Outcome after treatment of cerebral aneurysms

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To my wonderful parents, Anders & Nora, and my beloved husband Truls

Outcome after treatment of cerebral aneurysms

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ABSTRACT

A cerebral aneurysm is a saccular or tubular-like deformity of the arterial vessel wall which is usually thinner. The rupture of a cerebral aneurysm is associated with a high morbidity and mortality by causing an aneurysmal subarachnoid haemorrhage (aSAH). Treatment, which can be surgical or endovascular, aims to isolate the aneurysm from the normal blood circulation to prevent rupture. The decision to treat is based on several factors, including size, location, shape of the aneurysm, patient age, potential co-morbidities, potential risks associated with aneurysm treatment.

The aim of this thesis has been to report the long-term outcomes, both neurological and radiological, in patients that have been treated for an cerebral aneurysm, both ruptured and unruptured.

In study I, the neurological long-term outcome in patients that have previously suffered an aSAH was good, despite this; more than 60% of the patients still reported mental fatigue of some degree.

Study II assessed the neurological and radiological outcome in patients with refractory cerebral vasospasm that received intra-arterial nimodipine (IAN). We could with this study conclude that the majority still suffered an ischemic cerebral infarction and that a good clinical recovery was seen in almost half of the patients.

In study III, an 18-year follow-up in patients previously treated for an intracranial aneurysm (IA) was performed where we identified 13.6% of these with a de novo aneurysm.

In study IV, we performed a single centre follow-up of patients that had been treated at our institute with a flow diverter where we in the follow-up identified three-quarters of the aneurysms treated to have an aneurysm occlusion and that patients >70 years had a lower occlusion rate.

Conclusion and implications: A longer neurological and radiological follow-up time is deemed necessary, especially in the younger patient population, after having been diagnosed and treated for an intracranial aneurysm. A majority of the patients receiving intra-arterial nimodipine suffered a cerebral infarction; despite this, approximately half of all patients had a good neurological outcome after 6 months. Flow diverters have an acceptable occlusion rate in patients <70 years of age, and this treatment offers a reasonably safe alternative in patients with aneurysms posing a high risk of causing potential harm to the patients.

Keywords: Intracranial aneurysm, intra-arterial nimodipine, de novo aneurysm, flow diverter

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SAMMANFATTNING PÅ SVENSKA

Bakgrund

Aneurysm (pulsåderbråck) i hjärnan uppstår till följd av kärlsjukdom där en förtunning av en del av kärlväggen har skett och en utbuktning uppstår med tidens gång. Denna utgör själva aneurysmsäcken, och dess vägg är mycket skör. Förekomsten av aneurysm i den vuxna populationen uppskattas till mellan 1 och 5 %, men det är vanligare hos patienter med polycystisk njursjukdom, Marfans syndrom, Ehler-Danlos syndrom typ 4 och fibromuskulär dysplasi.[1,2,3] Subaraknoidalblödningar orsakade av brustna aneurysm, blödning mellan hjärnans hinnor, är en allvarlig form av stroke med hög dödlighet och med hög risk för neurologiska handikappande bortfall av olika grad. Dessa blödningar motsvarar cirka 5% av alla stroke och brustna aneurysm står för cirka 85% av alla subaraknoidalblödningar. Merparten av patienter som insjuknar genomgår akut åtgärd av sitt aneurysm, inom 24 timmar i de flesta fall, via den endovaskulära metoden eller via öppen mikrokirurgi, lämplig behandlingsmetod beslutas individuellt av erfaren neurokirurg tillsammans med neurointerventionist. Själva behandlingen och rehabiliteringen tar i regel lång tid där risken för att drabbas av neurologiska bortfall är som högst de första veckorna efter genomgången blödning. Efter att ha genomgått endovaskulär behandling har vi ett uppföljningsförlopp på 3 år där man ett år efter behandling genomgår en kärlröntgenkontroll och två år efter denna en magnetkamerakontroll av hjärnans kärl, så kallad MRA. Ser samtliga steg bra ut så har patienterna släppts avseende vidare radiologisk och klinisk uppföljning oavsett ålder på patienten. Efter öppen mikrokirurgi genomgår patienterna i regel en klinisk kontroll efter 3 månader och har man då mått bra så har man friskförklarats och släppts avseende vidare kontroller, både kliniska samt radiologiska, oavsett ålder. Senaste åren har vi dessvärre märkt av att patienter efter dryga tio år eller längre tid efter behandling aktualiserats ånyo då de

inkommit med nya subaraknoidalblödningar från antingen en halsrest som tillvuxit eller ett nytillkommet aneurysm som inte noterats på de äldre röntgenundersökningarna, ett så kallat de novo aneurysm. Vi har i samband med dessa patienter även noterat att många av dessa som återfått en ny blödning aldrig riktigt kunnat återgå till livet de levde innan sin blödning. Många hade fortsatt uttalad trötthet vilket hindrat de att återgå i arbete. Med anledning av att vi kände ett behov av att kunna undvika att man får en ny subaraknoidalblödning efter det att man blivit friskförklarad beslutade vi oss för att genomföra en långtidsundersökning av de patienter som behandlats hos oss dels för att undersöka hur återställda patienterna var neurologiskt men även hur pass hållbar deras behandling är på sikt.

