Pediatric Cerebral Artery Aneurysms

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Abstract

Background and purpose. Intracranial aneurysms in childhood are rare and population-based long-term follow-up studies are limited. In this study, a large clinical and angiographic long-term follow-up was carried out. The special characteristics of the patients and their aneurysms were assessed together with factors affecting early and long-term morbidity and mortality.

Materials and methods. All pediatric (≤18 years) aneurysm patients treated at the Department of Neurosurgery in Helsinki during 1937-2009 were followed from diagnosis until death or the end of the year 2011. For every patient, hospital records and radiological examinations were analyzed retrospectively. Later patient data were gathered from the referring hospitals. A new follow-up was organized as a written questionnaire to assess the latest clinical outcome. The long-term excess mortality was calculated by using relative survival ratio in these patients compared with the mortality of the general Finnish population matched by age, gender, and calendar time.

Results. Patients comprised 114 individuals with 130 aneurysms. The mean age of patients was 14.5 years (range 3 mths -18 yrs). The boy/girl ratio was 3:2. Altogether 89 patients (78%) presented with subarachnoid hemorrhage (SAH). The majority (n=116, 89%) of the aneurysms were in the anterior circulation, the most common location being internal carotid artery (ICA) bifurcation (n=36, 28%). The average aneurysm diameter was 11 mm (range 2-55 mm) with 16 giant aneurysms (12%). Of the aneurysms, 84 (65%) were treated surgically and 32 (25%) conservatively due to poor condition of the patient or for technical reasons during the early years of the series. After a mean follow-up time of 24.8 years (range 0-55.8 yrs), 71 patients (62%) had a good outcome, three (3%) were dependent, and 40 (35%) had died. Of the deaths, 68% were assessed to be aneurysm-related. Of the survivors, 91% lived independently at home and were meaningfully employed. Twenty-eight percent of the survivors were high school graduates. Factors correlating with a favorable long-term outcome were aneurysm location in the internal carotid artery or anterior communicating artery, operative treatment, and complete aneurysm closure postoperatively. Fourteen patients (12%) had a family history of aneurysms. Fifty-nine patients had long-term angiographic follow-up data (median follow-up 34 yrs; range 4-56 yrs). Of these patients, 24 (41%) were diagnosed with a total of 36 new aneurysms. There were 25 de novo-aneurysms and 11 recurrent aneurysms, and seven SAHs. The annual rate of development of de novo- or recurrent-aneurysm was 1.9% and that of hemorrhage 0.4%. There were no de novo aneurysms in patients with primarily unruptured aneurysms. Current or previous smoking (odds ratio [OR] 3.39, 95% confidence interval [CI] 1.02-11.29, p=0.047) was the only significant risk factor for de novo and recurrent aneurysm formation. Surprisingly, hypertension, gender, age at onset, initial number of aneurysms, initial rupture status, or family history had no statistically significant effect. No statistically significant independent risk factors for new SAH emerged. Cumulative risk of new SAH 40 years after the initial diagnosis was 15% (95% CI 5-25%). There was an overall excess mortality of 10% (cumulative RSR 0.90, 95% CI 0.80-0.95) and 19% (cumulative RSR 0.81, 95% CI 0.67-0.92) at 20 and 40 years after the diagnosis among one-year survivors, respectively. The excess mortality was particularly high in male patients. Aneurysm-related deaths included rebleedings from open or partially occluded aneurysms, epileptic seizures, de novo and recurrent aneurysms, or sequelae of SAH.

Conclusions. Most aneurysms were ruptured and of medium size. ICA bifurcation was the most common location, and males were predominantly affected. Most patients had a good recovery, but almost half of them developed de novo and recurrent aneurysms during a follow-up of 34 years, with smoking being a major risk factor. A long-term excess mortality exists in pediatric aneurysm patients, especially males, even decades after successful treatment of a ruptured aneurysm. The excess mortality is mainly aneurysm-related. A life-long angiographic follow-up is mandatory in these patients.

Tiivistelmä

Tausta ja tarkoitus. Aivovaltimoaneurysmat ovat harvinaisia lapsilla, ja tämän potilasryhmän väestöpohjaiset pitkäaikaiset seurantatutkimukset ovat rajallisia. Tässä tutkimuksessa suoritettiin kliininen ja radiologinen pitkäaikaisseuranta lapsuudessa aivovaltimoaneurysmadiagnoosin saaneille potilaille. Potilaiden ja aneurysmien erityispiirteet määritettiin, sekä selvitettiin tämän potilasryhmän pitkän aikavälin sairastuvuus sekä ylikuolleisuus. Potilaiden riski saada uusia aneurysmia sekä uusi aneurysmavuoto selvitettiin, sekä arvioitiin näihin vaikuttavat riskitekijät.

Materiaalit ja menetelmät. Kaikkien Helsingissä Neurokirurgian klinikassa vuosien 1937-2009 aikana hoidettujen aneurysmadiagnoosin saaneiden lapsipotilaiden (≤ 18 vuotta) sairaskertomushistoria selvitettiin. Potilaan kliiniset tiedot röntgenkuvineen analysoitiin, ja myöhempi sairaushistoria selvitettiin muista sairaaloista. Uusi seuranta järjestettiin kirjallisena kyselytutkimuksena. Pitkän aikavälin kuolleisuus laskettiin käyttäen suhteellista eloonjääntiä verrattuna ikä-, sukupuoli- ja kalenteri-ikä-vakioituun Suomen väestöön.

Tulokset. Seuranta-aikana hoidettiin 114 lapsianeurysmapotilasta, joilla oli yhteensä 130 aneurysmaa. Potilaiden keski-ikä oli 14,5 vuotta (vaihteluväli 3 kk -18 v). Poika/tyttö-suhde oli 3:2. 89 (78%) potilaalla oli lukinkalvonalainen verenvuoto (SAV). Suurin osa, 28%, aneurysmista sijaitsi sisemmän kaulavaltimon huipussa. Keskimääräinen aneurysman halkaisija oli 11 mm (vaihteluväli 2-55 mm) ja aneurysmista 16 (12%) oli kooltaan jättianeurysmia. Potilaista 65%:lla aneurysma hoidettiin kirurgisesti. Syynä konservatiiviseen hoitoon oli potilaan huono kliininen vointi tai aneurysman soveltumattomuus kirurgiseen hoitoon potilassarjan alkuvuosina. 24,8 vuoden (vaihteluväli 0-55,8 v) seurannassa potilaista 71 (62%) oli toipunut hyvin, kolme (3%) oli muiden hoidosta riippuvaisia ja 40 (35%) oli kuollut. 68% kuolemista arvioitiin olevan aneurysmaan liittyviä. Eloonjääneistä 91% asui itsenäisesti kotona ja oli työelämässä tai opiskeli. 28% eloonjääneistä oli suorittanut vähintään lukion oppimäärän. Suotuisaan pitkän aikavälin ennusteeseen vaikuttivat aneurysman sijainti sisemmän kaulavaltimon tai etummaisen yhdysvaltimon alueella, operatiivinen hoito ja täydellinen aneurysman sulku. Neljäntoista (12%) potilaan suvussa oli taipumus aivovaltimoaneurysmiin. Potilaista 59:llä oli radiologisia seurantatietoja aneurysmasta (mediaani seuranta-aika 34 v, vaihteluväli 4-56 v). Näistä 24 (41%) potilaalla diagnosoitiin yhteensä 36 uutta aneurysmaa, joista 25 oli de novo-aneurysmia ja 11 uusiutuneita aneurysmia. Seitsemän uutta SAV:tä diagnosoitiin. Vuotuinen riski de novo- tai uusiutuneelle aneurysmalle oli 1,9%, ja SAV:lle 0,4%. Nykyinen ja aiempi tupakointi (riskisuhde [OR], 3.39, 95% luottamusväli [CI] 1.02-11.29, p = 0,047) oli ainoa tilastollisesti merkittävä riskitekijä de novo- ja uusiutuneiden aneurysmien muodostumiselle. Verenpainetaudilla, sukupuolella, iällä diagnoosihetkellä, alkuperäisen aneurysman vuotostatuksella tai suvun aneurysmataipumuksella ei ollut tilastollisesti merkitsevää vaikutusta uusien aneurysmien syntyyn. Uudelle SAV:lle ei löytynyt tilastollisesti merkitseviä itsenäistä riskitekijöitä. Uuden SAV:n kumulatiivinen riski 40 vuotta ensimmäisen vuodon jälkeen oli 15% (95% CI 5-25%). Potilailla, jotka olivat elossa vuoden kuluttua aneurysmadiagnoosista, oli 20 vuoden kohdalla 10%:n (kumulatiivinen RSR 0,90, 95% CI 0,80-0,95) ja 40 vuoden kohdalla 19%:n (kumulatiivinen RSR 0,81, 95% CI 0,67-0,92) ylikuolleisuus. Aneurysmaan liittyvät kuolemat johtuivat mm. uusintavuodosta, joka aiheutui avoimesta tai osittain suljetusta aneurysmasta, epileptisistä kohtauksista, sekä de novo- ja uusiutuneiden aneurysmien aiheuttamista uusista SAV:sta.

Johtopäätökset. Useimmat aneurysmista olivat vuotaneita ja keskikokoisia. Sisemmän kaulavaltimon huippu oli aneurysmien yleisin sijaintipaikka. Valtaosa potilaista oli poikia. Useimmat potilaat toipuivat hyvin, mutta lähes puolella heistä todettiin uusi aneurysma yli 34 vuoden pitkäaikaisseurannassa. Tupakointi oli ainoa merkittävä riskitekijä uuden aneurysman synnylle. Lapsuudessa aivovaltimoaneurysmadiagnoosin saaneilla potilailla todettiin pitkäaikaisseurannassa ylikuolleisuutta vuosikymmeniä onnistuneenkin aneurysman hoidon jälkeen, etenkin miespotilailla. Tämä ylikuolleisuus johtuu lähinnä aneurysmariippuvista tekijöistä. Näiden potilaiden elinikäinen radiologinen seuranta on perusteltua.

