of education and job responsibilities were the most important factors regarding the repercussion of the cognitive deficits" (64).

Not being able to return to work after an often long and productive career is often extremely difficult and for many the thought of having to retire 15-20 years earlier than planned can cause great distress and might lead to psychological problems. An accurate knowledge of the rate of return to work is therefore extremely important when informing the patients about the consequences of an aneurysmal SAH and we therefore included analysis of the ability to return to work in three of our studies (see paper II, III and IV).

1.4.2 HRQOL and patients with Unruptured Intracranial Aneurysms

There is more agreement among outcome studies when it comes to HRQOL in patients with UIA's with most studies reporting a significant decrease in HRQOL prior to the surgery, followed by improvement shortly after surgery but not a complete recovery one year after surgery (161). Anxiety is probably the emotional reaction which is most likely to subside after surgery, due to the removal of the threat of aneurysm rupture. However, it is important to take into account that the natural history of anxiety when aneurysms are left untreated is unknown (150). Further, the patients frequently also report poorer coping skills and reduced well-being and social functioning scores on GHQ-30 and poorer role physical, general health, vitality, social functioning and mental health on SF-36 pre-operatively. Although one usually see improvement one year after surgery the UIA patients still have reduced HRQOL especially though experienced limitations in their ability to work or accomplish desired activities due to perceived physical or mental handicaps and pain. Yamashiro (238) found that as many as 86% of the patients who underwent surgery for an UIA showed a HRQOL similar to the reference population and therefore conclude that elective surgery for asymptomatic UIAs is a reasonable treatment, especially for patients that are troubled by the risk of rupture. They also suggested that decreased UIA post-surgery may not necessarily be associated with other chronic disorders rather than the surgery itself.

An aspect of UIAs that has been considered is the need for screening family members of patients with aneurysmal SAH. The need for such screening might be obvious from a diagnostic and treatment point of view but little is known of the effect on psychosocial functioning. Studies done on patients screened for other illnesses such as breast cancer have found a positive impact on HRQOL by for instance offsetting depression (184).Only one study have looked at such an effect in relatives of aneurysm patients. Wermer (231) showed a pronounced effect on HRQOL among relatives of patients with aneurysmal SAH that screened positive for aneurysms. They reported adverse outcomes in aspects of lifestyle, behavior, work and social and emotional functioning. On the other hand over half of these patients also reported changing to a healthier lifestyle. They therefore concluded that there is a substantial impact on health and psychosocial well-being of UIA detection in otherwise healthy individuals. Appropriate support and professional guidance is therefore important in relation to the decision about whether or not to proceed to surgery. Overall the literature seem to support the notion that general surgery for UIAs is believed to be relatively safe and meaningful when considering the positive impact is has on the patient's HRQOL.

1.4.3 HRQOL and patients in clinical condition Hunt & Hess grade V after aneurysmal SAH

There is relatively limited research on the HRQOL among patients in clinical condition Hunt & Hess grade V after aneurysmal SAH. In one of the few studies on patients in clinical condition Hunt & Hess grade V outcome after aneurysmal SAH Hütter (86) looked at 20 patients in Hunt & Hess grade IV and V on admission. Using the Sickness Impact Profile they found significantly more impaired ambulation, mobility, social contact, free-time activities, communication, autonomy and cognitive capacity among these patients compared to patients in Hunt & Hess grade I-III. They also found that only 30% of the Hunt & Hess grade IV and V patients had a good to acceptable HRQOL but this recovery was age dependent, with younger patients showing the best results. Mocco (133) also concluded that a substantial proportion of patients in Hunt & Hess grade IV and V experienced cognitive recovery, increased independence and improved HRQOL, and therefore delayed follow-up is necessary when evaluating functional recovery in Hunt & Hess grade IV and V. Overall HRQOL have been an integrated part of our studies (see papers II-IV) because it is such a vital part of the patient's rehabilitation process. We therefore aimed at describing the challenges the different groups of patients included in our studies face and also any changes in HRQOL that may occur over time in the groups that were tested repeatedly.

Based on this literature search the present thesis will focus on four aspects of cognitive functioning and HRQOL in relation to intracranial aneurysms. First, we will look at the time-course of improvement in cognitive functions, secondly we will explore the differences in cognitive functioning and HRQOL in ACoA and MCA patients, thirdly the difference in cognitive functioning and HRQOL among both ruptured and unruptured aneurysm will be evaluated and finally the impact of clinical condition Hunt & Hess grade V after an aneurysmal SAH on cognitive functioning and HRQOL will be investigated.

2 AIMS OF STUDY

STUDY I: COGNITIVE OUTCOME AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE: TIME-COURSE OF COGNITIVE RECOVERY AND RELATIONSHIP TO CLINICAL, RADIOLOGICAL AND MANAGEMENT PARAMETERS.

Many patients recovery satisfactory in terms of physical functioning after an aneurysmal SAH but disabling cognitive deficits may still be present. To our knowledge few studies had evaluated cognitive functioning in the same individuals at more than two points in time during the first year after aneurysmal SAH. Further, there is still much debate as to which clinical, radiological and management parameters that affect cognitive functioning after aneurysmal SAH. We therefore wanted to investigate:

1) Do all cognitive functions improve at the same rate during the first year post-aneurysmal SAH?
2) What clinical, radiological and management parameters affect cognitive functioning?

STUDY II: COGNITIVE FUNCTIONING AND HEALTH RELATED QUALITY OF LIFE AFTER RUPTURE OF AN ANEURYSM ON THE ANTERIOR COMMUNICATING ARTERY VERSUS MIDDLE CEREBRAL ARTERY.

The majority of earlier studies on aneurysmal SAH looked at ACoA patients but few studies have looked at the other major aneurysm site, MCA. Further, the studies on ACoA patients were done quite a few years ago and despite the development of new more sensitive frontal lobe test batteries in neuropsychology few researchers have utilized these to look at more subtle changes in ACoA patients. We therefore compared a group of patients with ruptured ACoA aneurysms and a group of patients with ruptured MCA aneurysms to investigate:

1) Do patients with ruptured ACoA and MCA aneurysms have different cognitive problems (i.e. do the aneurysm rupture cause a focal damage at the site of the rupture)?
2) Do patients with ruptured ACoA and MCA aneurysms experience any differences in HRQOL and are they able to return to work?

STUDY III: SURGICAL REPAIR OF UNRUPTURED AND RUPTURED MIDDLE CEREBRAL ARTERY ANEURYSMS: IMPACT ON COGNITIVE FUNCTIONING AND HEALTH RELATED QUALITY OF LIFE.

The treatment of unruptured aneurysms is still debatable due to the many possible medical complications that can occur on the one side and the well-being of the patient feeling inhibited in his/her life due to having a potential life threatening aneurysm on the other. Further, no study has directly compared the effect of a ruptured aneurysm with the effect of surgery for an untreated aneurysm in the same location. We therefore looked at:

1) Are there differences in cognitive functioning and HRQOL between operated for a ruptured versus unruptured MCA aneurysm?
2) How much of the cognitive deficits are caused by the surgery itself compared to the aneurysm rupture?

STUDY IV: COGNITIVE FUNCTIONING AND HEALTH RELATED QUALITY OF LIFE ONE YEAR AFTER ANEURYSMAL SAH IN PATIENTS IN CLINICAL CONDITION HUNT & HESS GRADE V.

Between 4-24% of aneurysmal SAH patients are in clinical condition Hunt & Hess grade V and many have a poor -prognosis. However, little is known about cognitive functioning and HRQOL in the patients that do survive. We therefore wanted to investigate:

1) What kind of and how serious are the cognitive deficits after a clinical condition Hunt & Hess grade V aneurysmal SAH?
2) Can we based on the both medical and cognitive outcome predict which patients that will have a satisfactory recovery?
3) How do the patients function in their daily life? Do they have a satisfactory HRQOL?

3 MATERIALS AND METHODS

3.1 Study population

Only patients suffering from an SAH as a result of an aneurysm rupture are included in the present studies. Patients that could or would not sign an informed consent were not included. The general exclusion criteria for all patients were a) death within one year after aneurysmal SAH b) history of earlier cerebrovascular or neurological disease c) age <18 or $\geq$ 70 years d) lack of fluency in Norwegian e) abuse of narcotic drugs or alcohol, and f) aphasia. In addition

specific requirements were applied to each study see each study for specific requirements (for example patients in clinical condition Hunt & Hess grade I-IV were not included in study IV, and only patients with ruptured ACoA or MCA aneurysms were included in study II).

3.1.1 Inclusion procedure and patient population

All patients were recruited from the Department of Neurosurgery at Rikshospitalet University Hospital from 2002 to 2007. The patients were included into the different studies by Wilhelm Sorteberg MD PhD and Angelika Sorteberg MD PhD.

In study I, a total of 73 patients were admitted with aneurysmal SAH between June and December 2003 in Hunt & Hess grade I-V. Ten (14%) died within one year of the ictus. Nine were excluded due to age > 70 years, seven due to dysphasia or inability to perform neuropsychological testing, two were non-fluent in Norwegian, two had prior neurological disease, three refused participation and eight were lost to follow-up. Thus, 32 subjects could be followed.