Metod

I delarbete 1 har vi gjort en neurologisk och radiologisk långtidsuppföljning på de patienter som insjuknat med en aneurysmal subaraknoidalblödning (aSAH) och som randomiserats till antingen endovaskulär behandling (EVT) eller mikrokirurgisk behandling (MST) mellan åren 1997-2001. Neurologiskt outcome bedömdes via modified Rankin scale (mRS), fatigue graderat i enlighet med Mental Fatigue Scale (MFS), och radiologisk outcome bedömt via magnetic resonance angiography (MRA). Mental fatigue scale (MFS) för denna grupp jämfördes med en kontrollgrupp.

I delarbete 2 undersöktes retrospektivt de patienter med refraktär cerebral vasospasm som genomgått en intraarteriell nimotopbehandling mellan åren 2009-2020. Neurologiskt outcome via modified Rankin scale (mRS) undersöktes efter 30 dagar och 6 månader. Förekomsten av cerebrala infarkter efter behandlingen identifierades likaså komplikationer relaterade till ingreppet i samband med behandlingen.

Delarbete 3 går ut på att efter mer än 18 år kunna se de radiologiska resultaten efter att ha genomgått endovaskulär behandling för ett aneurysm. Vi ville se om

det gick att detektera om några nytillkomna så kallade de novo aneurysm har tillkommit när vi jämförde med deras senast tagna radiologiska undersökning av hjärnan.

I delarbete 4 har vi valt att göra en längre tids uppföljning av endovaskulär SILK stent behandling av aneurysm intrakraniellt. Vår tanke är att kunna se hur denna behandling håller sig på sikt och vad som händer i det behandlade kärlet, i aneurysmet och ev intilliggande ischemier i omkringliggande hjärnparenkym.

Resultat

I delarbete 1 var merparten som svarade vid gott neurologiskt status idag, trots detta var det en fler än 60% som fortsatt upplevde uttalad trötthet. Vi kunde också konstatera att det inte var en helt obetydande andel patienter som var i behov av ytterligare uppföljning alternativt behandling för nyupptäckta aneurysm och/eller halsrester.

Delarbete 2 kunde vi se att patienter som bedömdes vara i ett sämre neurologiskt skick efter 30 dagar förbättrades neurologiskt vid 6 månaders uppföljning. Cirka 60% av patienterna utvecklade infarkter trots intensiv behandling med intraarteriell nimotop och 21% drabbades av procedurrelaterade komplikationer.

Delarbete 3 visade att ca 13.6 % av patienterna som genomgått långtidsuppföljning utvecklat nya aneurysm där ca hälften genomgått förnyad behandling för sitt de novo aneurysm >18 år efter att ha genomgått sin initiala behandling.

Delarbete 4 visade att 73.8% av de inkluderade patienterna uppnådde en ocklusionsgrad på 73.8% inom 14 månader efter behandling. Cirka 15.6% drabbades av procedurrelaterade komplikationer. Om patienterna var 70 år eller äldre hade de ett sämre behandlingsresultat inom 14 månader jämfört med de patienter som var yngre än 70 år.

Slutsatser

Långtidsuppföljningen i första studien bidrar till kunskapen om att patienterna hittills inte genomgått tillräcklig uppföljning då det på sikt finns en inte helt obetydlig risk att drabbas av en blödning igen från ett nytt aneurysm alternativt en halsrest, och behöva gå igenom samma procedur i form av behandling samt återhämtning om man lyckas överleva en andra gång. Lyckligtvis rör det sig inte om en stor andel patienter men resultaten är förstås viktiga för varje enskild patient. Att ändra och förlänga vår uppföljning är angeläget för att kunna identifiera patienter som har hög risk att utveckla nya aneurysm och kunna behandla dessa i tid.

Studien som utvärderat den experimentella behandlingen i form av intraarteriell nimotop har kunnat bidra till att ge oss bättre förståelse för de fördelar och risker som finns med denna behandling. Fyrtio procent av de som fått IAN klarade sig utan infarktutveckling, medan 21% fick en komplikation till behandlingen, dödsfall inom 30-dagar relaterad till svår vasospasm drabbade 8% av patienterna. IAN kan vara till nytta vid svår vasospasm där risken för bestående skada eller död är stor, men med tanke på att det finns betydande risk med behandlingen bör den endast erbjudas i utvalda fall där konventionell behandling är otillräcklig.

Avseende risken för att utveckla de novo aneurysm lutar vår studie åt att man bör rekommendera en längre tids uppföljning av den yngre patientgruppen som drabbats och/eller åtgärdat ett aneurysm i yngre ålder under en längre tid i deras liv.

Flow diverter behandling är i nuläget en relativt säker behandlingsmetod för fusiforma aneurysm, i synnerhet de som tidigare bedömts som svårbehandlade eller där ingen annan lämplig behandlingsmetod existerat.

LIST OF PAPERS

This thesis is based on the following studies.

I. Samuelsson, J, Jakobsson, H, Rentzos A, Jakola AS, Nilsson D. Neurological Outcome, Mental Fatigue, and Occurrence of Aneurysms >15 Years After Aneurysmal Subarachnoid Hemorrhage. *World neurosurgery* vol. 151 (2021): e122-e127.

II. Samuelsson, J, Sunila M, Rentzos A, Nilsson D. Intra-arterial nimodipine for severe cerebral vasospasm after aneurysmal subarachnoid haemorrhage - neurological and radiological outcome. *The neuroradiology journal* vol. 35,2 (2022): 213-219.

III. Samuelsson, J, Rentzos A, Rawshani A, Karlsson A, Ståleby M, Nilsson D. Risk of de novo aneurysm formation in patients previously diagnosed with a ruptured or unruptured aneurysm: 18-year follow-up. *Clinical neurology and neurosurgery* vol. 233 (2023): 107980.