Abstrakt

Bakgrund och syfte. Med ett aneurysm avses en tunväggig, påsartad dilatation av en artär. Ruptur av ett aneurysm i en hjärnartär leder till en subarachnoidalblödning (SAH). Intrakraniella aneurysm hos barn är ovanliga och det har publicerats endast ett fåtal populationsbaserade studier om långtidsprognosen. I detta arbete presenteras en stor klinisk och angiografisk långtidsuppföljning av aneurysm hos barnpatienter. Patienternas och aneurysmens kliniska särdrag evaluerades jämte faktorer som känt påverkar långtidsprognosen och dödligheten hos aneurysmpatienter.

Material och metoder. Alla pediatriska (≤ 18 år) aneurysmpatienter vid Neurokirurgiska kliniken i Helsingfors under 1937-2009 uppföljdes från diagnos till döden eller slutet av år 2010. Varje patients sjukhusjournaler och radiologiska undersökningar analyserades retrospektivt. Senare patientdata insamlades från andra sjukhus. De färskaste uppgifterna insamlades medelst en skriftlig enkät i syfte att utvärdera patienternas kliniska tillstånd. Långtidsöverlevnaden beräknades med hjälp av ett statistiskt program som jämför den relativa överlevnaden hos dessa patienter med genomsnittsöverlevnaden hos Finlands befolkning anpassat efter ålder, kön och kalendertid.

Resultat. Studien omfattar 114 patienter med 130 aneurysm. Medelåldern hos patienterna var 14,5 år (intervall 3 mån -18 år). Pojke/flicka förhållandet var 3:2. 89 (78%) av patienterna uppvisade en SAH. Majoriteten (n = 116, 89%) av aneurysmen var lokaliserade till den främre cirkulationen, och den vanligaste platsen var inre karotidartärens (ICA) bifurkation (n = 36, 28%). Den genomsnittliga aneurysm- diametern var 11 mm (intervall 2-55 mm) med 16 (12%) jätteaneurysm (största diametern över 25mm). 84 (65%) av aneurysmen behandlades kirurgiskt och 32 (25%) behandlades konservativt på grund av av patientens medtagna tillstånd eller av tekniska skäl under de första åren i serien. Efter en genomsnittlig uppföljningstid på 24,8 år (intervall 0-55,8 år) hade 71 (62%) patienterna ett bra resultat, tre (3%) behövde kontinuerlig vård och 40 (35%) hade avlidit. 68% av dödsfallen bedömdes vara aneurysmrelaterade. Av de överlevande bodde 91% självständigt hemma och hade ett självständigt arbete. 28% av de överlevande hade avlagt studentexamen. Faktorer som korrelerar med en gynnsam prognos var aneurysmets lokalisation i ICA eller främre förbindelseartären (ACoA), operativ behandling och fullständig tillslutning av aneurysmet postoperativt. Fjorton (12%) patienter hade en positiv familjehistoria för hjärnartäraneurysm. Femtionio patienter hade angiografiska långtidsuppföljningsdata (medianen för uppföljningstiden 34 år, intervallen 4-56 år). Av dessa diagnostiserades 24 (41%) med totalt 36 nya aneurysm. Det fanns 25 nya (de novo) aneurysm och 11 recidivaneurysm och sju patienter drabbades av en SAH under uppföljningstiden. Risken för utveckling av ett de novo eller recidivaneurysm var 1,9%/ år och för blödning 0,4%/år. Det fanns inga de novo aneurysm hos patienter med primärt inte rupturerat aneurysm. Fortgående och även tidigare avslutad rökning var den enda betydande riskfaktorn för bildning av de novo och recidivaneurysm(oddskvot [OR], 3,39, 95% CI, 1,02 till 11,29, p = 0,047). Förhöjt blodtryck, kön, ålder vid insjuknandet, ruptur/icke ruptur av aneurysmet primärt eller positiv släkthistoria hade ingen statistiskt signifikant betydelse. Det fanns inga statistiskt signifikanta oberoende riskfaktorer för en ny SAH. Den kumulativa risken för en ny SAH 40 år efter den första diagnosen var 15% (95% CI, 5-25%). Studien visade en överdödlighet på 10% (kumulativ RSR 0,90, 95% konfidensintervall (CI) 0,80 till 0,95) och 19% (kumulativ RSR 0,81, 95% CI 0,67 till 0,92) vid 20 respektive 40 år hos de patienter som överlevt åtminstone ett år efter det att diagnosen ställts. Överdödligheten var betydligt högre hos män. De aneurysmrelaterade dödsfallen innefattade återblödning från öppna eller delvis tillslutna aneurysm, epileptiska anfall, de novo och recidivaneurysm eller följder av en SAH.

Slutsatser. De flesta aneurysmen hade rupturerat och var medelstora. ICA bifurkationen var den vanligaste lokalisationen. Aneurysm förekom mera allmänt hos män. De flesta patienterna återhämtade sig väl, men nästan hälften av dem utvecklade de novo eller recidivaneurysm under en genomsnittlig uppföljning på 34 år med rökning som en viktig riskfaktor. Barnpatienter med hjärnartäraneurysm uppvisar en överdödlighet även decennier efter framgångsrik behandling av ett rupturerat aneurysm, speciellt hos män. Överdödligheten är huvudsakligen relaterad till aneurysmet. En livslång uppföljning med upprepade angiografier är av nöden hos dessa patienter.

Abbreviations

AC	Aortic coarctation
ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
ADPKD	Autosomal dominant polycystic kidney disease
AVM	Arteriovenous malformation
BA	Basilar artery
CCA	Common carotid artery
CFD	Computational fluid dynamics
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
DCI	Delayed cerebral infarct
DIND	Delayed ischemic neurologic deficit
DSA	Digital subtraction angiography
ELANA	Excimer laser-assisted nonocclusive anastomosis
ETV	Endoscopic third ventriculostomy
EVD	External ventricular drainage
FMD	Fibromuscular dysplasia
GDC	Guglielmi detachable coil
GOS	Glasgow outcome scale
HIV	Human immunodeficiency virus
HUCH	Helsinki University Central Hospital
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ISPN	International Society of Paediatric Neurosurgery
IVH	Intraventricular hemorrhage
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
NF-1	Neurofibromatosis type 1
OI	Osteogenesis imperfecta
OR	Odds ratio
PCA	Posterior cerebral artery
PCoA	Posterior communicating artery
PICA	Posterior inferior cerebellar artery
PXE	Pseudoxanthoma elasticum
RSR	Relative survival ratio
SAH	Subarachnoid hemorrhage
SCA	Superior cerebellar artery
TCD	Transcranial Doppler
WSS	Wall shear stress

List of Original Publications

I   Koroknay-Pál P, Lehto H, Niemelä M, Kivisaari R, and Hernesniemi J.
Long-term outcome of 114 children with cerebral aneurysms.
Journal of Neurosurgery: Pediatrics 2012 June; 9(6): 636-645.

II   Koroknay-Pál P, Laakso A, Lehto H, Seppä K, Kivisaari R, Hernesniemi J, and Niemelä M.
Long-term excess mortality in pediatric intracranial aneurysm patients.
Stroke. 2012 Aug; 43(8): 2091-2096.

III   Koroknay-Pál P, Niemelä M, Lehto H, Kivisaari R, Numminen J, Laakso A, and Hernesniemi J
De novo and recurrent aneurysms in pediatric patients with cerebral aneurysms.
Submitted.

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1. Introduction

Intracranial arterial aneurysms are a fairly common cerebrovascular disease, affecting about 1-5% of the general population.[241] Rupture of an aneurysm is a sudden and devastating incident that results in subarachnoid hemorrhage (SAH). Initial bleeding from a ruptured aneurysm is fatal in 12-15% of cases, with death often occuring before patients even reach the hospital.[90,93,211,222,262] Rebleeding of an aneurysm is a feared event, and its consequences have a significant impact on mortality and morbidity.[190] Ruptured aneurysms are therefore nowadays usually treated within 24-48 hours of the rupture. Treatment methods include microsurgical clipping of the aneurysm neck by a neurosurgeon or endovascular techniques where the aneurysm is occluded through intra-arterial techniques performed by a neuroradiologist.

Aneurysmal SAH affects about 100 000 people yearly in Western countries,[8,37,49,130,206] being most prevalent in the working population, in people in their 40's and 50's.[183,312] In children and adolescents, by contrast, intracranial aneurysms are rare, constituting only about 0.5-2% of all aneurysms. [3,81,87,117,207,216,249]

In adult patients, acquired risk factors for aneurysm growth and rupture are smoking, hypertension, and excessive alcohol consumption,[50] factors practically nonexistent in children. Connective tissue disorders causing fragile vessel walls, and congenital heart diseases causing elevated blood pressure are known risk factors for intracranial aneurysm formation in children.[207,216,254,264] Pediatric aneurysm patients differ from adults also regarding their clinical presentation, aneurysm morphology, and outcome.[135,270] There is a male predominance[159,207] and aneurysms tend to be larger in children.[3] Moreover, the location of aneurysms differs between children and adults.[225]

The overall one-year case fatality after SAH in adult patients is about 50%.[58,75] During the last decades the case-fatality rate has not improved markedly.[90] Patients who survive SAH have a higher occurrence of a new SAH than in the general population, even after successful treatment of the initial aneurysm, due to de novo- and recurrent-aneurysms.[20,321] Among adult SAH patients, long-term excess mortality has been described[101,242] to be mainly due to the high incidence of cardiovascular deaths.

Population-based long-term follow-up studies among pediatric patients are scarce. Over the years, some case reports,[43,65,67-69,71,105,157,182,188,200,223,231,271,272,289,291,325,336,337] and smaller patient series together with literature reviews [2,3,22,80-82,87,92,110,117,135,159,171,180,193,207,215,216,225,249,250,265,270,282,307,333] have been published. In pediatric patients, long-term angiographic follow-up studies are quite rare; available studies have mean follow-up times of 4-6 years.[86,117,250] No long-term excess mortality studies have been published among children and adolescents with intracranial aneurysms.