In study II, the study population was recruited from a total of 84 patients in pre-operative clinical condition Hunt & Hess grade I-III after rupture of an ACoA or MCA aneurysm that underwent aneurysm repair between June 1st 2003 and February 27th 2005. Five (5.8%) of them died within one year of the ictus. Seven were excluded due to age > 70 years, five were non-fluent in Norwegian, four had prior neurological or psychiatric disease, three refused participation, three had a history of alcohol and drug abuse, two were excluded due to uncertainty regarding which aneurysms that had bled (two or more aneurysm were found and repaired in these subjects), six had their controls at the referring hospital and three were lost to follow-up. Thus, 46 subjects, 24 with ruptured ACoA aneurysms and 22 with ruptured MCA aneurysms, were included in the study.

In study III, 15 patients admitted for prophylactic treatment of a MCA UIA between March 1st 2005 and November 30th 2006 and 22 surgically treated patients in pre-operative clinical condition Hunt and Hess grades I-III from a ruptured MCA aneurysm between January1st 2003 and February 27th 2005 were included.

In study IV, the patients included were based on a total of 102 patients admitted with a Hunt & Hess grade V from January 1st 2002 – June 30th 2007. Of the 102 patients in clinical Hunt and Hess grade V, 32 individuals either had bilaterally non-reacting dilated pupils/ reverberating blood flow velocities on transcranial Doppler upon arrival to our hospital or brain destruction to an extent where no meaningful treatment could be given. They were

therefore treated conservatively, and they all died within days. Seventy subjects were treated aggressively. Thirty five (50%) of them died early while the other 35 (50%) were alive one year after ictus. Two of the one year survivors were lost to follow-up, four could not be neuropsychologically tested due to neurological deficits including complete aphasia while three declined participation in the study. The remaining 26 subjects thus comprise this study.

Due to some overlap in time-intervals between the different studies, some patients were included in more than one study (see figure 4).

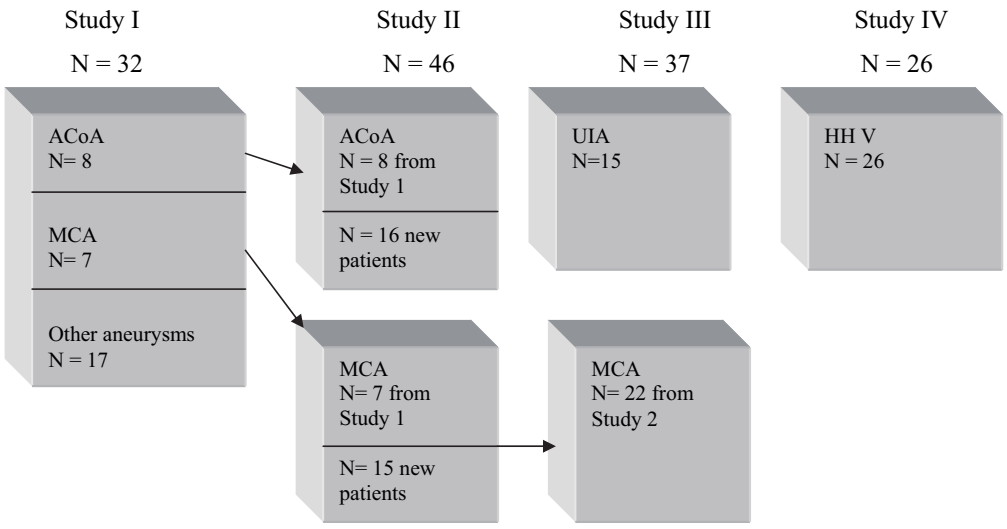

Figure 4: Diagram of inclusion in the separate studies.

3.2 Design, method and measures

3.2.1 Study design

The present studies are a series of prospective, longitudinal cohort studies, with a one-year follow-up of aneurysm patients. All patients were treated for their aneurysm according to protocol at the Department of Neurosurgery at Rikshospitalet University Hospital and evaluated using neuropsychological tests and HRQOL questionnaires. The studies consist of a large number of both medical, demographic, neuropsychological and HRQOL variables but common for all studies is that they have the neuropsychological/HRQOL variables as the dependent variables and medical/demographic variables as independent variables based on the

focus of the study. The following figures will schematically show the study design for each study.

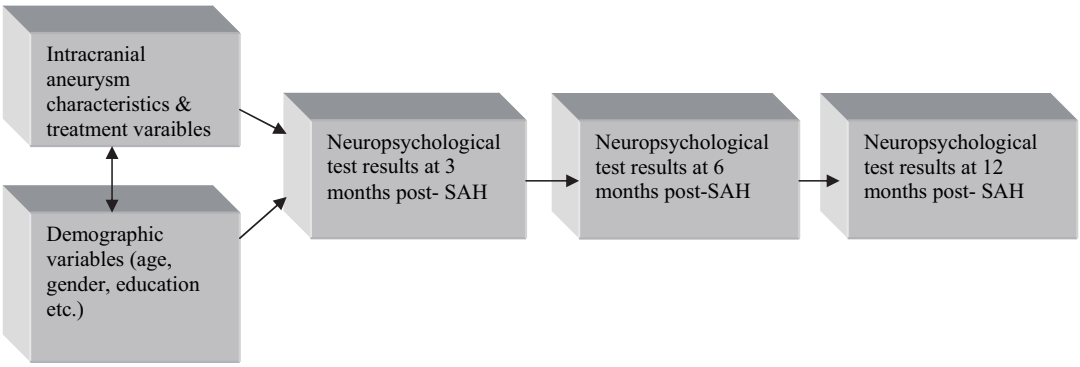

Figure 5: Study design for Study I

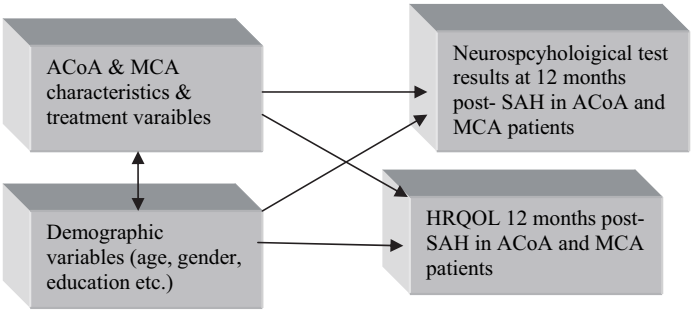

Figure 6: Study design Study II

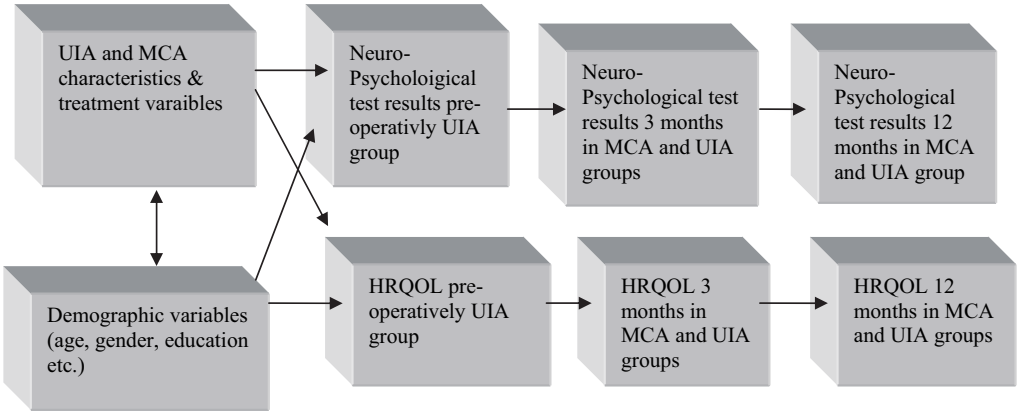

Figure 7: Study design Study III

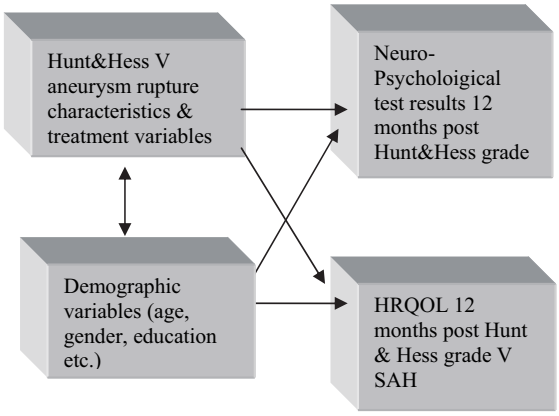

Figure 8: Study design Study IV

3.2.2 Data collection

All the neuropsychological testing and clinical psychological interviews were done by cand psychol Tonje K Haug, with the help of cand psychol Camilla Rønning and psychology student Wenche Brønn. All the medical data was collected and evaluated by Angelika Sorteberg MD, PhD and Wilhelm Sorteberg MD, PhD. All data was coded using anonym codes and stored in a database only accessible to the principal investigators in this study.

The neuropsychological evaluation at 3 months was done on day one or two of the patient's admittance to the Department of Neurosurgery. At the 12 month control the patient came for a clinical evaluation by the neurosurgeon and neuropsychological testing on the same day. Pre-operative evaluations in the UIA group were done the day before surgery. Neuropsychological testing was done in a quiet office where only the patient and test-administrator was present. The neuropsychological test lasted 2 and 3 hours and the patients were given at least one break during testing. Most tests were done in the early afternoon both pre-operatively and at 3 and 12 months post-operatively.

3.2.3 Measures and Clinical instruments

3.2.3.1 Clinical Instruments

Hunt & Hess scale

The Hunt and Hess scale (74) was developed to classify the clinical condition of individuals having suffered an SAH. It ranges from 1 to 5, with 1 indicating the best form of aneurysmal SAH and 5 the worst clinical condition (see table 1).