IV. Ceder E, Samuelsson J, Nilsson D, Björkman-Burtscher IM, Rentzos A.
Long-term follow-up of flow diverter treatments – a single center experience. Manuscript.

CONTENTS

ABBREVIATIONS

ACA Anterior Cerebral artery

Acom Anterior communicating artery

aSAH Aneurysmal Subarachnoid Haemorrhage

BA Basilar artery

BRAT Barrow Ruptured Aneurysm Trial

CE Contrast Enhanced

CI Confidence Interval

CTA Computed Tomography Angiography

CTP Computed Tomography Perfusion

CVS Cerebral vasospasm

DCI Delayed Cerebral Ischemia

DSA Digital Subtraction Angiography

EVT Endovascular Therapy

IAN Intraarterial nimodipine

ICA Internal carotid artery

ICH Intracerebral hematoma

ISAT International Subarachnoid Aneurysm Trial

ISUIA International Study of Unruptured Intracranial Aneurysms

IVH Intraventricular hematoma

MCA Middle cerebral artery

MFS Mental Fatigue Scale

MRA Magnetic Resonance Angiography

mRS Modified Rankin Score

MST Microsurgical Therapy

OR Odds ratio

Pcom Posterior communicating artery

PICA Posterior inferior cerebellar artery

PTA Percutaneous Transluminal Angioplasty

SAH Subarachnoid Haemorrhage

SCA Superior cerebellar artery

TCD Transcranial Doppler

TOF Time of Flight

VA Vertebral artery

WFNS World Federation of Neurosurgical Societies (scale)

1. INTRODUCTION

An intracranial aneurysm (IA) is a pouch-like abnormality in the walls and branching sites of the intracranial arteries. Most IAs remain asymptomatic and never rupture. If an aneurysm ruptures, blood can extravasate into the subarachnoid space surrounding the brain that is filled with cerebrospinal fluid (CSF), resulting in a subarachnoid haemorrhage (SAH).[4,5] There might also be intracerebral (ICH), intraventricular (IVH) or subdural (SDH) hematoma related to the haemorrhage. Subarachnoid haemorrhage (SAH) accounts for about 5 % of all strokes and poses a significant risk of mortality and permanent neurological morbidity.[6] The advancement of neuroimaging techniques, such as magnetic resonance angiography (MRA) and computed tomography angiography (CTA), over the last two decades has led to an increased diagnosis of non-ruptured or incidental IAs.[7] This has, in turn, simplified the follow-up of patients with previously treated IAs and increased the consideration of treatment for non-ruptured aneurysms.

A patient suffering from an aneurysmal subarachnoid haemorrhage (aSAH) can usually expect a period of intensive in-hospital treatment and a long rehabilitation. The neurological outcome after an aSAH is dependent upon the damage caused by the initial bleeding, the occurrence of disease-related complications (vasospasm, hydrocephalus and rebleeding) and complications from the treatment of the aneurysm.[8-11] As the mean age in patients with an aSAH is 55 years thus most patients have an expected remaining lifetime of more than 25 years, more data is needed on the long-term neurological and radiological outcome after an aSAH.[12,13] As the frequency of formation of de novo aneurysm after treatment of an intracranial aneurysm remain scarce, more data and guidelines are needed regarding the follow up regimen in the long term. This is especially important in the younger patient population suffering an aneurysm.

Severe vasospasm can lead to stroke in up to 30 % of patients, and intra-arterial administration of nimodipine has emerged as a promising method to reduce vasospasm, but few studies have addressed the efficacy of this treatment.[14-16]

Some aneurysms affect the entire wall of the vessel and cannot be treated by excluding the aneurysm from the circulation. For such aneurysms, the endovascular insertion of a "pipe-line" device or stent has become the preferred treatment method, but there is limited data on their long-term results.[17,18]

1.1 EPIDEMIOLOGY

The estimated prevalence of intracranial aneurysms in the population is approximately 5 %. However, only a small percentage show symptoms such as aSAH, mass effect or distal thrombosis.[17,18] The annual average risk of rupture of an aneurysm is 0.4 – 2.2 % in previous studies.[19-26] Other causes of SAH include trauma, Reversible Cerebral Vasoconstriction Syndrome (RCVS), arteriovenous malformation (AVM) and dural fistulas. Unlike aSAH, non-aneurysmal SAH generally has a favourable long-term prognosis with very low rebleeding and mortality rates.[27-29]

The mean age of aSAH patients is around 55 years, affecting individuals in their working years.[1,30] Previous studies have shown that the ability to return to work is important for life satisfaction and for well-being. Studies show that the rate of return to work varies between 10-70%.[31] Patients suffering an aSAH with a good neurological outcome still report cognitive symptoms several years after discharge making it harder for patients to get back in to their normal daily routine. The most common cognitive symptoms reported are impairment of memory, executive functions, and attention.[32]

The condition affects both genders but is more prevalent in females who smoke and suffer from hypertension.[1,30] Polycystic kidney disease, connective tissue disorders, and a strong family history of aneurysms are known associated comorbidities. The risk of IAs is 2-3 times higher in families with a history of IAs, and about one-third of IA patients have multiple aneurysms.[13,19]

The precise mechanism of IA formation remains unclear, though they are generally considered acquired lesions.[1,33] Morphologically, IAs are typically classified as saccular, characterized by a pouch-like protrusion, or fusiform, where the entire arterial segment dilates without a distinct base or neck, see figure 1. Most IAs are saccular and arise at arterial branching sites.[34]