In this study, data on long-term clinical and angiographic follow-up studies of pediatric intracranial aneurysm patients admitted to the Department of Neurosurgery, Helsinki University Central Hospital (HUCH), during 1937-2009 were gathered. Special characteristics of these patients and factors affecting long-term outcome were assessed. Patient survival was set to define long-term excess mortality. The annual rate of these patients to develop de novo- and recurrent aneurysms, and new SAH together with the risk factors for these events were assessed.

Finland is ideal for long-term follow-up studies due to our high-quality public health care system with population responsibility and accessible hospital records and patient registries together with a stable and geographically relatively isolated population of 5.4 million. Typically, patients can be located even after decades and most are willing to participate in follow-up studies.

2. Review of the literature

2.1 Intracranial aneurysms and subarachnoid hemorrhage in the adult population

The prevalence of cerebral aneurysms in the adult population is estimated to be 1-5%.[233,241] Thus, over 100 000 adults in Finland are potentially carrying unruptured aneurysms. Aneurysms are typically located at the branching points of arteries in the Circle of Willis (Figure 1). Saccular intracranial aneurysm disease is complex, like hypertension or diabetes type 2, with a familial predisposition.[100] Its genomics is currently being studied.[62,331,332] Risk factors for aneurysm formation are female gender,[233] hypertension, hypercholesterolemia, smoking, and heart disease.[103] In Finland, as in Japan, the incidence of SAH is threefold that of other industrialized countries,[57,211,252] and about 1000 new SAHs are diagnosed yearly. In about 30% of patients, multiple aneurysms occur.[234,236] Risk factors for aneurysm rupture are female gender, older age, smoking, exten-sive alcohol consumption, family history, and large size and location of aneurysms.[14,37,88,106,114,116,324,327] A recent study showed that the locations of ruptured and unruptured aneurysms varied, suggesting different etiological reasons for the formation and rupture of cerebral aneurysms.[100] Furthermore, the role of family history and genetics in aneurysmal SAH has recently been under discussion.[133] The differential impact of known risk factors on formation of intracranial aneurysms or rupture of the aneurysm wall is not clear. Minor proportions of aneurysms are due to direct vascular trauma (i.e. traumatic aneurysms)[10,137] or bacterial infection (i.e. mycotic aneurysms).[31,59,137] The overall case fatality during the first year is about 50%; this figure has remained the same over the last few decades.[90,222,273,280] Vasospasm and rebleedings have a major effect on outcome,[124] together with the neurological condition of the patient on admission, age, Fisher grade[54] (see Appendix I), aneurysm location,[243] and co-morbidities.[124] Overall, 60-80% of adult SAH patients have a favorable outcome (Glasgow outcome scale (GOS)≥4).[85,132,253] Previous SAH patients have a higher occurrence of a new SAH than in the general population, even after successful treatment of the initial aneurysm, due to de novo and recurrent aneurysms.[20,302,321]
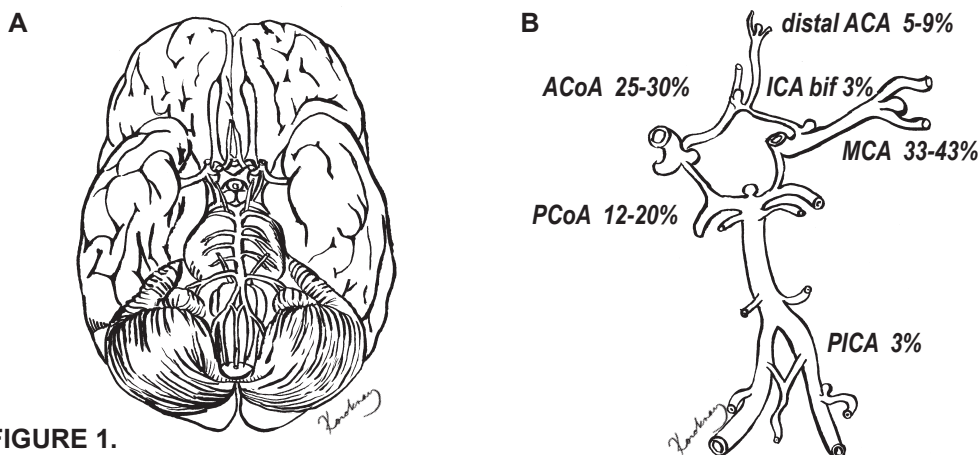
FIGURE 1.

Base of the brain and Circle of Willis (A). Typical locations of aneurysms with proportions in adult SAH patients (B).[35,84,100,166,168,234,235,319] ACA = anterior cerebral artery, ACoA= anterior communicating artery, MCA=middle cerebral artery, ICA bif =internal carotid artery bifurcation, PCoA =posterior communicating artery, PICA = posterior inferior cerebellar artery.

2.2. Pediatric hemorrhagic stroke

Pediatric stroke is a rather frequent cause of death in childhood, with an incidence of 2–13 /100 000 children.[30] About half of the strokes in the young are hemorrhagic,[109] including both intracerebral hemorrhages (ICH) and non-traumatic SAH. The other half, arterial ischemic stroke and cerebral venous thrombosis, are referred to as ischemic stroke, both resulting in venous infarction. The most frequent cause of hemorrhagic stroke in children is rupture of an arteriovenous malformation (AVM), constituting 30% of all hemorrhagic strokes.[30] Cerebral aneurysms account for about 13% of hemorrhagic strokes.[110] Cavernous malformations,[110,275] Moyamoya disease,[102,276] and sickle cell disease[286] may also present with hemorrhagic stroke in the pediatric population.[30]

Intracranial aneurysms in children constitute about 0.5-4% of all aneurysms.[3,159] Only a few institutional series (Table 1) and case reports (Table 2), have been published on these rare patients.

2.2.1. Pathobiology of aneurysms

In the adult population, intracranial aneurysms are regarded as acquired rather than congenital vascular lesions. However, risk factors for aneurysm formation that are common in the adult aneurysm population are virtually absent in the pediatric population, indicating distinct modes of pathogenesis of cerebral aneurysms in these populations.[1] Co-morbidities predisposing children to intracranial aneurysms include systemic connective tissue disorders and congenital heart diseases that elevate blood pressure. A classification according to the pathogenetic mechanism of pediatric intracranial arterial aneurysms has been proposed with eight distinct categories: idiopathic, traumatic, those due to excessive hemodynamic stress, vasculopathic, infectious, noninfectious inflammatory, oncotic, and familial.[1]

2.2.1.1. Development of intracranial arteries

Development of cerebral vasculature is staged according to Padgett's seven stages.[251] The arterial system in the fetal brain is determined early,[229] essentially achieving an adult pattern by the end of the embryonic period (embryonal week eight), whereas the venous system develops later in the fetal period.[251,301]

2.2.1.2. Normal arterial wall versus aneurysm wall

The wall of a normal healthy artery is divided into three distinctive layers, i.e. the tunica intima, tunica media, and tunica adventitia. Intracranial medium-sized arteries have smooth muscle cells in both intimal and medial layers and a prominent elastic membrane in the intimal layer. The main components in the connective tissue of the artery wall are collagen, elastin, and proteoglycans.[184] Collagen is the major connective tissue in the medial layer. In the arterial bifurcations, a common location for aneurysms, the collagen is organized in such a way that further stabilizes the bifurcation region.[52] The connective tissue maintains the configuration of the artery and is responsible for the stretching properties and tensile strength of the artery. The majority, 80-90%, of the collagens in arteries are of types I and III.[184] Type IV collagen exists in the basement membrane.[191]

The exact mechanisms by which aneurysms form are unknown. The wall of a cerebral artery is thinner than that of other equally sized arteries.[184] The intracranial arteries lack the outer elastic membrane between the tunica media and tunica adventitia. Furthermore, in the subarachnoid space, the cerebral arteries do not have physical support from surrounding tissues, contrary to the arteries in other parts of the body.[266]

TABLE 1.
Pediatric aneurysm patients series with year published, number of patients (No.), patient's age and proportion of patients presenting with subarachnoid hemorrhage (SAH).

Author	Year	No.	Age (yrs)	SAH (%)	Author	Year	No.	Age (yrs)	SAH (%)
Patel et al. [216]	1971	58	≤20	100	Krishna et al.[135]	2005	22	≤18	91
Sedzimir et al. [265]	1973	50	≤20	100	Huang et al. [92]	2005	19	≤18	58
Heiskanen et al. † [81]	1981	32	≤19	100	Sanai et al. [250]	2006	32	≤18	22
Ostergaard et al. [207]	1983	43	≤19	77	Sharma et al. [270]	2007	55	≤18	78
Pasqualin et al. [215]	1986	31	≤20	96	Stiefel at al. [282]	2008	12	≤16	100
Heiskanen et al. † [80]	1989	16	<20	100	Vaid et al. [307]	2008	27	≤18	100
Meyer et al. [193]	1989	23	≤18	57	Liang et al. [171]	2009	24	≤14	46
Herman et al. [82]	1991	16	≤18	44	Hetts et al. [87]	2009	77	≤18	32
Drake et al.[40] ‡	1996	49	≤18	49	Jordan et al. [110]	2009	15	≤19	100
Allison et al.[3]	1998	21	≤15	71	Songsaeng et al. [278]	2009	8	<16	25
Proust et al. [225]	2001	22	≤16	95	Lv et al. [180]	2009	25	≤17	11
Lasjaunias et al. [159]	2005	59	≤15	51	Sanai et al. [249]	2010	32	≤18	44
Agid et al. [2]	2005	33	≤17	36	Kakarla et al. [117]	2010	48	≤18	17
Present series		114	≤18	78	Present series		114	≤18	78

† patient material partly overlapping

‡ only posterior circulation aneurysms

TABLE 2.
Case reports of pediatric aneurysm patients with years published.