Table 1: Hunt & Hess Scale

Hunt & Hess score	Description
I	Asymptomatic, mild headache, slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
III	Drowsiness / confusion, mild focal neurologic deficit
IV	Stupor, moderate-severe hemiparesis
V	Coma, decerebrate posturing

Fisher scale

The Fisher scale (55) is a four point scale used to describe the amount of blood on CT scans (see table 2).

Table 2: Fisher scale

Fisher grade	Description
Grade 1	No hemorrhage evident.
Grade 2	Subarachnoid hemorrhage less than 1mm thick.
Grade 3	Subarachnoid hemorrhage more than 1mm thick.
Grade 4	Subarachnoid hemorrhage of any thickness with intra-ventricular hemorrhage (IVH) or parenchymal extension.

Glasgow coma scale (GCS)

The Glasgow Coma Scale (GCS) was developed by Teasdale and Jennet in 1974 (210) to assess the depth and duration of impaired consciousness and coma. It measures motor

responsiveness, verbal performance and eye opening on a scale from 3 (indicating deep unconsciousness) to 15 (no alteration in performance).

Table 3: Glasgow Coma Scale

GCS	1	2	3	4	5	6
Eyes	Does not open	Opens in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converse normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion/Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Glasgow outcome scale (GOS)

The Glasgow Outcome Scale (GOS) was published by Jennett and Bond in 1967 (90) and is perhaps the most commonly used outcome measure after traumatic brain injury (237)). The Glasgow Outcome Scale also categorizes patients that have suffered acute brain damage and place them into broad outcome categories. The scale is designed to reflect disability and handicap, rather than impairment, that is, it focuses on how the injury affect major areas of life rather than the particular deficits and symptoms caused by injury. As a result it does not give detailed information about the specific difficulties patients face, but instead offers a general index of overall outcome. The scale is therefore relatively basic; assigning very general aspects of outcome related more to functional disability than to cognitive deficits. In brain damaged patients with no/minimal impairment (GOS 5) the patient can return to his or her previous life even though there might be minor neurological and psychological deficits. Patients with a modest disability (GOS 4) function well enough to travel by public transportation and work in sheltered environments and are therefore able to live independently, even if some of the activities, either at work or in social life, are no longer possible. These patients are therefore what is called “independent but disabled” (91). The disabilities these patients often have are different degrees of dysphasia, hemiparesis, or ataxia,

as well as intellectual and memory problems and personality changes (90). The severely impaired patients (GOS 3) are dependent on daily support from family and medical personnel due to mental and physical disabilities caused by the brain injury. Most often the dependency is caused by a combination of physical and mental disability. Patients in a vegetative state (GOS 2) are unresponsive and speechless for weeks or months until they eventually die. The vegetative patients are able to breath, open their eyes, as well as some reflex movement in their limbs, however they cannot obey commands or utter words. Finally, the last category of patients (GOS1) is dead as a result of the brain damage.

The modified Rankin scale

The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke (163). It was originally introduced in 1957 by Rankin (163) and modified in 1994. The scale runs from 0-6, running from perfect health without symptoms to death (see table 4).

Table 4: The Modified Rankin Scale

Rankin score	Description
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead.

Montgomery and Aasberg Depression Evaluation Scale (MADRS)

MADRS is a 10-point clinical interview. It is not a diagnostic instrument but is used to measure the depth of a depressive condition and evaluate further treatment (135). The questions evaluates, based on a 0 to 6 point scale, external signs of sadness, reported sadness, internal tension, reduced sleep, reduced appetite, concentration difficulties, lack of initiative, reduced emotional ability, pessimistic thoughts and suicidal thoughts within the last 3 days. Scores ranging from 0 to 6 indicate no depression, 7-19 light depression, 20-34 moderate depression and 30-60 severe depression.

Apathy Evaluation Scale Clinicians version (AES-C)

The AES-C is an 18 item scale covering the behavioral, emotional, and cognitive aspects of apathy (124). Each item is rated on a 4-point Likert-type scale, from 1 =not at all characteristic to 4 = very characteristic, with total AES-C scores between 18 and 72, higher score indicating more apathy. We have used a cut-off of 34 to indicate the presence of apathy.

3.2.3.2 Neuropsychological tests

A neuropsychological assessment study brain function through looking at behavior, but also by using many of the same techniques, assumptions and theories as psychological assessment. Neuropsychological assessment therefore involves "the intensive study of behavior by means of interviews and standardized scaled test and questionnaires that provide relatively precise and sensitive indices of behavior" (116). Historically, neuropsychological assessment was used to locate the lesion sites in brain injury patients, but the recent development of advanced imaging techniques, such as CT and MRI scans, has taken over much of this function. Instead, a neuropsychological assessment investigates the level of cognitive and social impairments. A patient may therefore be referred to a neuropsychological assessment 1) to determine if the patient has experienced a brain trauma, 2) to determine if the patient has developed a psychiatric dysfunction or 3) to determine whether the patient has both an organic and a psychiatric complaint (201).

Neuropsychology therefore, "covers not only the cognitive functional level but also the emotional state, the behavior and the subjective experience of patients with brain damage as well as their interactions. According to these demands, neuropsychology could be defined as the scientific, diagnostic or therapeutic occupation with the interaction between physiological or pathological states of the central nervous system and cognitive processes as well as the subjective experience and behavior of living beings"(78). The use of neuropsychological tests

are as a result many, they can be used to make the correct diagnosis or assist in making a diagnosis, to evaluate the degree of functional deficits, to plan and execute a rehabilitation program and to help the patient get back to the occupational life or education. Neuropsychological assessment can also be useful in assessing the efficacy of clinical interventions in both comparing groups and monitoring individual progress. In addition, neuropsychological testing provides a sensitive, objective, reliable, and valid means to evaluate the function of the brain to determine the effect of the trauma (201).

Motor functioning

Grooved Pegboard

The Grooved Pegboard Test is a manipulative fine sensorimotor finger dexterity task, which consists of placing 25 identical small key-formed pegs into 25 grooves with randomly oriented slots (the pegs must be rotated into the grooves) (116). The time required to finish the task with each hand is recorded separately. The score for each hand is equal to the time (in seconds) the patient took to finish the task.

Attention

Digit Span

Attention deficits are distractibility or the inability to focus behavior, and attention capacity is measured by span tests which expose the patient to increasingly larger amount of information with instructions to indicate how much of the stimulus was immediately taken in by repeating what was heard. The Digit Span test in the Wechsler Adult Intelligence Scale III (WAIS-III) batteries is used to measure span of immediate memory and attention (229). The test consists of two different sub-tests, Digits Forward and Digits Backwards, which involves different mental activities and is affected differently by brain damage. Both tests consist of seven increasingly linger strings of random number sequences that the examiner read out loud at the rate of about one per second. Both tests therefore involve both auditory attention and short-term retention capacity. In the forward span task, the patient's task is to repeat each sequence exactly as given. When the patient correctly repeats a sequence the examiner reads the next longer number sequence, continuing until the patient fail a pair of sequences or repeats a nine-digit sequence correctly. The normal range for Digits Forward is 6 +/- 1 and education does have a marked effect on this task (116). The second part of this task, Backward span, consists of having the patient reversing the sequence (i.e. starting with the last number and working his or her way backwards to the first number given by the examiner). As in the forward span task,

the examiner proceeds by adding one more number to the sequence until the patients makes two consecutive errors at a given span length. Digit span is scores by adding forward and backward span.

Verbal memory

California Verbal Memory Test (CVLT-II)

The CVLT-II test examines not only verbal memory, but also the interaction between verbal memory and conceptual ability (36). Each of the 16 items on the CVLT-II belongs to one of four categories (animals, fruits, clothes, furniture). The list is read out loud by the examiner, and the patient's task is to recall as many of the items as possible. This pattern is repeated five times for the first list. The CVLT-II also includes a second list, as an interference trial, before the patient is asked to recall the first list again first as a free-recall task ("tell me all") and as a cued-recall task ("what kind of fruits were there?") (Short-term delay retest). Finally, there is a long-term recall after a 20-minute delay with a free-recall, a cued recall and a forced-recall task.

Visual memory

Rey Osterrieth Complex Figure

The complex figure is used to investigate both perceptual organization and visual memory (116). The patient is shown the complex figure and then instructed to copy the figure onto a plain white sheet. After a 30-minute delay, the patient is given a blank sheet of paper and told to draw as much of the figure as they can remember. The test is scored based on the accuracy of the drawings, paying special attention to whether the drawings are incomplete, sketchy or distorted.

Continuous Visual Memory Test (CVMT)

CVMT consist of 112 figures with seven target figures (116). The patient's task is to recognize which of the figures he or she has seen before. Each of the target figures are seen seven times. There is also a recognition trail after a 30-minute delay, where the patient is asked to recognize which out of seven similar figures that actually were in the first set of figures. The test is scores both in terms of how many items the patient can actually identify and how many false positives the patient has.

Psychomotor functioning

Digit Symbol

The Digit Symbol task consists of four row containing 100 small blank squares, each paired with randomly assigned numbers from one to nine (229). Above these rows is a printed key that pairs each number with a different nonsense symbol. The patient will practice on the first seven squares, the patient is then given a total of 90 second to fill in as many squares as possible. The score is the number of squares the patient managed to complete within the 90-second time limit.

The Digit Symbol test is a test of psychomotor speed that is quite unaffected by education, memory or learning in most adults. The Digit Symbol test also requires sustained attention, visuomotor attention, response speed and motor persistence all under time pressure. In addition patients that learn the number-symbol association fast will have a higher performance.