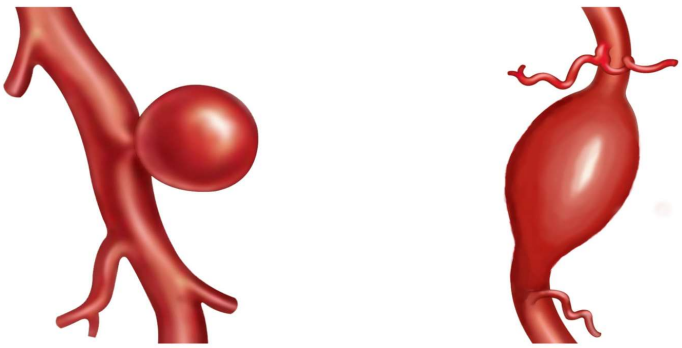

Figure 1 shows a saccular aneurysm to the left and a fusiform aneurysm to the right. Illustration licenced by Shutterstock and modified by T. Råmunddal.

1.2 RUPTURE OF INTRACRANIAL ANEURYSMS

Rupture of an IA is the leading cause of nontraumatic SAH, accounting for approximately 85% of SAH cases. Most IAs remain clinically silent until they rupture causing an aneurysmal subarachnoid haemorrhage (aSAH)[2,30] While aneurysm size, gender, age, hypertension,and smoking status have been examined as predisposing factors for IA development and rupture, there are complexities in predicting ruptures.[30,33]

Aneurysm size has for many years been considered a risk factor for rupture of IAs. The largest study on unruptured saccular IAs, the International Study of Unruptured Intracranial Aneurysms (ISUIA), reported that the rupture rate for aneurysms smaller than 7 mm was significantly lower than for those larger than 7 mm.[35] However, in both the ISAT study and in our clinical experience we see many IAs smaller than 7 mm rupture and cause a subarachnoid haemorrhage (SAH).[12,36] Aneurysms located in the posterior circulation and aneurysms arising from the posterior communicating artery (PcomA) pose a higher risk of rupture relative to anterior circulation aneurysms.[35] Anterior communicating Artery aneurysms (AcomA) have the highest rupture rate among the anterior circulation aneurysms.[35] A recent review published that the anterior communicating artery and posterior communicating artery have the highest risk of rupture. They also found indications of the fact that hyperlipidemia and atherosclerosis had a protective effect on aneurysm rupture.[37] Intracranial aneurysms are more frequently diagnosed in women, with women being 1.6 times more likely to experience aneurysmal SAH than men.[3,38,39]

Women face a higher risk of aneurysm rupture, particularly post-menopause, possibly due to the effects of oestrogen on the vascular wall.[3]

The annual rupture risk of IAs increases cumulatively with age to peak between 40-65 years of age.[40] In patients with a family history of aneurysmal SAH, the IAs tend to rupture at a younger age.[41]

Hypertension is the most frequently reported health condition associated with the formation of IAs and their subsequent rupture.[3] Hypertension has also been found to be a risk factor for multiple IAs and for the rupture of smaller IAs (below 7 mm).[41] Smoking and alcohol consumption are lifestyle risk factors associated with aneurysmal SAH.[3]

1.3 DIAGNOSIS

Clinically, patients with aSAH commonly present with a sudden, severe headache, nausea, vomiting, neck pain, photophobia, and possible loss of consciousness. At the physical examination patients have a neck stiffness, might have associated retinal haemorrhage and/or a wide range of various neurological deficits depending on the extension and location of the haemorrhage. Computerized tomography (CT) of the brain is highly sensitive (95-100%) in the detection of the SAH. A lumbar puncture is indicated only when patients are presenting with the above-mentioned symptoms and the brain CT shows no signs of SAH. Most patients also do a CT angiography (CTA) at the same time when there is a suspicion of this diagnosis, this should always be done at the same time as the plain CT of the brain. Next step is usually, depending on what the CTA has shown, digital subtraction angiography (DSA).[42]

Currently, there are several grading systems for describing the patients' clinical condition and prognosis. One of these is the World Federation of Neurological Surgeons scale (WFNS).[43] Also, the amount and extension of SAH on the CT is graded according to the Fisher scale.[44]

Not all IAs are detected when patients are suffering an aSAH, some are detected when causing mass effect or distal thrombosis. With advancements in neuroimaging techniques, there has been a surge in the diagnosis of non-ruptured or incidental IAs. This has led to a rise in considering treatment for non-ruptured aneurysms.[45]

1.4 MANAGEMENT

The first step is to prevent rebleeding in patients with aneurysmal SAH, depending on the routines in different institutions, patients are given tranexamic acid in order to stabilize the clot at the aneurysmal rupture site.[46]

All patients with a Glasgow Coma Score (GCS) below 8 are intubated at all times, patients in the need of a transfer to larger hospitals with a neurosurgical facility and on the verge of being unconscious are all intubated before transport.[47,48] Patients presenting with associated hydrocephalus are given ventricular drainage acutely. All IAs are generally treated within 24 hours to prevent re-rupture, as rebleeding carries a mortality rate of 70-90%.[6,49] Following this, the main goal is to manage the complications with a SAH, particularly cerebral vasospasm (CVS). Intravenous nimodipine is given to all our patients as a vasospasm prophylaxis for three weeks post ictus. Usually the patients are given oral nimodipine after 1 or 2 weeks depending on different routines at different neurosurgical clinics. The use of nimodipine has been shown to reduce the risk of a poor outcome after suffering an aSAH with 40%.[39] Nowadays, when all medications and neurointensive care fails, endovascular methods are being increasingly used to treat CVS.[50,51]