Author	Year
Vapalahti et al. [313]	1969
Manz et al. [188]	1979
Iob et al. [105]	1983
Lansen et al. [157]	1989
Nishio et al. [200]	1991
Willemsen et al. [325]	1997
Gewirtz[65]	1998
Young et al. [336]	2000
Grosso[71]	2002
Zhang et al. [337]	2002
Sungarian et al. [289]	2003
Gralla[69]	2004
Gonzales-Portillo[68]	2006
Prochazka et al. [223]	2007
Tanaka et al. [291]	2007
Eddleman[43]	2007
Mahadevan et al. [182]	2008
Reig et al.[231]	2009
Goedee[67]	2009
Shih et al. [272]	2010
Shelton et al. [271]	2011
Sabanci et al. [247]	2012

Age has an impact on the thickness of the intimal layer; children have a thin layer, while in older vessels the intimal layer has thickened due to lipid deposits. Hypertension affects the medial layer by increasing the amount of smooth muscle cells, whereas atherosclerosis affects the intimal layer with lipid accumulation and fibrofatty lesions. In the aneurysm wall, fibrosis of the medial layer is found at the expense of loss of muscle mass, i.e. there are gaps in the media layer where normal muscle tissue is replaced by connective tissue.[52] In studies of pediatric human immunodeficiency virus (HIV)-related intracerebral aneurysms, destruction of the internal elastic lamina and hyperplasia of the intimal layer were also found.[41,140] Studies focusing on the histology of ruptured aneurysm walls have revealed the underlying role of inflammation processes.[60,304,305] The complement system becomes activated by the classical pathway in intracranial aneurysm walls.[303]

2.2.1.3. Flow dynamics

Blood flow dynamics inside cerebral aneurysms and in their vicinity has been implicated in aneurysm study. Computational fluid dynamics (CFD) simulations of intracranial aneurysm hemodynamics have in recent years been used to evaluate the risk of growth and rupture of unruptured aneurysms.[53] Wall shear stress (WSS) expresses the force per unit area exerted by the wall on the fluid along the local tangent plane.[126] Vessel wall remodeling as a result of WSS alteration is accompanied by synthesis and secretion of nitrogen oxide, growth factors, and metalloproteins.[212] The temporospatial variations of aneurysm wall pressure and WSS in the aneurysm are assumed to correlate with continuous expansion and eventual rupture.[309] These simulations usually adopt simplifications of Newtonian and non-Newtonian[53] blood rheology models. Models are used to produce intra-aneurysmal flow patterns and surface distributions of shear rate, blood viscosity, and WSS. CFD has also been implicated

in the hemodynamic effects of aneurysm coil embolization.[263] A recent study suggested that the combination of high WSS and high positive spatial WSS gradient focused on a small segment of the arterial wall may have a role in the initiation of aneurysm formation.[136]

2.2.2. Special characteristics of pediatric patients

Altogether 26 patient series on pediatric cerebral aneurysms together with 22 case reports were found in the literature (Tables 1 and 2). The total number of patients in the literature review was 871, with 949 aneurysms. The majority (56%) of the patients were males.

2.2.2.1. Gender and age

There is a male predominance throughout the literature in pediatric aneurysm patients.[159,207] In a series with 59 patients, the overall male to female ratio was 3:2; however, among children under two years of age, the incidence of aneurysms was higher in girls (girl:boy ratio 5:1).[159] Aneurysms in infants are extremely rare.[313] In patients harboring aneurysms during the first year of life, 21% were reported to have co-morbidities such as cutaneous vascular disorder, autosomal dominant polycystic kidney disease (ADPKD), or brain tumors.[22]

2.2.2.2. Predisposing factors

Disorders generally known to predispose children to intracranial aneurysms include ADPKD, tuberous sclerosis complex, Marfan syndrome, osteogenesis imperfecta, Ehlers-Danlos syndrome, and fibromuscular dysplasia. Aortic coarctation causing elevated blood pressure in the vascular system above the coarctation causes extensive hemodynamic stress to intracranial arteries. The incidence, patterns of inheritance, and systemic manifestations of these disorders are presented in Table 3.

Autosomal dominant polycystic kidney disease

ADPKD is the most common inherited kidney disorder.[296] Patients with ADPKD have an increased frequency of intracranial aneurysms, with estimates of prevalence ranging from 4% to 41%, and the morbidity of aneurysmal SAH is higher in patients with ADPKD.[17,25] In a recent study,[328] over 350 patients with ADPKD aged 7-78 years were screened for intracranial aneurysms, and 12% were found to harbor them, this figure being more common than in previous studies.[98,245] There was only one patient with aneurysms under the age of 29 years; however, information about the exact age is not provided.[328] The prevalence of intracranial aneurysms increases with age, reaching a peak value of 23% in patients over 60 years of age, and being higher in patients with a positive family history for aneurysms.[328] Thus, the study recommends systematic screening of intracranial aneurysms for patients with ADPKD, particularly adult patients (>30 years) or patients with a positive family history for aneurysms.[328] A Finnish study showed that members of ADPKD families share a high risk of having intracranial aneurysms, but the risk is comparable with that of familial intracranial aneurysm families.[240] For pediatric patients, it has been proposed that ADPKD in a child with a positive family history for intracranial aneurysms warrants screening for intracranial aneurysms.[238]

TABLE 3.

Connective tissue disorders predisposing to intracranial arterial aneurysm formation in childhood.
AD=autosomal dominant, ADPKD=autosomal dominant polycystic kidney disease, AR=autosomal recessive.

	Incidence	Inheritance	Manifestations
ADPKD[33]	1-2/1000	AD	Hypertension, hepatic cysts
Marfan Sdr[226]	1/5000	AD	Aortic stenosis, myopia
Osteogenesis imperfecta[310]	6–7/100 000•[281]	AD†	Bone fractures, hearing loss
Tuberosis sclerosis[248]	1/6000	AD	Hamartomas, giant cell astrocytoma
Pseudoxanthoma elasticum[306]	1/25000•[26]	AR‡	Ocular, dermal and cardiovascular
Ehlers-Danlos Sdr type IV[12]	0.4-1/100000	AD	Arterial, intestinal and uterine ruptures
Neurofibromatosis type I[185]	1/3000[202]	AD	Neurofibromas, optic glioma
Fibromuscular dysplasia[297]	2/100	AD	Hypertension, ischemic renal atrophy

• birth prevalence
† 10% recessive variants in eight other genes[310]
‡ rarely AD[220]

Tuberous sclerosis complex

Tuberous sclerosis complex is a neurocutaneous syndrome with a variable clinical expression. It is a multisystem disorder that may be associated with hamartomas in multiple organs in an unpredictable manner. However, vascular involvement in tuberous sclerosis is rare.[248] Central and peripheral aneurysms and large- and medium-sized arterial stenotic-occlusive disease have been reported.[271,248,298] In a review article, 15 cases of tuberous sclerosis patients diagnosed with intracranial aneurysm were identified.[9] However, no screening for aneurysms in asymptomatic patients is recommended.[9] Intracranial aneurysms associated with tuberous sclerosis are mainly fusiform in shape.

Marfan sydrome

Marfan syndrome usually manifests with abnormalities in bones, eyes, heart, and vascular system.[226] Marfan syndrome results in abnormal elastic tissue, with a defect in the fibrillin gene. Recent studies have also revealed the role of dysregulation of cytokine-transforming growth factor beta signaling in Marfan syndrome.[13] Neurovascular symptoms associated with this syndrome include arterial dissections and (saccular) intracranial aneurysms.[257] In an autopsy study[260] with adult Marfan syndrome patients, 29% were diagnosed as having intracranial aneurysms. On microscopic examination, the cerebral arteries had intimal proliferation, medial degeneration, and fragmentation of the internal elastic lamina.[260]

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a heterogeneous group of heritable disorders characterized by increased bone fragility.[310] The neurologic complications mostly concern skeletal disorders such as basilar invagination. OI is associated with type I collagen abnormalities, which may cause vascular complications. However, the cerebrovascular system is not usually involved in OI.[218] Some cases of carotid-cavernous fistulae and vertebral artery dissections in OI patients have been reported.[257] Aneurysmal SAH is extremely rare.[189]

Ehlers-Danlos syndrome type IV

Ehlers-Danlos syndrome is a diverse group of connective tissue disorders.[184] Typical findings include abnormal skin elasticity, impaired healing of wounds, joint hypermobility, and overall tissue fragility. Patients diagnosed with Ehlers-Danlos syndrome type IV, also called vascular Ehlers-Danlos syndrome, notoriously have fragile blood vessels due to abnormal procollagen III synthesis,[12] and the reported mortality rate for any type of vascular surgical procedure is high.[63,204,256] Typical neurovascular complications of Ehlers-Danlos syndrome are carotid-cavernous fistulae, intracranial aneurysms, and cervical artery dissections.[257] The youngest child described with Ehlers-Danlos syndrome type IV and intracranial aneurysms is a 5-year-old girl.[125]

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum (PXE) mainly presents with anomalies of the skin, eye, heart, and vascular system.[306] It is characterized by ectopic mineralization and fragmentation of elastic fibers of connective tissues.[306] Premature arteriosclerosis in small- and medium-sized arteries leads to ischemic consequences.[184] Neurovascular disease in PXE is characterized by intracranial aneurysms and cerebral ischemia caused by premature arterial occlusive disease.[257]