Color-Word Interference Test Condition 1 & 2

The color-word interference test Condition 1 & 2 is a test of processing speed, selectivity and word finding capacity (37). Condition 1 requires the patient to name 50 different squares in red, blue or green as fast as possible and is therefore a measure of the patient's ability to name high-frequency words (i.e. colors). The second condition evaluated the patient's ability to read high-frequency, repeating words (red, green and blue) as quickly as possible. For both conditions the completion time is recorded and transformed into scaled scores.

Trail Making Test Conditions 1, 2 & 3

The trail making test Condition 1, 2 & 3 are tests of visual attention and scanning abilities, as well as basic number and letter sequencing abilities and motor functioning (37). The tests consist of A3 size sheets of paper with both number and letters scattered around the page. In the first visual scanning condition the patient is required to find and cross out all of the number 3's as fast as possible. The second condition requires the patient to connect the numbers (from 1 to 16) in ascending sequence and the third condition connects the letter (from A to P) as fast as possible. For all conditions the time to complete is recorded.

Intellectual functioning

Verbal functioning/language

Vocabulary

The Wechsler Abbreviated Scale of Intelligence (WASI-R) vocabulary test consists of 40 words to be defined (228). The words are listed by order of difficulty (from "fish" to "panegyric" in the Norwegian version). Among the WASI-R subtests "Vocabulary" is recognized as the strongest measure of a G factor ("general intelligence") and as showing the highest correlation with the overall IQ score. It is also primarily considered a good measure of verbal comprehension and it generally shows little deterioration with normal aging. It should also be noted that performance on "vocabulary" is however highly related to socioeconomic level, amount of schooling and verbal experience. The test is discontinued after four consecutive errors.

Similarities

The WASI-R similarities test consists of 13 orally presented items that test the patient's verbal concept formation (228). The patient's task is to name a similarity between the two words read out loud by the examiner, preferably the closest common denominator. The level of difficulty increases gradually throughout the test. The test is discontinued after four consecutive errors.

Visuo-spatial functioning

Block Design

The Block Design is a construction test where the patient is given either four or nine blocks (depending on the item) and is asked to construct copies of different designs within either 60 or 120 seconds (228). Each block has two white and two read sides, and two half-red half-white sides with the colors divided along the diagonal. The first items are scored only depending on whether or not the patient is able to make the design. In the remaining items more points are earned the faster the patient can complete the design.

Matrices

The Matrices test consists of pictures that create a certain pattern, but with one piece missing (228). The patients' task is to choose the missing piece from five possible answer choices. The patterns get increasingly more difficult and the test is discontinued after four consecutive errors or after four errors in the last five answers.

Executive functioning

Color-Word Interference Test Condition 3 & 4

The color-word-inference test Condition 3 & 4, measure the strength of controlled information processing in relation to the strength of automatized processing by assessing susceptibility for interference, cognitive flexibility and inhibition (37). Condition 3 requires the patient to inhibit the automatic reading process in favor of naming the inconsistent color of the ink the word is printed in. Condition 4 requires the patient to switch between naming the ink color and actually reading the word which is printed. The times to complete the tasks are recorded.

Trail Making Test Condition 4

The Trail Making Test Condition 4 is a measure of cognitive flexibility (37). To successfully complete the task the patient must alternate between letter and number sequencing (i.e. A-1-B-2-C-3 etc.) as fast as possible. The time to complete is recorded.

Verbal Fluency Test

The verbal fluency test measures a number of mainly left sided frontal (and temporal) lobe functions including initiation, simultaneous processing, systematic retrieval of phonemically similar lexical items, words from a high-frequency semantic category and simultaneous retrieval from semantic knowledge and cognitive flexibility in shifting between two semantic categories (37). The first task requires the patient to generate as many words they can within a 1 minute time period on a give letter (F, A, S) , on the second task the patient need to generate words from a semantic category (animals and boys names) also within a 1 minute period. The final task has an added switching component to access the cognitive flexibility ability by asking the patient to alternate between naming fruit and furniture also within a one minute timeframe. The numbers of correct answers are reported.

Design Fluency Test

Design fluency test measures non-verbal component skills such as basic visual attention, motor speed, visual-perceptual skills and constructional skills, in addition to initiation of problem solving behavior associated mainly with damage to right frontal areas (37). The test requires the patient to construct a number of different figures using four straight lines connecting either structured or unstructured dots within one minute. This test also has three different conditions with increasing degree of difficulty the last condition also has a switching

component to access the cognitive flexibility ability in a non-verbal setting. The numbers of correct designs are counted.

Sorting Test

The sorting test consists of two conditions, a free sorting condition and a sort recognition test (37). In the free sorting condition the patient is presented sic mixed-up cards that display both perceptual features and printed words. The patient is then asked to sort the cards into two groups with three cards in each group, according to as many different concepts as possible, and to describe the concepts used to generate each sort. Each of the two card sets has a maximum of eight sorts (five based on visuo-spatial features and three based on semantic information. In condition 2, the examiner sorts the same card sets in two groups each containing three cards according to the eight target sorts. After each sort the patient is required to identify and describe the correct concepts used to generate the sorts. The patient's responses are scored on both accuracy of both the sorting responses and the description of the sorting concepts. The Sorting test measures a variety of executive functions but mainly initiation of problem-solving behavior, creativity in forming both verbal and non-verbal concepts, flexibility in switching between concepts and transfer of conceptual knowledge into-goal directed behavior (37).

For all neuropsychological tests, raw scores are transformed into scaled scores based on published norms for each test.

3.2.3.3 Health Related Quality of Life Questionnaires

GHQ-30

The General Health Questionnaire (GHQ) is a 30 item self-administered screening test, designed to identify short-term changes in mental health (depression, anxiety, social dysfunction and somatic symptoms) (63). The respondents are asked to evaluate how much they feel that their present state "over the past few weeks" is unlike their usual sate. The GHQ therefore focuses on the client's ability to carry out "normal" functions and the appearance of any new disturbing phenomena. GHQ-30 provides subscales on anxiety, depression, well-being, coping and social functioning, as well as Likert, chronic and case scores. GHQ-30 is scored on a 0-3-point Likert scale (0 = not at all, 1=not more than usual, 2=more than usual, 3=a lot more than usual). The Likert score is the sum of all items, giving a possible score

range of 0-90, with higher scores indicating that the patient have mostly answered "more than usual" or "a lot more than usual" (i.e. poor HRQOL). The anxiety, depression, well-being, coping and social functioning subscales on GHQ-30 are calculated using the total score for the items belonging to the subscale divided by the number of questions (for example social dysfunction = [(Questions5+10+11) / 3]), a high score on these sub-scales therefore indicates poor HRQOL.

SF-36

SF-36 is based on the Medical Outcome Survey and is the most commonly used Health Related Quality of Life questionnaire (226). SF-36 provides subscales on physical functioning (10items), role physical (4 items), bodily pain (two items), general perception of health (five items), vitality (four items), social functioning (two items), role emotional (three items) and mental health (five items). On SF-36 the subscales have scores ranging from 0 to 100, with 100 indicating optimal HRQOL and 0 indicating poor HRQOL.

3.3 Data analysis

All levels of significance were calculated based on raw-scores. Due our results not being normally distributed non-parametric tests (Mann-Whitney) were used to calculate the levels of significance. We report $p<0.05$ and $p<0.01$, but in some instances results that show a trend towards significance (i.e., $p<0.1$) are also reported. Further all normed neuropsychological test results were converted into and reported as z-scores (mean 0 ± 1) for easier comparisons. A *z-score* represents the distance between the tests raw score and the population mean in units of the standard deviation (i.e. $z= x - \mu/ \sigma$ where x is a raw score to be standardized; μ is the mean of the population and σ is the standard deviation of the population. The *z-score* is negative when the test raw score is below the mean, positive when above. Effect sizes, which measure the magnitude of a treatment effect by stating the standardized difference between two means, are also reported. As an effect size we used Cohen's d (28), defined as the difference between the means, M1 – M2, and divided by the standard deviation, σ, of either group. ($d = M1-M2/\sigma$ where $\sigma = \sqrt{[\sum(X-M)^2/N]}$ where X was the raw score, M is the mean and N is the number of cases). An effect size of d =0.2 is defined as small, d=0.5 as medium and d=0.8 as large. Statistical analysis was conducted according to the procedures of SPSS 13.0 or 15.0 for Windows.

3.5 Ethics

The study was approved by the Regional Ethics Committee and the Privacy ombudsman at Rikshospitalet University Hospital. Written and oral informed consent was obtained from all the included individuals.

4 SUMMARY OF PAPERS- MAIN RESULTS

4.1 Paper I: COGNITIVE OUTCOME AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE: TIME-COURSE OF COGNITIVE RECOVERY AND RELATIONSHIP TO CLINICAL, RADIOLOGICAL AND MANAGEMENT PARAMETERS.

Even though many patients show a satisfactory physical outcome after aneurysmal subarachnoid hemorrhage (SAH), disabling cognitive dysfunction may still be present. This study focused on the time-course of cognitive recovery during the first year after aneurysmal aneurysmal SAH, and related the neuropsychological test results to clinical, radiological and management parameters. Thirty-two patients were followed prospectively with neuropsychological examinations 3, 6 and 12 months after aneurysmal SAH. Test results were compared with clinical entry variables, management variables as well as pre- and post-operative radiological findings.