Sudden or gradual onset of decreasing level of consciousness, worsening headache, neurological deficits such as affected speech and/or motor deficits are all clinical symptoms of CVS. Cerebral vasospasm (CVS) after aSAH is the second most common cause of mortality, after rebleeding from the aneurysm.[52]

Severe CVS is a dominant factor of secondary morbidity and mortality after aSAH.[27,28,53] However, with new protocols in the management of SAH, the combined risk of death and long-term disability have been reduced by approximately 10% compared with the past.[54] Also, with modern SAH management, CVS will lead to brain infarction with permanent disability in up to 47 % of SAH patients.[55] CVS is detected in approximately 70% of all patients with SAH, around 30% having verified angiographic vasospasm are clinically symptomatic.[56]

Delayed Cerebral Ischemia (DCI) is defined as clinical or radiographic signs of ischemia and is an important cause of morbidity contributing to poor outcome

after SAH when associated with cerebral infarction.[57,58] One main cause for DCI has long been considered to be vasospasm identifiable on angiography. Hydrocephalus or seizures are other complications of aneurysmal SAH.[59,60] More common anaesthesiologic complications include stress cardiomyopathy and neurogenic pulmonary edema.[61-64]

2. RADIOLOGICAL METHODS FOR DIAGNOSING IA

The gold standard for detecting IAs, if not shown on CTA, is digital subtraction angiography (DSA). It can very well show the localization of the IA, shape and size. It is, however, an invasive procedure, which can be associated with complications such as stroke, bleeding from puncture site and thrombosis amongst some of the complications.[65] The overall complication rate for a DSA has been reported to be up to 5%.[66]

The use of non-invasive techniques, mainly CTA nowadays, when patients present with an aSAH has largely replaced DSA when evaluating the cerebral vasculature and the decision planning for adequate further microsurgical or endovascular treatment. The majority of data in the literature showed that CTA has a good diagnostic efficiency which is comparable to DSA with a high sensitivity, specificity and accuracy of 95-98 %, 90-100 % and 94-98 %, repectively.[67] Due to the comparability to DSA, sensitivity and specificity but also due to the short scanning time and the fact that it is a readily available technique, the CTA is the preferable radiological technique for patients presenting with an aSAH. The CTA also enables the surgeon and neurointerventionist to do a 3D reconstruction which helps when it comes to planning the most suitable treatment strategy.

Magnetic Resonance Angiography (MRA) is another adequate non-invasive technique mainly used for screening for or for the follow-up of unruptured IAs but usually not for emergency cases due to its limited availability during off-

hours, difficulty to complete MRI safety checklist in emergency settings and lastly due to the fact that a radiologist experienced in reading MRI scans might not be available.[68] This diagnostic tool is unfortunately not possible in patients with non-MRI compatible implanted devices such as some pacemakers.

The MRA techniques usually used are Time of Flight (TOF-MRA) and Contrast-Enhanced (CE-MRA) and is a commonly used non-invasive examination for the detection and characterization of intracranial aneurysms.[69] TOF-MRA is standardly applied, CE-MRA is only applied when asked for. Regarding the evaluation of intracranial aneurysms, CE-MRA is superior to TOF-MRA for assessment of sac shape, detection of aneurysmal neck, and visualization of branches originating from the sac or neck itself.[70] Regarding TOF-MRA, the sensitivity and specificity for aneurysms that have previously undergone endovascular therapy were 88% and 94%, respectively. For CE-MRA, the sensitivity and specificity were 88% and 96%, respectively. For those patients that had previously undergone stent-assisted coiling (SAC) and flow diverter treatment (FD), sensitivity and specificity of TOF-MRA were 86% and 95%, respectively. CE-MRA had sensitivity and specificity of 90% and 92%.[71-73]

The magnetic resonance imaging (MRI) technique is continuously evolving and so has the TOF-MRA which has become better when it comes to dealing with artefacts from the stents but also when evaluating the shape and size of the aneurysm.

3. TREATMENT OF INTRACRANIAL ANEURYSMS

Walter Dandy performed the first clipping of an internal carotid artery (ICA) aneurysm in 1937. Due to the efforts of Yasargil in the 1960s, microsurgery for IAs began.[74] Microsurgery remained the only definitive treatment until the early 1990s, which is the time point when the endovascular treatment era began

to slowly enter the field.[50] The present era in the endovascular treatment of IAs using detachable coils was initiated in the early 1990s by Guglielmi.[75]

With microsurgery, treatment of an IA is based on excluding the aneurysm from the intracranial circulation and various branches of the normal intracranial vasculature. The aneurysm neck is included in the clipped area whilst maintaining the normal vasculature and avoiding parenchymal injury.[76] Aneurysm clipping is performed by vascular neurosurgeons with extensive experience and training in this complex surgery.

Each patient is individually assessed when diagnosed with an intracranial aneurysm. Two types of treatments exist for patients with both ruptured and unruptured aneurysms, the endovascular method (EVT) and the microsurgical method (MST). Factors such as age, co-morbidities, neurological status, size and location of aneurysm is also taken into consideration when choosing the most adequate treatment for each individual patient.