Neurofibromatosis type 1

Even though neurofibromatosis type 1 (NF-1) is mainly defined by neurocutaneous findings, this syndrome is associated with severe abnormalities of bones, arteries, and veins.[185,202,244] Intracranial occlusive arterial disease is the most common neurovascular manifestation of neurofibromatosis, followed by cervical arteriovenous fistulae and aneurysms and intracranial aneurysms.[257] In a retrospective analysis of 22 adult patients with NF-1 undergoing head MRI, incidental intracranial aneurysms were detected in 9%.[261] In a review article of 316 patients with NF-1 who underwent brain MRI, 8 children (2.5%) were reported to have an abnormality of the cerebrovascular system, including narrowed or ectatic vessels, vascular stenoses, aneurysm, and moyamoya.[244] Intracranial aneurysms in pediatric NF-1 patients are rarely reported.[47] In fact, in an autopsy study with neuropathological investigation of 25 NF-1 patients no intracranial aneurysms were found.[34]

Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is an uncommon, segmental, nonatherosclerotic, and noninflammatory arterial disease of unknown etiology.[297] It commonly affects the renal and cervical internal carotid arteries and sometimes the vertebral arteries.[129] Although often asymptomatic, FMD can also be associated with spontaneous dissection, severe stenosis, and intracranial aneurysms.[297] A few case reports of pediatric patients with FMD and intracranial aneurysms exists.[201,203,213]

Aortic coarctation

In a study from Mayo Clinic,[259] congenital heart disease was diagnosed in 8% of the children with intracranial aneurysms. Coarctation of the aorta (AC) accounts for 4-8% of congenital heart diseases.[24,173,195] AC is a narrowing of

the aorta, most commonly distal to the origin of the left subclavian artery, thus causing elevated blood pressure and hemodynamic stress to arteries proximal to the coarctation. The incidence of AC is ca. 0.3-0.4/1000 live births,[208] and approximately ten new cases are diagnosed yearly in Finland. The narrowing of the aorta is treated by open surgery or angioplasty and stenting, depending on the child's age.

Intracranial aneurysms are found more often in patients with AC than in the general population, and aneurysm rupture occurs much earlier in the lives of these patients when there is coexistent AC.[264] The main pathobiology behind this has been thought to be high blood pressure in cranial arteries.

2.2.3. Special characteristics of aneurysms in children

In the literature review of 871 patients, the most common location for aneurysm in a pediatric patient was the internal carotid artery (ICA), typically the ICA bifurcation (Figure 2). The aneurysms were of medium size and 65% had ruptured. Of vertebrobasilar artery aneurysms in children, the most common locations are the midbasilar trunk (31%) and basilar bifurcation (16%).[40]

2.2.3.1.Size, location, and number of aneurysms

Intracranial aneurysms are divided into four groups according to size; small aneurysms have a diameter of under 5 mm, medium-sized aneurysms 6-15 mm, large aneurysms 16-24 mm and giant aneurysms 25 mm or more. Among pediatric aneurysm patients, the tendency for giant aneurysms in series from the 1980s was reported to be high, between 20% and 54%.[64,193,284] However, recent patient series report much lower proportions of giant aneurysms, 0-14%,[110,135,225] with the
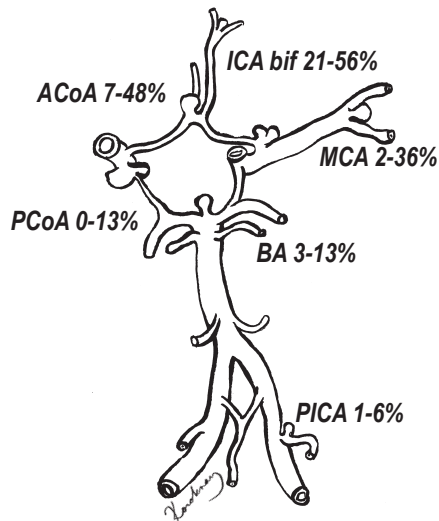
FIGURE 2.

Typical locations of aneurysms with proportions of pediatric aneurysm patients of the reported patient series described in Table 1. ACoA= anterior communicating artery, BA = basilar artery, ICA bif = internal cerebral artery bifurcation, MCA=middle cerebral artery, PCoA =posterior communicating artery, PICA = posterior inferior cerebellar artery.

exception of a large series from a tertiary referral center (22%).[117] Multiple aneurysms are uncommon among pediatric aneurysm patients.[1] In the literature review, aneurysms were multiple in 0-14% of cases, which is lower than that reported for adult patients (15%-28%).[100,142,312] A recent study of adult aneurysm patients in Finland reported that ruptured and unruptured aneurysms have different location distributions.[100]

2.2.3.2. Etiology

In adult series, the majority of intracranial aneurysms are considered idiopathic. In pediatric patients, traumatic and infectious aneurysms are more common than in adult patients. Roughly 30% of aneurysms in children are idiopathic, 50% are related to arterial dissection, and 15% are associated with infection.[134] About 5-10% are related to head trauma.[134]

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Dissecting aneurysms

Dissecting aneurysms are common among pediatric aneurysm patients. Pediatric patients account for about 7% of all intracranial arterial dissections.[258] In a review of intracranial aneurysms in children, 45% were reported as dissections.[159] However, pediatric patients with dissecting aneurysms usually present with ischemia rather than hemorrhage.[162] In pediatric dissecting aneurysms with local lesion and evidence of mural hematoma, spontaneous healing is regularly observed and conservative treatment is thus recommended.[159]

Traumatic aneurysms

Traumatic aneurysms are a result of a head trauma, either penetrating or non-penetrating. Penetrating injuries may cause direct injury to the artery.[76,91,128,194] Traumatic aneurysms as a result of closed head injury without direct injury to the arteries are caused by acceleration forces, usually rotational, resulting in shear stress of the artery wall. Some of the aneurysms regarded as traumatic aneurysms are actually false aneurysms, or pseudoaneurysms, which are caused by the rupture of entire vessel wall layers.[210] In these cases, the angiographically visible aneurysm is usually only extravasation of contrast media and the walls of the "aneurysm" are formed by the surrounding cerebral structures. In a true traumatic aneurysm, the walls of the aneurysm sac resemble that of an idiopathic aneurysm, i.e. the intima, internal elastic lamina, and media layers are disrupted, but the adventitia is intact.[194] The most common locations of traumatic aneurysms are the base of the skull, typically involving the petrous, cavernous, or supraclinoid ICA or peripheral branches of the anterior cerebral artery (ACA).[21] Traumatic distal ACA aneurysms are secondary to trauma against the falcine edge. Also distal cortical artery aneurysms associated with an overlying skull fracture have been reported.[21]

The reported risk of hemorrhage in posttraumatic aneurysms is 19-60%,[6,21] with an associated mortality rate of 31-54%.[6,55,214] The hemorrhage from a ruptured traumatic aneurysm typically presents 2–4 weeks after the initial head trauma.[134] Traumatic aneurysms comprise less than 1% of all intracranial aneurysms, but 25–75% of traumatic aneurysms occur in patients aged under 18 years.[314] A rare cause of traumatic aneurysms in a young child is battery (i.e. shaken baby syndrome).[155,170] Piatt and Clunie[219] reported a superior cerebellar artery aneurysm as a result of a birth trauma with precipitous delivery causing stretching of the tentorium, thus causing vascular trauma.

AVM-related aneurysms

One to two percent of patients with intracranial aneurysms also have an AVM,[40] and of the patients with an AVM 16-25% have an associated aneurysm.[40,181] If a patient with both an aneurysm and an AVM presents with SAH, in two-thirds the aneurysm has ruptured.[40] AVM-related aneurysms are graded based on their relationship to the nidus and feeding artery. These aneurysms usually develop on the main feeding arteries of the AVM due to hemodynamic stress. Flow-related aneurysms coexisting with cerebral AVMs frequently are associated with initial hemorrhage presentation.[181] In most cases, treatment of the AVM will eventually lead to disappearance of the aneurysm.

Mycotic aneurysms

Infectious aneurysms, traditionally called mycotic aneurysms, comprise both bacterial and fungal infections. The suggested pathomechanism by which a pathogen in the bloodstream is able to cause an aneurysm is that bacteria from septic emboli escape through the vasa vasorum and cause severe inflammation of the tunica adventitia.[139] The inflammation spreads and arterial pulsatile force weakens the inflamed vessel wall, finally resulting in aneurysm formation.[139] Mycotic aneurysms ac-

count for 1-7% of all intracranial aneurysms[121] and carry a high-mortality rate when they rupture.[139] Mycotic aneurysms are typically small and located in the terminal branches. In the literature review with 871 pediatric patients, 52 mycotic aneurysms were present among a total of 949 aneurysms, yielding a proportion of 5.5%. Almost all patients with a bacterial aneurysm have vegetative endocarditis. There are some reports of HIV-related arterial angiopathies[41,140] and cerebral aneurysms in pediatric patients.[182] Other viral infections, e.g. varicella zoster or cytomegalovirus of the vasculature, mainly cause vasculitis.

2.2.3.3. Presentation

The majority of ruptured aneurysms in children present with SAH,[110] and 7% present with ICH only.[110] Unruptured giant aneurysms typically present with epileptic seizures, cranial nerve deficits, or neurologic symptoms.

2.3. Aneurysmal SAH in childhood

2.3.1. Incidence of aneurysmal SAH in children

In a population-based study with 2.3 million children aged under 20 years, the incidence of spontaneous hemorrhagic stroke was 1.4/100 000 person-years.[110] Of these patients, 13% had cerebral aneurysms thus yielding an incidence of 0.18/100 000 person-years for aneurysmal hemorrhagic stroke in childhood and adolescence.[110] According to the same study, the incidence was higher, 0.52/100 000 person-years, in children aged 15-19 years compared with those aged 0-14 years, 0.06-0.09/100 000 person-years.[110]

In autopsy studies of adults, the prevalence of cerebral aneurysms is between 1.6 and 4 per 1000 persons.[233] To date, no studies on the true incidence of pediatric aneurysms have emerged.