The results showed a mild to moderate cognitive deficit at 3 months but an overall improvement towards 12 months. However, the time-course of cognitive recovery after aneurysmal SAH was heterogeneous, with motor functions convalescing within the first 6 months. Grooved pegboard was significantly reduced bilaterally at 3 months, but showed a significant improvement at 6 months ($p<0.01$) and remained stable at 12 months. On the other hand, verbal memory did not improve significantly until at least 6 months after the ictus. CVLT-II total learning and long-term memory both showed significant improvement from 6 to 12 months ($p>0.001$) but no improvement from 3 to 6 months. Clinical and radiological parameters reflecting the impact of the bleed were related to memory function, intelligence and aphasia. The site of aneurysm and mode of treatment could not be linked to neuropsychological outcome. The time length of volume-controlled mechanical ventilation as a indicator of the aggregated consequences of being subjected to an aneurysm rupture correlated with both motor- and psychomotor functioning and memory performance predominantly 6-12 months after aneurysmal SAH.

We therefore concluded that the various cognitive functions have different time-courses of recovery with verbal memory requiring the longest time. Further, parameters reflecting the impact of the bleed and patient management can be linked to neuropsychological outcome.

4.2 Paper II - COGNITIVE FUNCTIONING AND HEALTH RELATED QUALITY OF LIFE AFTER RUPTURE OF AN ANEURYSM ON THE ANTERIOR COMMUNICATING ARTERY VERSUS MIDDLE CEREBRAL ARTERY.

The cognitive functioning and HRQOL after aneurysmal SAH have largely been believed to be unrelated to the location of the ruptured aneurysm. However, this notion needed verification because in the recent years, the management of aneurysmal SAH patients has enhanced with refined techniques during aneurysm surgery and the introduction of endovascular techniques for aneurysm repair. The general outcome may therefore have improved and the aneurysm specific impact on neuropsychological outcome may emerge clearer. Moreover, we have in recent years also seen a development of better neuropsychological test batteries investigating frontal lobe functioning. We therefore investigated patients with ACoA and MCA aneurysm rupture in clinical condition Hunt & Hess grade I-III using a comprehensive neuropsychological test battery with special emphasis on memory and executive functions one year after the ictus. We wanted to investigate if ACoA patients would display a specific pattern of deficits consistent with potential frontal lobe pathology. Further, we also included self reported HRQOL and data on return to work in the two subgroups of aneurysmal SAH patients. We found a trend towards a poorer Hunt & Hess grade immediately after the ictus in the patients with a MCA aneurysm ($p=0.059$) but otherwise the two patients groups were similar in clinical outcome at 12 months in terms of mRS score and GOS. Further, there were no significant differences between the two groups on AES-C and MADRS, with the means for both groups below the cutoff values indicating clinically significant presence of apathy and depression, respectively. There were no significant differences in HRQOL between ACoA and MCA patients as evaluated with the SF-36 and GHQ-30 questionnaire. Compared to norm both groups scored significantly lower on a number of measurements. Only about half of the patients in both groups employed full-time prior to their aneurysmal SAH returned to a full-time position. In the MCA group most of the patients not returning to their full-time position had a part-time position 12 months post-aneurysmal SAH while in the ACoA group five patients previously employed full-time

were still on sick-leave 12 months post-aneurysmal SAH. Almost all scores on the neuropsychological tests were within 1 SD of the population mean indicating that patients with ruptured ACoA or MCA aneurysms in clinical condition Hunt & Hess grade I to III did not develop extensive cognitive deficits. We observed slight reductions on the first conditions on the D-KEFS tests, and some measures of memory functions in the ACoA patients. We interpreted these findings as ACoA patients seemingly having problems with initiation of problem solving behavior consistent with a medial frontal lobe pathology, which may explain the special apathy reminiscent behavior often observed in these patients. Our results further showed the value of choosing neuropsychological tests that are specific and sensitive enough to uncover subtle changes in cognitive function after aneurysmal SAH.

4.3 Paper III- SURGICAL REPAIR OF UNRUPTURED AND RUPTURED MIDDLE CEREBRAL ARTERY ANEURYSMS: IMPACT ON COGNITIVE FUNCTIONING AND HRQOL.

In order to assess the impact of surgical treatment of unruptured and ruptured MCA aneurysms on cognitive functioning and HRQOL we prospectively enrolled fifteen patients with unruptured and 22 patients with ruptured MCA aneurysms in post-ictal clinical good condition. Patients with unruptured aneurysms underwent pre-operative neuropsychological testing and answered two HRQOL questionnaires. Both patients with ruptured and unruptured aneurysms were investigated three and twelve months post-operatively, using a comprehensive neuropsychological test battery, clinical investigation and interview assessing the mRS scale, GOS, employment status, and two HRQOL questionnaires. Pre-operative cognitive deficits were aggravated three months after surgery for the unruptured MCA aneurysm group, but after twelve months these patients performed at their pre-operative level. Subjects clipped for ruptured MCA aneurysms had reduced verbal memory twelve months post-operatively, otherwise close to normal cognitive functioning. There were no difference in mRS score or GOS between the two groups. High pre-operative levels of anxiety and depression markedly decreased after repair of an unruptured aneurysm, however, in both groups HRQOL were reduced on the same measures even twelve months after surgery. Patients treated for unruptured MCA aneurysms regained their pre-operative employment status, whereas only 60% of those that had bled from their aneurysm had returned to full-time work after twelve months**.**

We therefore concluded that surgical clipping of an unruptured MCA aneurysm did not cause new cognitive dysfunction. Patients with ruptured MCA aneurysms that were in a

post-ictal good clinical grade had only reduced verbal memory twelve months after surgical aneurysm repair. Although high pre-operative levels of anxiety and depression are resolved by surgery, both the patients with unruptured and ruptured aneurysms report decreased HRQOL on the same measures even one year after surgery. Despite of a reduced HRQOL, patients treated for unruptured MCA aneurysms regained their pre-operative employment status, whereas only 60% of those that had bled from their MCA aneurysm could return to full-time work after twelve months.

4.4 Paper IV- COGNITIVE FUNCTIONING AND HRQOL ONE YEAR AFTER ANEURYSMAL SAH IN PATIENTS IN PREOPERATIVE CLINICAL CONDITION HUNT & HESS GRADE V.

Improved management of aneurysmal SAH patients has raised the frequency of survivors among the patients in clinical condition Hunt and Hess grade V, but their cognitive functioning and HRQOL have not been accurately described.Thirty five (50%) of 70 patients in clinical condition Hunt & Hess grade V managed with urgent aneurysm repair and maximum medical treatment were alive one year after ictus, of whom 26 underwent neuropsychological testing. Two distinct patient groups were identified. A cognitively well functioning group of 14 patients with mainly mild cognitive deficits (i.e. scores mostly around 0.5 SD below population mean) and a cognitively poorly functioning group of 12 patients with more severe cognitive deficits (i.e. a number of scores falling more than 2SD below the population mean). In the cognitively poorly functioning group the deficits were especially large in motor functioning, as well as verbal and visual memory. Individuals of the cognitively well functioning group were younger ($p=0.04$), had more years of education ($p=0.005$) and smaller preoperative ventricular sizes (III-ventricles ($p=0.004$), cella media ($p=0.001$) and ventricle score ($p=0.020$) than the patients in the cognitively poorly functioning group. Clear, but not as distinct differences between the two groups were found in mRS and GOS. In terms of HRQOL, only SF-36 physical functioning was significantly different between the groups. Compared to mean the group as a whole scored significantly lower on SF-36 Role Physical and General Health. Separated into the cognitively well and poorly functioning groups, the 14 patients in the cognitively well functioning group scored significantly lower only on SF-36 General health ($p=0.001$) and SF-36 Role Emotional ($p=0.04$) compared to the population mean. In the 12 patients in the cognitively poorly functioning group SF-36 Physical functioning ($p=0.04$), SF-36 Role physical ($p=0.004$) and SF-36 General health ($p=0.001$) was significantly reduced. Only SF-36 Physical functioning

(p=0.03) was significantly different between the cognitively well and poorly functioning groups.Work status and living status showed that in the cognitively well functioning group only about 20% of the patients had returned to a full- or part-time position, and in the cognitively poorly functioning group only one patient (8.33%) had been able to return to work.

We therefore concluded that approximately half of the patients in clinical condition Hunt and Hess grade V that survived an aneurysmal SAH had relatively intact cognitive functions, but likely somewhat reduced compared to pre-aneurysmal SAH functioning. The patients with poor cognitive functioning had especially large problems with memory and motor functioning; they were however physical independent. Age, years of education, and preoperative ventricular sizes are important prognostic factors for cognitive functioning of the preoperative deeply unconscious individuals one year after an aneurysmal SAH.

5. DISCUSSION

5.1 METHODOLOGICAL ISSUES

5.1.1 Sample size and Statistical Significance

Clinical research is time-consuming and resource exhausting so gathering a large enough sample size is challenging. Research on aneurysm patients is also limited by the fact that there were limited numbers of patients available, so even though we gathered data over quite an extensive time interval it proved to be difficult to gather large sample sizes. Our studies were therefore largely based on patient groups of between 20-35 individuals, which we estimated would be sufficient. We did however get quite a few correlations that were significant only at the 0.1 level suggesting that our groups preferably could have been somewhat larger. Small sample sizes are susceptible to extreme highs or lows making analysis difficult. To adjust for the relatively small sample sizes we used statistical analyses (Mann-Whitney test) that were not based on a large number of co-variates and hence not requiring an extensively large sample size. Overall one should still be careful when evaluating data based on small sample sizes especially if statistical analyses were used that does not allow calculations on small sample sizes. Further, since our data proved largely not to be normally distributed a non-parametric test (Mann-Whitney test) was used. All statistical analysis on neuropsychological test results was based on raw-scores to avoid the possible error made when converting to scaled scores which are based on raw-score intervals. Further, the degree of cognitive impairment was based on scaled scores compared to norm in order to have a

standardized reference. An advantage for all our studies is that all patients were continuously collected from the same department and hence there were no selection bias.