Endovascular treatment for intracranial aneurysms was initially intended for those aneurysms that were difficult or more surgically inaccessible, especially for patients with complicating co-morbidities or for those with aneurysms in the posterior circulation (basilar tip aneurysms for example). After publishing the initial result from the International Subarachnoid Aneurysm trial (ISAT) study in 2002, which deemed endovascular treatment a safe treatment option, management strategies changed worldwide.[12] The endovascular treatment method became gradually the first choice of therapy in many hospitals worldwide.[77]

A fairly new-generation treatment are the flow diverter stents that are placed in the parent artery at the level of the aneurysm neck to disrupt the intra-aneurysmal flow in order to promote intra-aneurysmal thrombosis. There are some series that have reported up to 85% occlusion rate at the first post-procedural follow-up after three months.[78] Based on these and other data, we

have at our institute, switched from our regular follow-up comprised of a follow-up DSA one year post procedure and a 3-year follow-up MRA, to a 1-year follow-up MRA. Seeming as the risk of aneurysm recanalization is not insignificant in the long term (0.7% rebleeding rate at one year[12]) this flow diverter treatment has been used more widely due to the results seen so far. However, patients are in the need of dual antiplatelet therapy months after when compared to coil embolization where a regimen of single antiplatelet therapy for a few months post procedure is used. There is no real consensus when it comes to the medical strategy post neurointerventional procedure. Most flow diverter devices in our series have been used in unruptured aneurysms due to the delay to obtain complete occlusion, which could be considered as a limit of its technique. The rate of complete occlusion in the long term would be interesting to define seeming as not many studies have been made yet.

4. OUTCOME

Spontaneous aneurysmal SAH carries a mortality rate of up to 35%.[79] Approximately one-third of all survivors remain severely disabled and functionally dependent.[13,36,79] The overall prognosis depends on the volume of the initial bleed, rebleeding and the degree of delayed cerebral ischemia (DCI), which is one of the most important causes of morbidity and mortality in these patients.[27,28,80] A study following patients that suffered an aneurysmal SAH at 6 months and 1 year showed that more than half of the patients scored a better mRS score at the first follow up at 6 months but not an insignificant number still made progress at 1 year and went from a bad neurological outcome (mRS 3-5) to a good neurological outcome (mRS 0-2).[81]

Previous studies have shown that the outcomes for those patients with aSAH and ICH from a ruptured IA were worse.[82-84]

Fatigue is commonly reported after aSAH and can be a major obstacle in

resuming the previous life of the patient, also several years after the bleeding and in patients with a good functional outcome as assessed by standard outcome measures.[85,86] It is a debilitating long-term neurological sequela that significantly impacts the patient's ability to work and their social life.[87] Only one previous study has reported on the prevalence of mental fatigue more than 15 years after aSAH.[88] This kind of fatigue in comparison to the "normal" fatigue appears more quickly and during non-demanding tasks and recovery is not complete despite rest. It limits physical and cognitive tasks, interferes with rehabilitation and return to work.

Assessment of fatigue is difficult and not a lot of treatment studies have been made, neither pharmalogical nor therapeutical.[89] In order to try and assess the degree and severity of mental fatigue a group of researchers developed the Mental Fatigue Scale (MFS).[90] The MFS comprises 15 items regarding the mental aspects of fatigue including cognitive and sensory symptoms, and evaluating their intensity, frequency and duration. This scale is nowadays not only used for assessing mental fatigue in patients that have suffered brain injuries but also as a follow up in various diagnoses.[91] However, they also concluded like previous studies that more knowledge of the origin of mental fatigue and its underlying mechanisms is needed in order to develop a more targeted therapeutic method.[90,92]

5. AIMS

5.1 Study I.

The aim was to report the long-term follow-up of the neurological and radiological outcome in the patients included in the ISAT from the Western part of Sweden >15 years after experiencing an aSAH.

5.2 Study II.

The aim was to evaluate the neurological and radiological long-term outcome in patients previously treated with intra-arterial nimodipine (IAN) in relation to cerebral infarction, procedural related complications and clinical outcome.

5.3 Study III.

The aim was to determine the rate of de novo aneurysm formation in previously treated aneurysms at our institute, both ruptured and unruptured, in the long term (>18 years).

5.4 Study IV.

The aim was to do a radiological and neurological follow-up of patients that had undergone SILK stent treatment at our institute and to evaluate their long-term results.

6. METHODS

6.1 Study I.

In our first study, the aim was to report neurological and radiological outcome >15 years after an aSAH in patients from the Western part of Sweden. The patients were initially included in the ISAT study (1999-2002) and randomized to either endovascular or microsurgical treatment. We included 46 patients that had undergone treatment at the time of ISAT, 18 had MST and 28 had EVT, additionally we managed to collect 5-year data from some patients that unfortunately were not able to be included in the 15-year follow-up. We could grade the neurological outcome for all the included patients, both current and the neurological outcome for the patients in the 5-year follow-up. Twenty-nine patients agreed to do a radiological follow-up. Moreover, alongside the questionnaires sent out to the patients, we included the mental fatigue scale (MFS), a valuable tool for assessing the levels of fatigue experienced by patients more than 15 years after their initial aSAH event.

6.2 Study II.

In our second study, the aim was to evaluate the neurological and radiological outcome in patients treated with intra-arterial nimodipine (IAN) in relation to cerebral infarction and clinical outcome. We included 48 patients with refractory CVS in the time period of 2009-2020, they all had IAN.

6.3 Study III.

In our third study, our aim was to conduct a long-term follow-up (>18 years) to determine the rate of de novo aneurysm formation in patients previously treated at our department for both ruptured and unruptured aneurysms. Magnetic resonance angiography (MRA) is a part of the radiological follow-up in most institutes. We assessed the rate of de novo aneurysm formation using MRA. Variables associated with de novo aneurysm formation were analysed.