2.3.2. Special characteristics of SAH in children

2.3.2.1. Rebleeding

Of the overall SAH population, about 9% of patients suffer from a rebleed.[177] Rebleeding is the major factor causing mortality and morbidity among SAH patients,[190] and has been associated with such complications as hyponatremia, respiratory failure, and hydrocephalus.[177] Rebleeding is particularly common in the pediatric SAH population, partly due to the rarity of this disease in this age group causing a delay in diagnosis.[225] Rebleeding rates of up to 52% in pediatric SAH patients have been reported.[225] Rebleeding often occurs within 6–24 hours after the initial bleeding.[123, 177]

Rebleedings are prevented by total bed rest of the patient until the aneurysm has been secured (preferable within 24-48 hours) and subsequent management of blood pressure. An antifibrinolytic agent, mainly tranexamic acid, is used for SAH patients with unsecured aneurysms until day three from the bleeding to prolong the formation of a clot inside the ruptured aneurysm.[56]

2.3.2.2. Hydrocephalus

Hydrocephalus occurs in approximately 20-30% of SAH patients. The onset of hydrocephalus can be acute, within 48 hours of SAH, or chronic (i.e. late onset), occurring weeks and even months after the hemorrhage. Acute hydrocephalus is diagnosed in about 18-20% of

SAH patients.[179,311] Hydrocephalus can be obstructive due to a blood clot inside the ventricular system preventing normal cerebrospinal fluid (CSF) circulation, while in communicating hydrocephalus the blockage of CSF is in the subarachnoid space.[131] Correlations between chronic hydrocephalus and admission Hunt & Hess grades (see Appendix I) and Fisher grades (see Appendix I) have been reported,[308] whereas timing of surgery[292] and treatment modality for aneurysms, i.e. clipping versus coiling, were not risk factors.[269] Overall, 9-20% of patients develop chronic hydrocephalus demanding shunting.[141,308]

In children, compliance of the brain to the extra volume demand caused by the arrest in CSF circulation is lower than in adults. Thus, symptoms of hydrocephalus occur more rapidly.

The treatment of acute hydrocephalus is extraventricular drainage (EVD). Chronic post SAH hydrocephalus is treated with shunting.

2.3.2.3. Vasospasm

Blood outside of an artery or in the CSF causes the smooth muscle cells of the tunica media to contract, thus narrowing the arterial lumen, i.e. causing vasospasm.[318] The change in the caliber of the vessel is to some degree compensated by an increase in blood velocity. The blood supply to cerebral tissue is eventually compromised and delayed neurologic symptoms occur. A recent publication, however, challenges this reasoning, proposing that the arterial narrowing is not the only cause of delayed clinical deterioration and that the entire picture of delayed clinical deterioration may be multifactorial, including early brain injury and cortical spreading depression, with all of these factors contributing to overall mortality and morbidity.[221] Vasospasm is usually divided into angiographic vasospasm and clinical vasospasm, the latter sometimes also called delayed ischemic neurologic deficit (DIND); and occasionally leading to delayed cerebral infarct (DCI).[177] The highest incidence of vasospasm is

between the fourth and eleventh posthemorrhage day.[318] Among adult SAH patients, angiographic vasospasm is diagnosed in about 45% and DIND in about 20% of patients.[246] Approximately 30% of patients develop DCI.[317] Risk factors for the development of symptomatic vasospasm include a large-volume, persistent subarachnoid clot,[227,334] as well as poor neurological condition on admission, smoking, and hypertension.[51]

Computed tomography angiography (CTA), digital subtraction angiography (DSA), and transcranial Doppler (TCD) are widely used to monitor the temporal course of vasospasm. Treatment of vasospasm consists of calcium channel blocker agent (nimodipine) and classic triple-H-treatment (hypertension, hemodilution, and hypervolemia). Novel techniques in severe vasospasm include endovascular techniques such as balloon angioplasty and intra-arterial infusion of vasodilatators.[175,199]

In an adult SAH study from St. Louis, vasospasm was associated with younger age (<50 years),[119] however, in another study[246] no differences between ages were found among adult SAH patients. Among pediatric patients, symptomatic vasospasm is rare.[160,225] An explanation for this may be the greater potential of leptomeningeal collateral circulation among children.[159] The leptomeningeal collateral circulation, i.e. leptomeningeal anastomoses, is the collection of pial arteries that are connect branches between two major cerebral arteries supplying two different cortical territories.[19] These are also called secondary collaterals, in contrast to primary collaterals (arteries in the Circle of Willis).[172,192] The age of the patient is an independent factor in the compensatory capacity of leptomeningeal anastomosis, possibly due to manifestation of atherosclerosis in older vessels.[19] There is interindividual variability in leptomeningeal collateral size, number, and localization.[19] The clinical meaning of these secondary collaterals is mainly discussed in management and outcome after cerebral stroke. The methods used to grade the efficacy of this circulation have yet to be assessed.[192]

2.4. Treatment of aneurysms in children

Treatment of intracranial aneurysms aims to exclude the whole aneurysm from the bloodstream without sacrificing normal blood supply. A ruptured aneurysm should be treated as soon as possible to eliminate the risk of rebleeding. Among adult series, a debate exists about the natural history of small unruptured aneurysms.[28,114,232] A large multicenter study (International Study of Unruptured Intracranial Aneurysms, ISUIA) came to the conclusion that unruptured aneurysms of 7 mm or smaller should not be surgically treated.[104,324] ISUIA has been criticized for recruitment and selection bias.[11,283] Intracranial aneurysms in children are a different focus. The long lifespan expected for a child is a factor advocating an active and enduring treatment.

2.4.1. Observation

Conservative treatment for a ruptured aneurysm is not an option in modern medicine. In the 1940s and 1950s, operative mortality was high and the risk related to anesthesia was not inconsiderable. Also patients were not operated on immediately; bed rest of 2-3 weeks was recommended after SAH to improve operative conditions, i.e. diminish brain swelling. In many cases, the Hunt & Hess scale (see Appendix I) improved, but at a cost of rebleedings during the waiting period.

A study from the late 1970s stated that in the first six months after SAH at least 50% of patients with untreated artery aneurysms will rebleed; however, if the patient survives the first six months the natural history of their ruptured aneurysms will resemble that of unruptured ones.[107]

2.4.2. Microsurgery

Surgical treatment of aneurysms is varied, including such options as clipping, proximal occlusion with or without bypass, trapping, and wrapping (Figure 3). The most common surgical procedure is to clip or ligate the neck of the aneurysm (Figure 3 A). The ligation was formely done with a linen knot, today with a string clip, which comes in variable sizes and forms. In trapping (Figure 3 B), the aneurysm is treated by occlusion of the parent and distal arteries. With this method, the aneurysm can be fully excluded from the bloodstream; however, the parent artery is sacrificed. Wrapping is a method in which the aneurysm is strengthened by wrapping a piece of muscle, fascia, or cotton around the aneurysm with or without a clip (Figure 3 C). The parent artery is spared; however, the risk of rupture of the aneurysm might not be completely eliminated. Aneurysm can also be treated by occlusion of the parent artery proximal to the aneurysm either extra- or intracranially. In extracranial occlusion, the common carotid artery (CCA) or ICA is occluded by a stitch, clip, or instrument, e.g. Crutchfield® instrument, where occlusion of the artery can be performed while the patient is awake, thus inspecting possible neurological deficits. However, occlusion of ICA is a risk factor for subsequent de novo aneurysm formation.[237] With the aid of a bypass graft, the blood flow is secured by providing a detour. Complex aneurysms might need a bypass operation combined with proximal ligation. In the excimer laser-assisted nonocclusive anastomosis (ELANA) technique, large-caliber bypass revascularization is possible without temporary occlusion of the parent artery.[16,156,285] Bypasses usually need antiplatelet medication to prevent thrombosis of the bypass. The thrombosis of a bypass vessel is also a risk when the flow-dynamics do not match,[4] and in aneurysm surgery bypass operations are usually accompanied by proximal occlusion.
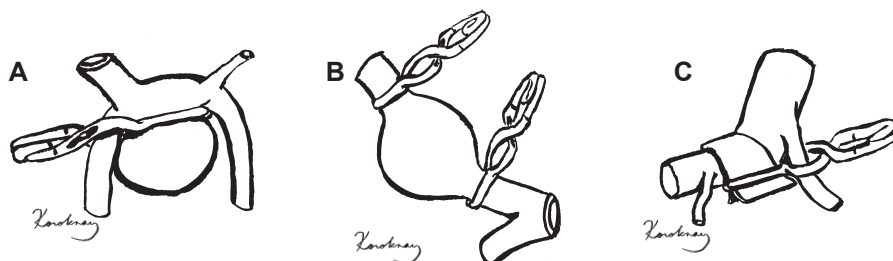
FIGURE 3.
Examples of microsurgical occlusion methods for aneurysms; clipping (A), trapping (B), clip-aided wrapping (C).

2.4.2.1. Patient series

In the literature review, the majority of pediatric patients with intracranial aneurysms were treated microsurgically.