5.1.2 Control groups and Study Comparisons

The use of a suitable control group is essential in clinical research. In two of our studies (Study I and Study IV) we compared the neuropsychological test-results to published norms for each neuropsychological test. This might however have been a source of error since these often only are adjusted according to age and not to gender and education, but as already mentioned our results seem to be comparable to other aneurysm research. Thus, suggesting that the results on the levels of cognitive deficits after an aneurysmal SAH are believed to be valid. Further, a possible problem with interpreting the neuropsychological test results is that there are few Norwegian norms available on these tests. To address this problem research conducted in association with translating the tests to Norwegian (37) has shown that the Norwegian population is comparable to the American population and hence it is not believed that there are any large biases.

For our other two studies we have compared different groups of aneurysm patients (Study II and Study III) which also might cause some methodological problems: First of all there is no consensus as to whether or not there are any qualitative differences between different aneurysm sites, hence making direct aneurysm group comparisons difficult. Secondly, studies comparing different aneurysmal SAH groups have shown differences in neuropsychological test results between groups relative to the published norms despite a few differences between tests at different points in time. This might suggest that studies comparing mean performances in patients with published norms may overestimate the effect of aneurysmal SAH. Therefore the perhaps best control group in our studies would be the UIA patients which allow us to separate the effect of the surgery and the damage of the aneurysm rupture.

Comparing results from different studies on cognitive function after aneurysmal SAH is also difficult since there are major differences in patient selection between the different studies. Some studies (for example 120, 195) excluded patients with transient or permanent focal neurological deficits, other studies included only good outcome patients (17, 80, 211), while some studies have included patients non-aneurysmal and unoperated aneurysmal SAHs (132) and finally some have excluded older patients (132).

5.1.3 Patient inclusion and Test administration challenges

In all clinical research one will encounter patients that for different reasons are not willing to participate. It has been speculated that these patients may have more severe deficits (84). Fortunately, we do not have a large non-participation rate in our studies. The majority of patients not included in our studies were hence excluded due to medical complications or because they were untestable. Very few thus refused participation. Further, a related problem that might have affected our results is the possible confounding effect in the UIA patients which were tested that day before surgery. These patients might have been anxious or lacking concentration due to the thought of the pending operation. Our experience does not however support this hypothesis since the majority of patients did not show extensive concentration problems and many experienced being calmer the day before surgery because they knew the waiting period was over. In addition, we believe the increased anxiety and depression as reported on the HRQOL questionnaires reflects the "last few weeks" as specified in the instructions on the questionnaires. The patients with ruptured aneurysms, on the other hand, could have other issues that might have affected their performance. For the entire group tiredness seemed to be the major problem. The patients often had a wide range of examinations they went though when they came to their control at the hospital (for example CT/MR, neurological examination, clinical evaluation by the nurses) and a 2 to 3 hour long neuropsychological testing session was therefore in a few instances difficult to complete. However, this was mainly the case among the poorest functioning patients. To alleviate this problem we tried to adjust the number of tests taken and give the patients as many breaks as they needed to complete the testing. In some cases it was also necessary to do the testing on two separate days. Finally, it was also a problem that pre-aneurysmal SAH data was not available for the aneurysmal SAH patients. It was therefore difficult to evaluate whether especially the mild or moderate cognitive deficits reflected a true reduction or a patients pre-morbidly reduced level of functioning, or if it was a much greater reduction if the patient functioned at a higher than average level prior to the aneurysmal SAH. However, considering the age, educational level and lack of previous neurological deficits in our patient groups there is little reason to believe their pre-SAH cognitive functioning should be below the population mean.

The two subgroups of aneurysmal SAH patients we expected would be most difficult to get reliable results from are the extremely cognitively poorly functioning patients (i.e. clinical condition Hunt & Hess grade V) and ACoA patients. With regard to the cognitively poorly functioning patients it could be difficult to get a realistic picture of their functioning

since many had very poor functioning (i.e. they had very few or no correct answers on many tests) and hence it was difficult to complete an entire test-battery. We therefore tried to use some abbreviated versions of the tests (for example CVLT-II short form) where necessary. In addition, these patients were easily distracted and were easily tired, making testing difficult. With AcoA patients the major problem was often lacking of insight into their own problems due to frontal lobe damage and hence under-reporting their problems. To alleviate these problems relative information was essential and whenever possible we thus interviewed the relatives to confirm the information given by the patient.

Finally, a methodological problem possibly affecting our results is our decision to include only clinical condition Hunt & Hess grade V patients while other research has included both clinical condition Hunt & Hess grade IV and V in their studies. The reason for only including clinical condition Hunt & Hess grade V in our study was that patients in clinical condition Hunt & Hess grade IV is always treated at our department but it greater uncertainty regarding whether or not to treat clinical condition Hunt & Hess grade V patients. Our goal was therefore to take a closer look at the outcome of just the clinical condition Hunt & Hess grade V patients without the interfering effect and often better prognosis seen in clinical condition Hunt & Hess grade IV patients, but as a result comparions with other studies was difficult.

5.1.4 Test choices and Levels of Deficits

In neuropsychology the choice of tests are many and hence the tests used may differ from study to study. To alleviate this problem we largely used the same tests in all our studies, but we also had to adjust the test battery some of the studies due to the patients level of functioning. In our studies we also used tests that are well known in the neuropsychological literature and have established norm material, but also included new tests that are believed to be more sensitive to for example frontal lobe functioning. Despite these potential methodological problems of choosing different test in different studies research has consistently shown that neuropsychological evaluations gives a more detailed and correct outcome measure than other clinical outcome measures such as GOS and mRS.

Another issue which is substantially discussed in the neuropsychology literature is the definition of what constitutes as a cognitive deficit. We have classified the deficits as mild if the scores fell between 0 to -0.5SD, moderate from -1 to -2SD and severe below -2SD. Although this might be the most commonly used classification there is no general consensus

in the literature suggesting this being the most "correct" classification since the level of deficiency may affect each individual differently based on pre-morbid level.

Similarly, the choice of HRQOL questionnaires and their ability to give an accurate measure of HRQOL has been subject for debate. Stroke illnesses, under which aneurysmal SAH also can be classified, is among the diagnoses that have been studied the most in relation to HRQOL (with over 2000 references in pubmed). HRQOL scales such as SF-36 and GHQ-30 have in a number of these studies shown satisfactory validity and reliability and are generally believed to be suitable for descriptive examinations and group-comparisons in our patient group. We therefore included these questionnaires as measures of HRQOL in all our studies. The SF-36 also has a Norwegian norm material, making it a suitable instrument for our studies. However, it is also important to remember that on any self-report questionnaires the patient's insight into their own functioning might be limited in some poorly functioning or frontal patients and hence the reported level of HRQOL might not be accurate.

5.1.5 Reliability/Validity and Retest issues

The test we used in our studies are established test that are believed to have good reliability and validity (i.e. it is believed to measure the characteristics being measured, rather than being influenced by chance errors). However, external factors such as the patients' motivation, temporary fatigue and fluctuations in the patient's attention and mood must always be considered when evaluating neuropsychological test results.

A reliability of a test is most often computed in terms of a correlations between two scores obtained a tests at different points in time or alternate versions of the test. Test-rest reliability is an important question and should therefore be discussed. Generally, the higher the test-retest reliability, the less susceptible the test is to random changes in the patient's state or the testing environment. Retest effects as a result of repeated testing causing a learning effect over time is therefore an issue which must be considered (131). There it relatively little consistent research on re-test effects but overall there seem to be an agreement that the retest effect varies for different tests and different diagnoses. To our, knowledge no test-retest reliability have been made on aneurysm patients, but there are some studies with repeated testing on other cerebrovascular diagnoses and traumatic brain injury patients that may apply to aneurysm patients (131). Unfortunately these vary significantly not only according to patients included but also which tests are used and do therefore not give a definite answer to the question regarding the retest effects. A recent study found an overall effect size of 0.26 across 107 samples on retest effect (70) suggesting that although there is a retest effect but it

is relatively mild. In an attempt to alleviate some of the retest effect we have therefore used alternate versions whenever possible and have included control groups, but the fact that some of our tests were only 3 months apart may have influenced our results. On the other hand, our results are comparable to other neuropsychological studies which tested only at one point in time. This suggests that the levels of deficits obtained in our studies are representative for the aneurysm population.

5.2 MAIN RESULTS DISCUSSION

Previous research on cognitive deficits after aneurysmal SAH has shown that there are mild to moderate cognitive deficits mainly affecting memory and motor functioning after a "good outcome" (i.e. GOS 4-5). Our results support these findings both though group norm comparisons. In an attempt to take this research a step further we investigate more specific research questions regarding the global or focal damage caused by an aneurysmal SAH, the improvement in cognitive functioning over time, the impact of surgery on cognitive functioning and finally the impact a clinical condition Hunt & Hess grade V after an aneurysmal SAH on cognitive functioning and HRQOL.

5.2.1 What is the rate of recovery in cognitive function after aneurysmal SAH? Are the cognitive deficits seen after an aneurysmal SAH caused by a diffuse cerebral damage or a focal damage at the site of the aneurysm? What is the effect of medical and radiological parameters on cognitive functioning?