6.4 Study IV.

In our fourth study, we aimed to report a neurological and radiological long-term follow-up of patients that have been treated with a flow diverter. Patients were retrieved from a database. The selected patients were treated in between 2008-2020 at the neurointerventional department at Sahlgrenska University hospital. Baseline characteritics were collected from the medical records and clinical information and data were extracted. The treatment strategy, duration and types of anticoagulants used were all collected. Sixteen patients were also eligible for a more recent follow up MRA.

7. STATISTICAL METHODS

7.1 Study I.

Variables in both groups are presented with descriptive statistics. Fisher exact test and Pearson test were used when comparing groups. Independent samples *t*-test or Mann-Whitney *U* test were used for continuous data based on the data distribution.

7.2 Study II.

Binary logistic regression was used to study potential risk factors for vasospasm associated cerebral infarction after IAN treatment.

7.3 Study III.

Logistic regression was used to study variables associated with de novo aneurysm formation. Missing data were imputed using chained random forests. A data-driven model for the prediction of de novo aneurysm was created to calculate the relative variable importance of ten clinical features.

7.4 Study IV.

Continuous variables are described with Mean, SD, median, minimum, and maximum and categoric variables with numbers and percentages with exact 95% confidence interval (CI). For analyses of changes over time within groups, Fisher's non-parametric permutation test for paired observation was used for continuous variables and Sign test for dichotomous variables. Logistic regression analyses were used to predict dichotomous outcome variables. The results are given as odds ratios (OR) with 95% CI. In analysis with dichotomous predictors where one of the groups has 0 events Firth´s penalized method have been used to estimate OR with 95% CI. All significance tests were two-sided with 5% significance level. SAS System Version 9.4, Cary, NC, USA has been used for all analysis.

8. RESULTS

8.1 Study I.

I t was evident that the long-term neurological outcomes were generally favourable, regardless of the chosen treatment modality. A good neurological outcome was seen in 100% of the patients that had endovascular treatment and in 88.8% of the patients that had previous microsurgical treatment. However, an important observation was the persistence of varying degrees of fatigue among most patients, despite their positive neurological outcomes. More than 60% still experienced some degree of mental fatigue. Additionally, our study identified that approximately 17% of patients presented with either residual or de novo aneurysms, necessitating further treatment or follow-up.

Overall, this study provided valuable insights into the long-term effects of aSAH treatment and the ongoing challenges faced by the patients, shedding light on areas where medical care and support can be optimized.

8.2 Study II.

A good neurological outcome (mRS 0-2) was seen in 25% of the patients at 30 days and in 47% of the patients at 6 months. Cerebral infarction in relation to the vasospastic vessel was seen in 60% of the patients. Procedure related complications were seen in 10 patients in 10 different procedures.

8.3 Study III.

De novo aneurysms were identified in 13.6% of the patients, most were females with a median follow-up time of 20 years. More than half of these patients were treated for their de novo aneurysm.

With these results in mind, one should consider a longer follow-up regime at least for the younger patient population suffering an aneurysm. For uncomplicated patients that have gone through a coil embolization of an

aneurysm with or without stent, a 1-year diagnostic subtraction angiography (DSA) is part of our protocol before continuing on to do a 3-year follow-up MRA. For patients that have had their aneurysm microsurgically treated have previously only been followed clinically and not radiologically. Data on the rate of de novo aneurysm formation in patients previously treated for an aneurysm still remain scarce and differ in various studies.

8.4 Study IV.

This study included 77 patients, 6 out of these had more than one treatment. The mean imaging follow-up time was 47 months. The occlusion rate within 14 months was 73.8%. The follow-up aneurysm growth was 7.8%. We identified a 4% procedure-related mortality rate and a morbidity rate of 12%. Major complications occurred in 15.6%. At the time of the latest clinical evaluation 12% (10 patients) had a poor neurological outcome (mRS 3-6). An age of 70 years or older correlated poorly with occlusion within 14 months.

9. DISCUSSION

Cerebral aneurysms may lead to a sudden or acute condition with devastating both short- and long-term consequences. The importance of long-term follow-up post-cerebral aneurysm treatment is paramount, ensuring stability of the treated aneurysm and monitoring for potential development of de novo aneurysms or residual neck remnants. Wermer et al. highlight the significance of risk factors like hypertension, smoking, and family history in the development of de novo aneurysms.[93] Our findings underscore the necessity of secondary prevention, particularly in younger patients with modifiable risk factors like smoking and hypertension, due to their extended life expectancy.

In our initial study, we observed a high proportion of patients with favorable long-term outcomes across various treatment modalities. This contrasts with findings from Molyneux et al., where neurological outcomes in our cohort were superior to those in the UK cohort.[36] This discrepancy raises questions about potential selection bias in our study group or the possibility of more effective treatment protocols at Sahlgrenska University Hospital. In line with the 10-year follow-up of the Barrow Ruptured Aneurysm Trial (BRAT) and the ISAT long-term follow-up, we found no significant difference in good neurological outcomes between treatment groups[36,94]

The ISAT study indicated that coiling led to better short-term outcomes, like reduced morbidity and mortality, but long-term outcomes presented a more complex picture.[12] A study by Raymond et al. reported a higher rate of aneurysm recanalization after coiling compared to clipping in long-term follow-ups.[95]

Mental fatigue is a debilitating symptom frequently reported by patients recovering from aSAH.[96] It is characterized by reduced mental stamina and cognitive exhaustion, and it significantly impacts the quality of life and the

ability to resume to work or daily activities in patients recovering from their aSAH. Naidech et al.'s study emphasized its prevalence, with about 80% of aSAH survivors experiencing mental fatigue in the first year post-hemorrhage.[96] As it has previously been described in our studies, aSAH patient survivors often struggle with cognitive impairments that may persist long after the haemorrhage itself has been treated. Addressing mental fatigue in aSAH patients requires a comprehensive approach including cognitive rehabilitation, neuropsychological education and evaluation and support from a neurorehabilitation institute. Our study found that mental fatigue persisted in some patients more than 15 years post-aSAH, underscoring the need for specialized neurorehabilitation follow-up.