2.4.3. Endovascular treatment

In endovascular treatment, the aneurysm is excluded from the bloodstream using intra-arterial techniques. Soviet neurosurgeon and member of the Burdenko Neurosurgery Institute Fedor A. Serbinenko can be regarded as the father of endovascular neurosurgery.[294] He invented and perfected the technique of balloon embolization,[268] which revolutionized the practice of endovascular surgery. Nowadays, Guglielmi detachable platinum coils (GDC®s)[73,74] and occasionally stents and balloons are used in the procedure. Coils are detached from the guiding wire by electrical current, which in turn is believed to enhance the thrombosis of the aneurysm. The aneurysm sac is filled with platinum coils. Occasionally, when coiling a broad-neck aneurysm, stents or balloons are used. Intra-arterial stents require life-long antiplatelet medication. Moreover, migration of the coils or stent outside the lumen has been described.[38,138] Also, in the long run, coil impaction resulting in aneurysm recurrence is a recognized problem.[197,198,230]

Therefore, angiographic follow-up, most often with magnetic resonance angiography (MRA), is advised. Coil impaction might require additional treatment of the aneurysm; however, with pre-existing coils, the treatment is challenging.[239]

Diagnostic angiography itself carries a risk for thromboembolic complications, dissection, inguinal pseudoaneurysm, and groin hematoma. The frequency of all neurologic complications is 0.45-2.3%[72,163] and the frequency of persistent neurologic deficits is 0.09-0.4%.[72,163] In one study, non-neurologic complications were observed in 14.7% of the examinations.[163]

In a study with 241 diagnostic DSA in children, there were no intraprocedureal complications; however, one child with a complex dural arteriovenous fistula experienced a fatal intracranial rehemorrhage secondary to a posterior fossa varix rupture 3 hours after the diagnostic angiogram, yielding a postprocedural complication rate of 0.4%.[23]

2.4.3.1. Radiation dose

There is no safe limit when considering the radiation dose to living tissue. Effects of radiation on tissue are cumulative; therefore, the ALARA (As Low As Reasonably Achievable) concept is used. The unit describing biological effectiveness of ionizing radia-

tion is Sievert [Sv]. Energy deposited in the target (absorber) is described as absorbed dose (unit Gray [Gy]). Different tissues tolerate radiation in different ways. The doses in radiological studies have become smaller within the last 40 years. The absorbed doses in different radiological studies and interventions used in treating of intracranial aneurysms are presented in Table 4. In a recent phantom study,[187] the effective dose for CTA assessment of cerebral vessels was approximately one-fifth the dose for DSA. The younger the patient, the most vulnerable the tissue is to radiation. Exposure to high doses of radiation at a younger age carries a risk for leukemia[217] and intracranial tumors, especially meningiomas. Meningiomas have been reported to occur after radiation doses of 1800 cGy.[29] At very high doses, over 4000-5000 cGy, there is a risk of radiation-induced leukoencephalopathy.[39] Even though these doses are far higher than the doses in the diagnosis and endovascular treatment of cerebral aneurysms, the threshold for radiation-induced damage cannot be determined.

TABLE 4.
Radiation doses (in Gray [Gy]) for common radiological procedures in the cerebrovascular diagnosis and treatment of cerebrovascular lesions in pediatric patients. CT=computed tomography, CTA=computed tomography angiography, DSA=digital subtraction angiography.

Procedure	Radiation dose (mGy)
Head CT	34-72[158,274,329]
CTA	50•[32,316]
DSA	252[66]
Uncomplicated coiling	390[290]

•for adults

2.4.4. Multidisciplinary collaboration

Intracranial aneurysms in children are often complex, requiring multidisciplinary work between neurosurgeons and neuroradiologists. As stated by Sanai et al.,[249] *"Nowhere in neurosurgery is there a clearer need for neurosurgeons and neurointerventionalists to work in specialized teams than with the pediatric aneurysm patient"*.

2.5. Outcome

Kassell et al.[124] stated over twenty years ago that *"the study of factors affecting morbidity and mortality is essential in effectively planning, developing, and evaluating therapeutic methods for improving the outcome in patients with SAH"*. Outcome of patients with a neurological disaster has traditionally been estimated and categorized by structured scales such as the Glasgow outcome scale (GOS)[108] and the modified Rankin Scale (mRS)[48] (Tables 5 and 6). These outcome scales are focused on the activities of daily living and on the management of patients with or without assistance. The main emphasis in these scales is on independent living and on the ability to walk.

TABLE 5.
Glasgow outcome scale (GOS).[108]

GOS	Description
1	Dead
2	Persistent vegetative state
3	Severely disabled. Counscious, but disabled
4	Moderately disabled. Disabled but independent.
5	Good recovery.

TABLE 6.
Modified Rankin scale (mRS).[48]

mRS	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**

It would be logical to assume that the plasticity of the brain in young children might lead to improved outcome following SAH at an early age. However, studies of pediatric stroke have provided increasing evidence that younger age at time of brain insult is a predictor of worse outcome, particularly for the cognitive and neuropsychological domains.[30,109,186] Heiskanen and Vilkki[81] performed comprehensive neuropsychological tests on pediatric patients with ruptured cerebral aneurysms and diagnosed some cognitive deficits. A common feature of the deficits was an impairment of active retrieval and searching of memory, with common cognitive skills usually remaining unaffected.[81] Furthermore, in most cases these deficits did not affect the daily life of patients, and they tended to be unaware of the deficits.[81]

2.5.1. Early outcome

In a previous study of pediatric aneurysm patients, the early clinical outcome was favorable (i.e. GOS≥4) in 92%.[117] Early mortality varied between 0% and 23%.[117,225,249] Treatment-related neurological deficits were reported to occur in 0-7% of patients.[80,249] The main factor affecting early outcome was the initial hemorrhage. In a recent study[122] from Kuopio, Finland, the mortality during the first three days after SAH was predicted by Hunt & Hess grades (see Appendix I) IV-V, ruptured aneurysm ≥ 15 mm, and acute subdural hematoma. According to the same study,[122] patients in good condition on admission had a low mortality rate at 12 months, regardless of age.

2.5.2. Long-term outcome

Favorable long-term outcome in pediatric series has been reported in 64-100%,[117,225,249] however, these series have variable proportions of patients with ruptured and unruptured aneurysms. The follow-up times in these studies vary between 1 month and 18 years.

Unfavorable long-term outcome in pediatric aneurysm patients is associated with initial hemorrhage, parent artery occlusion, and vasospasm. This is in agreement with adult studies; the Fisher grade and the Hunt & Hess grade correlated with favorable outcomes.[174] Other factors in adult patients associated with poor outcome are advanced age, hyperglycemia on admission, high Hunt & Hess grade, and larger aneurysm size.[196]

2.6. Long-term excess mortality

It has previously been thought that a SAH patient whose aneurysm was completely treated and who survived the first year after SAH would attain the life expectancy of the general population.[205] A study with distal ACA aneurysms found no excess mortality in patients after surviving the first three years after SAH.[167] However, among adult SAH-patients, long-term excess mortality has been described, being mainly due to increased incidence of cardiovascular deaths, followed by cerebrovascular deaths.[242] This is reasonable because both aneurysmal SAH and cardiovascular diseases share the same risk factors, i.e. hypertension and smoking. The role of new SAH in long-term mortality has been modest.[242] A recent study showed that after the initial diagnosis of cerebral aneurysm patients have an increased incidence of lung cancer in long-term follow-up.[99]

Until this study, no studies have existed on long-term excess mortality among pediatric aneurysm patients.

2.7. Long-term radiological follow-up

Patients who survive SAH have a higher occurrence of a new SAH than the general population, even after successful treatment of the initial aneurysm, due to de novo and recurrent aneurysms.[20,302,321] The annual occurrence of de novo aneurysms in adult SAH patients has been reported to be 0.3-4%.[27,36,113,321] A study with adult aneurysm patients showed that the cumulative risk of de novo aneurysm formation becomes significant after nine years.[302] Among adult patients, the risk factors for de novo aneurysm formation are female gender, younger age, hypertension, multiple aneurysms at onset, and smoking.[228,295,335]

In the past, carotid artery occlusion was used to treat ICA aneurysms that were otherwise untreatable. Formation of de novo aneurysms is a well-known late sequela of carotid occlusion. In a review article,[5] the risk of de novo aneurysm formation was 4.3% in patients with previous ICA occlusion. The most common locations in these patients for de novo aneurysms are reported to be ACoA and posterior communicating artery (PCoA),[5,15] probably due to hemodynamic changes and increased flow from the contralateral ICA. The mean time for de novo aneurysm formation is 9-10 years.[5,15,61] Other common risk factors for aneurysm formation, i.e. female gender, hypertension, and smoking, most certainly have a role in de novo aneurysm formation among patients with previous ICA occlusion.

Almost 20 years ago, Rinne and Hernesniemi[237] proposed that young SAH patients could benefit from long-term neuroradiological follow-up to screen and treat de novo aneurysms early. Several pediatric aneurysm series advocate life-long clinical and minimally invasive radiological follow-up of these patients; however, only a few publications provide precise guidelines for the follow-up protocol. Sanai et al.[250] recommended angiography 3-5 years after microsurgical therapy and 6 and 24 months after endovascular therapy, with additional surveillance examinations according to the findings of these studies.

2.8. Historical aspects

2.8.1. Pediatric neurosurgery

Pediatric neurosurgery owes most of its routine, techniques, and instrumentation to the neurosurgery of adults, but, as we know, there are important differences in scale, anatomy, physiology, and pathology.

Kenneth Till 1975

Neurosurgery was sporadically practiced on children from prehistoric times until the Harvey Cushing era.[209] The history of pediatric neurosurgery dates back to the early 1930s, when dedicated general surgeons specialized in neurosurgery and trained neurosurgeons began providing tailored care for children.[95] The growth and development of pediatric neurosurgery started at Boston Children's Hospital under the direction of Dr. Franc Ingraham, a pupil of Cushing's, and Dr. Donald Darrow Matson in the 1950s.[209] Ingraham graduated from Harvard Medical school in 1925 and spent three years under Cushing's training.[95] He gained his surgical and research experience at John Hopkins University and Oxford University. Ingraham returned to Boston in 1929 and received Cushing's blessing to focus on children's neurosurgery. Ingraham was accompanied by a skilled neurosurgeon, his successor, Dr. Matson, and in 1954 Ingraham and Matson published the first textbook of pediatric neurosurgery "*Neurosurgery of Infancy and Childhood*".[94] The book contains information about congenital anomalies, hydrocephalus, trauma, intracranial and intraspinal tumors, infection, cerebrovascular disorders, epilepsy, lead encephalopathy, and pediatric neurosurgical anesthesia.[7]

Another pioneer in the field of pediatric neurosurgery, Dr. Kenneth Till was the first full-time pediatric neurosurgeon in the UK.[18] Till graduated from the University of Cambridge in 1944, and trained at Atkinson Morley's Hospital, Wimbledon, in South London, and at Children's Memorial Hospital, Chicago, as well as in Boston with Matson.[18] Till was a founder member in 1972 of the International Society of Paediatric Neurosurgery (ISPN). Organization of pediatric neurosurgery had gradually begun and the European Society for Pediatric Neurosurgery (ESPN) had been established a few years earlier, in 1967[95]. Till published his monography "*Paediatric neurosurgery for paediatricians and neurosurgeons*" in 1975, at a time when children's neurosurgery relied heavily on the personal experience of neurosurgeons.