In agreement with a number of other studies (164) our research show a mild to moderate cognitive deficits in aneurysmal SAH patients in good outcome (GOS 4-5). Memory, concentration and motor function seemed to be mostly affected while intellectual functioning seemed to be relatively unaffected by the aneurysm rupture. The reason for the unaffected intellectual functioning is most likely due to intellectual functioning being a more stable cognitive function in the case of a mild general cerebral damage. Support for this hypothesis can also be found in the traumatic brain injury literature (48, 97, 106, 125), which is believed to cause somewhat similar damage as a aneurysmal SAH (78).

We found different patterns of improvement in cognitive functioning in our patients, with motor functioning improving rapidly during the first 6 months while memory functions first improved after 6 months. At the present time, few other studies have looked at cognitive improvement at more than two points in time so more research is needed to confirm our hypothesis. Our findings do however concur with clinical observations and, if proven to be

correct, should have an impact on rehabilitation in these patients. The major rehabilitation focus during the first 6 months should be on physical training and after 6 months cognitive training should be emphasized. One should keep in mind that our results might be influenced by retest effects since the tests were done at such close intervals but since little research has been done of retest effects in aneurysm patients and the retest effect varies between tests it is difficult to evaluate how much this influences our results.

Our results support the notion that aneurysmal SAH cause a more diffuse cerebral damage rather than a localized damage at the aneurysm site although we did find some problems specific to ACoA aneurysms which will be discussed later. We also found support for the notion that it is the aneurysmal SAH itself that causes the cognitive deficits rather than the treatment. This conclusion is based fist of all on the correlations found between the acute medical variables (for example acute hydrocephalus, and time on ventilatory support) and cognitive functioning, and secondly based on failing to find many significant differences between the UIA and aneurysmal SAH patients suggesting that the treatment itself does not cause any additional damage. It therefore seems like the ceasing of circulation and the damage caused by the blood entering into the brain at the time of the aneurysm rupture (for example haematoma and blocking CSF pathways causing hydrocephalus) may be the major causes for cognitive dysfunction.

5.2.2 Are there differences in cognitive functioning after ruptured MCA and AcoA aneurysms?

Although our research largely points towards an aneurysmal SAH causing a general cerebral damage, we did find evidence suggesting that the damage an ACoA aneurysm to the frontal lobes may result in some special behavioral and cognitive challenges for these patients.

Overall, we found few differences between the ACoA and MCA group on many measures of cognitive functions, including executive functions such as inhibition or cognitive flexibility. This lack of significant deficits on executive functions in patients with aneurysmal ACoA bleed could possibly be explained by the highly structured nature of the test situation helping them use their cognitive resources better, thereby improving their performance. It could also be that the dorsolateral areas associated with executive functions are spared when there is an ACoA rupture but no studies have looked specifically at these hypotheses.

In our study, we did however find a consistent pattern of results on the D-KEFS tests and some measures of memory in the ACoA patients interpreted as impaired initiation of problem solving behavior consistent with basomedial frontal damage. The ACoA patients had

consistent significantly or borderline significantly poorer results on the first easier conditions on each D-KEFS test, but performed as well as the MCA group of patients on more complex tasks of executive functions. Similar results indicating problems with initiation of problem solving was also seen on memory tests, although not as vividly as on the D-KEFS tests. Similar results were also found by Alexander (3) who reported that patients with frontal damage showed slow improvement in learning across trials on CVLT-II but performed fairly normal by trial 5 and in delayed recall.

Further, seven of the ACoA patients also scored well below the mean on the D-KEFS subtest and five of these had visible frontal medial damage on CT-scans. Further, there were no consistent pattern of correlations between the AES-C, MADRS, GOS or mRS and the neuropsychological test results. Compared to the MCA group the ACoA patients were not scored as more depressed on MADRS or had higher scores on apathy on AES-C. Similarly there were no differences between the groups on any of the subscales on SF-36 or GHQ-30. Therefore, despite their subjective description of lack of energy and loss of motivation the ACoA patients were neither scored as depressed or having apathy by the interviewer or rated themselves as suffering from depression or apathy on the questionnaires. Our results we suggested that rather than a pure psychomotor deficit or emotional change in terms of apathy or depression, there may be a general decrease in initiation of a novel task among the ACoA patients. These results are however preliminary and need to be investigated further.

As described earlier it is also believed that ACoA patients have confabulation problems caused by damage to inferior medial prefrontal systems (either orbital or anterior cingualte) rather than pure amnesia problems (216). Our results from the ACoA patients seem to support this hypothesis, since we found an elevated number of false positives on both CVLT-II and CVMT. These findings might also be linked to medial frontal lobes involvement since the medial frontal lobes are believed to be involved in conflict and error processing (61, 209).

An important distinction which has not been studied is the direction of the ACoA aneurysm (i.e. if the aneurysm fundus projects in front of the axis formed by the pericallosal arteries or if the fundus projects behind this axis) and its impact of cognitive functioning (158). According to Vander Ark (218) 70% of ACoA aneurysms projects inferiorly and 30% superiorly, making it difficult to collect a large enough sample of aneurysms projecting superiorly. Our sample was also too small to do any statistical analysis but it was interesting to note that three out of four patients in our sample, which had an ACoA aneurysm pointing in a posterior direction, were among the patients with both visible frontal basomedial damage on

CT and excessively low scores on D-KEFS. It might therefore be interesting to look closer at this distinction in the future.

Overall, our results in this study are based on small sample sizes and must therefore be interpreted cautiously, but it is interesting to note that in addition to the results already reported poining towards ACoA patients having problems with initation of problem-solving behavior, they there is a also a difference in the ability to return to work. ACoA patients seem to stay longer on sick-leave compared to MCA patients, which also might reflect an inability to initiate problem-sloving behaviors and hence greater difficulty returning to work, but as already pointed out these results are preliminary and hence need to be studied further.

5.2.3 Does elective treatment of Unruptured Intracranial Aneurysms affect cognitive functioning?

Our research showed that the elective surgical treatment of an unruptured MCA aneurysms did not cause any substantial damage to cognitive functions (i.e. patients that underwent surgical clipping of an UIA MCA aneurysm had cognitive performance at their pre-operative level after twelve months). It should, however, be mentioned that there was a trend towards (significant at the 0.1 level) the UIA patients having a transient reduction in memory functions at 3 months, which subsequently improved to the pre-operative level at 12 months. The results for the ruptured MCA group were also largely consistent with previous research showing a mild to moderate cognitive deficit at three months but close to normal functioning at twelve months, but no pre-morbid data exists for this groups making it difficult to evaluate the degree of reduction in function. Further, due to our relatively small sample size the study should be replicated using a larger sample size.

In terms of HRQOL, both groups reported reduced HRQOL possibly reflecting the psychological consequence of suffering from a life-threatening disease. This becomes most obvious on the pre-operative very high scores for anxiety and depression in patients with unruptured MCA aneurysms and subsequent normalization of these scores three months after clipping. One could argue that the proximity of the testing to the operation (one day prior to surgery) utterly increased the anxiety and depression levels. However, our experience is that their extreme fear of having an aneurysm rupture actually had subsided somewhat the day before surgery since they knew they were about the have the threat removed. Further we would also expect decreased concentration problems on the neuropsychological tests if the patients had been extremely anxious or depressed, but few patients showed any extensive concentration problems. In addition, we believe the reported high levels of anxiety and

depression on both SF-36 and GHQ-30 correctly reflects the wording on the questionnaire which specifically state that the patients should consider the last few weeks when answering each item. It is also interesting to note that even though patients with a ruptured MCA aneurysm reported similar HRQOL, the psychosocial impact after having suffered an aneurysmal SAH was much larger in that only 60% of them had managed a return to full-time employment after one year. This may therefore suggest that the impact of an aneurysmal SAH is much greater than elective surgery of an UIA even if the aneurysmal SAH is classified as having a "good outcome" and few cognitive deficits are seen.

5.2.4 How does clinical condition Hunt & Hess grade V after an aneurysmal SAH affect cognitive functioning?

A clinical condition Hunt & Hess grade V after an aneurysmal SAH may cause significant decrease in cognitive functioning, but the differences in the degree of the deficits are reflected in the patient's pre-aneurysmal SAH functional level. We found that younger patients with many years of education showed mild to moderate cognitive deficits one year post-aneurysmal SAH. This levels of cognitive deficits is however believed to be decline compared to their pre-aneurysmal SAH functioning which most likely was at or above the norm. On the other hand, older and less educated patients fell in the cognitively poorly functioning group and hence were left with few cognitive resources after their aneurysmal SAH. There were significant age differences (median ages 46 versus 52 years) between individuals of the cognitively well functioning and cognitively poorly functioning groups probably reflecting the better ability of a younger brain to functionally recover after a devastating blow such as an aneurysmal SAH.

One may therefore speculate that a younger person that has undergone a longer time period of cognitive training (i.e. years of education) has a better ability to regain his or her cognition after a devastating blow to the brain, but it is also possible that being younger and better educated they could possibly have scored better if similar cognitive testing prior had been carried out prior to ictus; i.e. a difference in cognition could have been present even before the ictus.

Further by comparing results from all our studies on selected neuropsychological variables (see figure 9), we see that the cognitively well functioning group among the clinical grade Hunt & Hess grade V patients show cognitive deficits that are comparable with patients

with UIAs and patients with an “good outcome” (GOS 4-5), while the cognitively poorly functioning group are show more severe cognitive deficits.