Cerebral vasospasm is a severe complication following SAH, often leading to DCI. As an experimental and often last resort treatment, IAN is used for the most severe cases of CVS. A study performed by Lannes et al. reported favourable outcomes in patients with SAH who received intra-arterial nimodipine. Their findings suggested improved cerebral blood flow, reduced incidence of DCI, and better clinical outcomes when compared to standard treatment alone.[97] Another systematic review and meta-analysis performed in the same year showed similar results.[98] However, our follow-up indicated that while half of the patients receiving IAN showed good neurological outcomes at six months, most had developed cerebral infarction despite the treatment. While the potential benefits of IAN are promising, the potential risks associated with this invasive procedure, such as catheter-related complications and potential embolic events, must be weighed carefully. Cagnazzo et al. found a low incidence of such complications, but emphasize the importance of judicious patient selection[99] However, like previously mentioned careful patient selection is deemed necessary in order to minimize the risks associated with this procedure. With these numbers in mind and with our follow-up

performed, almost half of all included patients experienced a good neurological recovery after 6 months. There were procedure related complications also in our study, which is like previously mentioned an important factor to be taken into consideration before planning for IAN. All these factors are important to consider when planning an adequate strategy for the few patients suffering CVS to the extent where we even consider IAN.

Flow diverter treatment has become an alternative for managing complex aneurysms or aneurysms previously not able to treat. Girdhar et al.'s meta-analysis reported high rates of complete occlusion or significant aneurysm size reduction following this treatment.[100] However, it's associated with risks like thromboembolic events, in-stent stenosis, and delayed aneurysm rupture.[99] Brinjikij et al. reported a 4.2% rate of major complications in a large cohort of patients treated with flow diverters, with thromboembolic events being the most common.[101] Our data also highlights the risk of in-stent stenosis and parent artery occlusion in acute treatments were higher due to the inability to premedicate the patients, however like stated above this treatment option has evolved since their introduction into the neurointerventional field 2007.

Minor adverse events in our study, occurred in 19.5% of cases, and ischemic complications were seen in 15.6%, pointing to the need for meticulous patient selection and strict management post-treatment.

10. CONCLUSION

The management and follow-up of patients with cerebral aneurysms are complex and several factors need to be taken into consideration when planning a treatment or follow-up strategy for each individual patient. With advances in diagnostic methods and treatment options, the prognosis and outcomes for patients have improved. However, challenges remain in regard to predict aneurysm rupture, optimize treatment, and ensure long-term patient well-being.

Long-term follow-up should be offered to either treatment modality chosen, to monitor for potential recurrences or de novo aneurysms, especially in the younger patient population.

Mental fatigue is a prevalent and challenging symptom in patients recovering from aSAH, also in the long-term. Addressing this early on in the neurorehabilitation process is essential for optimizing the quality of life and functional outcomes of aSAH survivors.

Intra-arterial nimodipine treatment is potentially an effective therapeutic option for managing cerebral vasospasm, however it is essential that this procedure is not without risks which is why careful patient selection are utmost essential.

Flow diverter treatment offers a huge potential for durable aneurysm occlusion, especially in the more complex and challenging cases. As the endovascular field continues to evolve, flow diverters are likely to play an increasingly important role in the endovascular treatment of intracranial aneurysms. Further development in this stent technology will make this treatment safer and more accessible in the future.

11. FUTURE PERSPECTIVES

Patients surviving an aSAH have a life expectancy of more than 25 years in most cases making long-term outcomes an important concern. The neurological outcome following an aSAH is influenced by various factors, including the severity of the initial bleeding, disease-related complications (such as vasospasm, hydrocephalus, and rebleeding), and complications related to aneurysm treatment. These complications can significantly affect a patient's long-term quality of life.

A randomized trial would have been interesting to conduct in order to compare the results in patients receiving IAN to those that do not. Seeming as this is still considered an experimental treatment, this would be an interesting study to conduct in the future.

Perhaps more intense neurorehabilitation and more long-term studies pointing towards a specific treatment regime in aSAH survivors suffering mental fatigue should be considered seeming as previous studies are all describing this symptom as extremely debilitating, also in the long-term. One might consider neuromarkers to play an increasingly larger role in the future, to evaluate if there is a correlation between the patients mental fatigue and their neuromarkers measured.

Given the limited data on de novo aneurysm formation after treating intracranial aneurysms, there is a growing need for additional data and guidelines for long-term follow-up, particularly among younger patients. Long-term studies are required to understand the natural history of aneurysms treated microsurgically or through the endovascular approach.

The flow diverter technology will continue to evolve and we will hopefully see the development of stents being less thrombogenic making them a safer treatment choice, especially in the acute phase when there are no possibilities

to premedicate the patients with dual antiplatelet therapy.

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