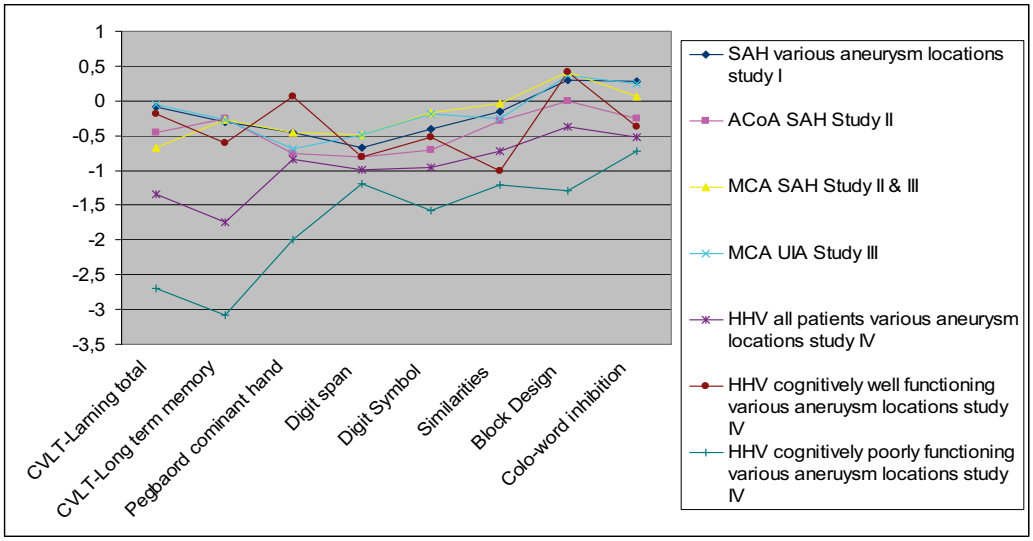

Figure 9: Comparison of selected neuropsychological test results across all four studies.

Of all the pre-, intra-, and early postoperative medical parameters, the only significant difference between the two groups were that the neuropsychological poor functioning group had larger preoperative ventricular scores on preoperative CT scans. In contrast, the ventricular scores of the two groups were similar early postoperatively and at one year follow up. This, for us unexpected, difference in preoperative ventricular score, may indicate that periventricular tissue, i.e. the fornix, of the subjects of the poor functioning group were exposed to a larger degree of acute pressure and stretching preoperatively, but not postoperatively, than that of the neuropsychological good functioning group. This may then have resulted in more damage to the periventricular area and thus poorer functioning of especial of tissue located in this area. With the close anatomical relationship between the memory pathways of fornix and the ventricular walls this could lead to especial large differences in memory functioning between the two groups, such as those observed in our study.

We found no major different in self- reported HRQOL between the patients which also possibly support the notion that although one patient group seemingly have mild cognitive deficits they still experience significant reduction in functioning. This might be explained by the well functioning patients also experiencing marked reductions in HRQOL compared to their pre-SAH functioning despite having recovered a significant portion of their cognitive functioning and having returned to work. The poor functioning patient group did however report more problems with social functioning and well-being, which might partly be the result of not having returned to work to the same extent as those of the cognitively well functioning group.

We also found differences between the two groups in terms of work-status both pre- and post-SAH. All patients in the good functioning group were in a full time position prior to their SAH, and half of them had returned to work in either full- or part-time positions one year after SAH. In the poor functioning group two-thirds of the patients were in a full- or part-time position pre-SAH but only one patient had been able to return to a part-time position one year after SAH. These results show that also pre-SAH resources are important in determining whether or not the patient will have a successful recovery.

This study therefore emphasizes the importance of attempting to save an increasing numbers of patients in clinical condition Hunt & Hess grade V after an aneurysmal SAH patients since about half of the patients who survive will continue to have a productive life.

6 CONCLUSIONS AND IMPLICATIONS

6.1 CONCLUSIONS

Overall there is therefore a growing body of evidence suggesting that the most important factor for the functional outcome after aneurysmal SAH is the hemorrhage itself and associated secondary brain damage, rather than the location of the aneurysm or the surgical intervention. Along with improved surgical techniques it is therefore necessary to improve the final outcome evaluation of aneurysmal SAH patients beyond using GOS or GCS. We therefore believe that such an evaluation should include measures of HRQOL, personal changes, social changes and occupational changes along with a comprehensive neuropsychological evaluation.

In our studies we found:

- Cognitive functions improve at different rates with motor functions improving rapidly the first 6 months, while memory functions first improve between 6 and 12 months post-aneurysmal SAH
- Parameters reflecting the impact of the bleed and post-operative patient management can be linked to neuropsychological outcome.
- An aneurysm rupture most likely cause a global cerebral damage rather than a focal damage, but focal damage is possible mainly as a result of haematoma causing cerebral damage at the site of the aneurysm rupture. We found problems with initiation of problem solving behavior in a subgroup of ACoA patients which we believe is the cause of focal damage in the medial frontal lobes.
- Treatment of UIAs causes a significant improvement in HRQOL.
- Surgical treatments of UIAs are not associated with any extensive cognitive problems.
- Lower age and many years of education are important predictors for improvement in cognitive functioning and HRQOL in patients with a clnincal condition Hunt & Hess V after an aneurysmal SAH.
- All our studies have shown the importance of using more sensitive instruments when evaluating outcome after ruptured and unruptured intracranial aneurysms.

Our studies show the importance of repeated neuropsychological testing to understand the rate of improvement in both cognitive functioning and HRQOL, but additional research is needed to confirm these finding. If these results prove to be correct they could have a major impact on rehabilitation after aneurysmal SAH because they suggest that during the first six months post-aneurysmal SAH focus should be on physical rather than cognitive training and that most beneficial cognitive training will occur after 6 months. Further, aneurysmal SAH patients also have a massive need for information and a closer follow-up of the emotional consequences after aneurysmal SAH. We have completed a study on aneurysmal SAH patients need for information and satisfaction with treatment which confirms this but this study has not been included in the thesis.

More research is also needed in order to fully understand the impact of an aneurysmal SAH on cognitive function and HRQOL. For example more research is needed on ACoA aneurysm rupture to distinguish further between the emotional (depression/apathy) aspects versus the possible medial frontal lobe damaged patients with initiation of problem solving behavior problems. Beyond using standardized neuropsychological tests and HRQOL questionnaires an increasing number of other techniques (for example ERP and fMRI) are also available which might contribute in to this research, but so far only two studies (58, 164) have used ERP (event related potential) on ACoA patient so more research is needed using these techniques hence Fontanella (58) concluded that ERP might be an objective parameter in the follow-up of aneurysmal SAH patients with cognitive impairments.

Further research should also look at the poor-outcome patients in order to further explore the somewhat surprising distinction between the good and poor functioning patients. A better understanding of the cognitive functioning and HRQOL over a longer time-span than 12 months is also needed to see if the deficits seen are static or improve further over time. Finally, a better understanding of the outcome and the effect of treatment of patients in clinical condition Hunt & Hess grade V aneurysmal SAH patients will also help in deciding whether or not to treat a severely ill patient.

6.2 IMPLICATIONS

All our studies have shown that most patients with a "good outcome " (GOS 4-5) survive their aneurysmal SAH with only mild to moderate disabilities. We have also seen that even a large percentage of patients in clinical condition Hunt&Hess grade V will recover and although they might not function exactly at their pre-morbid level they still have a satisfactory cognitive functioning and HRQOL, suggesting that an aggressive treatment of these patients is justified. Finally, we have also seen that treatment for UIAs does not cause any long term effect on cognitive functioning and it significantly reduced anxiety and depression in these patients, making surgery a good option for those patients that suffer with the notion of having an aneurysm which might rupture.

We also believe that psychologists should be an integrated part of any neurosurgical department to complement the treatment of patients with intracranial aneurysms. Psychologists should be involved from the acute stage both to evaluate the patients' cognitive function and to be an emotional support for the patient and their relatives. Further neuropsychological testing should be a standardized procedure at both 3 and 12 months post-treatment of intracranial aneurysms. Most patients are overwhelmed at the time of discharge

and may therefore not fully understand the impact the aneurysmal SAH might have on their cognitive functioning and daily life. The weeks between being released from the hospital and the 3 month control can therefore often raise a number of questions and concerns. Patients should therefore be given written information describing the most common problems after aneurysmal SAH at the time of discharge and have the option of calling a resource-person either at their local hospital or at the neurosurgical department. Patients should also have the opportunity to contact a psychologist during the rehabilitation period to avoid any post-traumatic stress reactions. A number of patients experience a feeling of confusion and insecurity after an aneurysmal SAH as a result of on the one side being happy about surviving such a devastating disease without any major physical problems, but on the other hand experiencing often "invisible" problems such as mild memory or concentration problems that cause difficulties in their daily living. In addition such problems are often difficult to admit to others since they are often greeted with "you look so good" and "you have been so lucky to survive." A psycho educative approach along with neuropsychological testing should be offered to the patients to help them understand and cope with the often "invisible" changes in function they experience. A number of patients have also enquired about the possibility to arrange support groups for aneurysm patients because they often are referred to stroke support groups which have different agendas and often greater disabilities than the aneurysm patients. Lastly, there is also a great uncovered need for cognitive training among aneurysmal SAH patients which should be addressed. The majority of patients admitted to rehabilitation hospitals will be required to have severe cognitive and physical deficits, and hence most aneurysmal SAH patients will not qualify for such treatment even though they would benefit greatly from such training. Additional institutions focusing on rehabilitation for patients with mild to moderate sequelae are therefore greatly needed.

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