Today, pediatric neurosurgery is a recognized sub-speciality in the field of neurosurgery. It exists as a member of the family of neurosurgery with its own training programs, process of accreditation, national and international conferences, and scientific journals.[326] ISPN has its 40th Annual Meeting in 2012, with 350 active members from 40 countries.

2.8.2. Pediatric neurosurgery in Helsinki

The Finnish Red Cross Hospital (later Töölö Hospital) was founded in 1932 by Marshall Mannerheim and his sister Sophie Mannerheim. It served as the only neurosurgical department in Finland until 1966 (Figure 4).
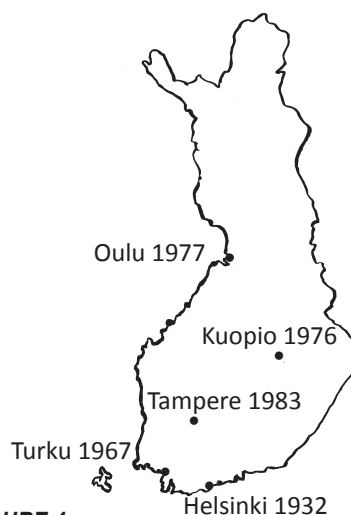
FIGURE 4.
Neurosurgical departments in Finland with year of inception provided.[165]

Before the Second World War, general surgeons in our country were responsible for children's surgery.[315] On December 1st, 1946, a young surgeon, Matti Sulamaa (1910-1988), was appointed as a resident at the Children´s Hospital in Helsinki.[178,287] Later, the same surgeon became the first chief surgeon of pediatric surgery at the Children's Hospital in Helsinki. Professor Sulamaa can be regarded as a pioneer of pediatric surgery in Finland. He collaborated closely with n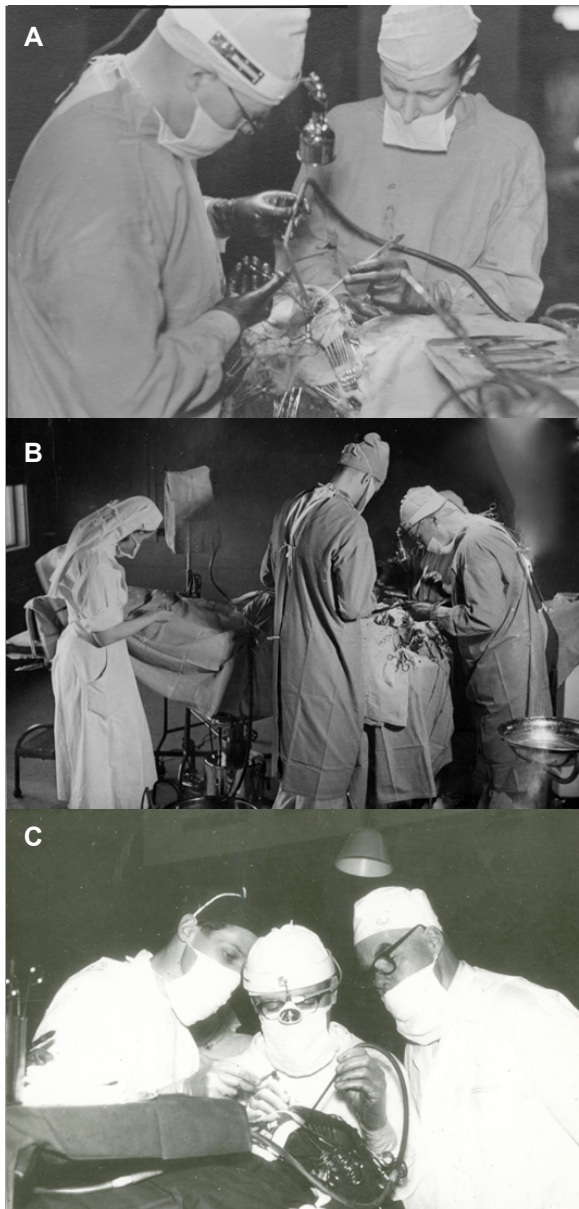eurosurgeons at the Finnish Red Cross Hospital, where he started his surgical career as a fellow of Professor Aarno Snellman in the 1930s (Figure 5).[287] Professor Snellman had acquainted himself with the field of neurosurgery at the Karolinska Institute at Stockholm by working with Professor Herbert Olivecrona in1935, and Professor Snellman can be considered the founder of neurosurgery in Finland.[165] Professor Sulamaa studied hydrocephalus under the guidance of Professor Snellman.[287] A young surgeon Lauri V. Laitinen began his surgical career at Children's Hospital under the guidance of Professor Sulamaa before starting a residency in neurosurgery.[287] The first ventriculocisternal (Torkildsen) shunts to treat hydrocephalus were implemented in Finland at the Finnish Red Cross Hospital (later Töölö Hospital) in the 1950s. The first modern shunt operation with a Spitz-Holter valve was performed by Dr. Laitinen in March 1960. The patient was a 14-year-old boy with a tumor in the fourth ventricle. The PhD thesis of Dr. Laitinen in 1956 was entitled "*Craniosynostosis; premature fusion of the cranial sutures: An experimental, clinical and histological investigation with particular reference to the pathogenesis and*

FIGURE 5.
Dr. Sulamaa (left) assisting Professor Snellman in a craniotomy at the Finnish Red Cross Hospital (later Töölö Hospital) in 1941 (A). Sister Laina and an overview of the operating room (B). The "Three Professors" performing a neurosurgical operation: Professor Troupp on the left serving as assistant, Professor ad Björkesten in the center as the main surgeon, and Professor Snellman on the right as a spectator (C).

etiology of the disease".[143] He performed the first surgeries for craniosynostosis in Finland together with Dr. Sulamaa. Laitinen later established his position as an innovative developer of stereotactic and functional surgery.[153,154] The neurosurgeons in Helsinki were active in publishing their experiences on pediatric neurosurgical patients (Table 7).

TABLE 7.
First publications in the 1950s and 1960s on pediatric neurosurgery in Helsinki.

Year	Authors	Title
1952	Sulamaa M Vara P[288]	An investigation into the occurence of perinatal subdural hematoma; its diagnosis and treatment.
1954	Laitinen L Miettinen P[146]	Unilateral coloboma nervi optici combined with a homolateral block of aquaeductus monro; a case report.
1954	Laitinen L Sulamaa M[148]	Craniosynostosis; symptoms and results of treatment.
1955	Laitinen L Sulamaa M[149]	Some results of operative treatment for craniosynostosis.
1956	Laitinen L Miettinen P Sulamaa M[147]	Ophthalmological observations in craniosynostosis.
1956	Laitinen L Sulamaa M[150]	Craniosynostosis; symptoms, treatment and results of treatment. II
1960	Troupp H[299]	Pathology, diagnosis, and treatment of supratentorial tumours in infancy and childhood.
1961	Laitinen L[144]	Medical defects in the cerebral arteries of newborn infants.
1961	Kauhtio J Törmä T[127]	Subtotal hemisphrectomy for intractable convulsive seizures.
1964	Laitinen L[145]	Arterial aneurysm with subarachnoid hemorrhage in children.
1965	Laitinen L[152]	Short-term results of stereotaxic treatment for infantile cerebral palsy.
1967	Heiskanen O[79]	Spina bifida.
1969	Vapalahti PM, Schugk,P Tarkkanen L af Björkesten G[313]	Intracranial arterial aneurysm in a three-month-old infant. Case report.

Neurosurgeon Olli Heiskanen was interested in pediatric neurosurgery, in both clinical practice and research. Dr. Heiskanen visited Dr. Matson in Boston and worked as his fellow during 1965-1966, closely observing Dr. Matson´s work.[300] Dr. Matson visited Helsinki soon after Heiskanen's return and performed a pediatric operation in Helsinki in 1967. The patient was a 12-year-old boy with a teratoma in the pineal region. Professor Matson, Professor af Björkesten, and Dr. Heiskanen extirpated the tumor on December 27th 1967; however, the patient was reoperated on three days later due to postoperative epidural hematoma. Dr. Heiskanen later worked at Children's Hospital with Dr. Sulamaa. After returning to Töölö Hospital, he served as the consulting pediatric neurosurgeon for 25 years, and from 1972 onwards operated on all pediatric neurosurgical patients.[300]

2.8.2.1. First pediatric aneurysm patients

The first patient with an intracranial aneurysm was treated in Helsinki in 1937. The first pediatric patient with intracranial aneurysm was admitted in 1943. The patient was an 18-year-old girl. The patient presented with a thunderclap headache on October 1st 1943, followed by meningmus. The headaches continued and were accompanied by vertigo and nightly nausea and vomiting. The patient was examined by an ophthalmologist due to blurred vision. The ophthalmologist diagnosed bilateral papil edema, and patient was admitted to the Department of Neurosurgery on December 27th 1943. On admission, a mild right-sided clumsiness and balance difficulties were diagnosed. Bilateral carotid angiographies were performed, revealing a 7-mm right-sided ICA bifurcation aneurysm. The aneurysm was considered inoperable and the patient was discharged with a good early neurological outcome (GOS 4). The patient died in June 1945 due to re-bleeding.

The next pediatric aneurysm patient was admitted in December 1951. The patient was an 18-year old boy with SAH at the end of October 1951. The patient had two rebleedings. Carotid angiography showed a 10-mm right-sided middle cerebral artery (MCA) aneurysm. On January 4th 1952, a craniotomy was performed to ligate the aneurysm; however, the operation did not advance beyond the exploratory stage and ligation was not attempted. A ventriculostomy was placed. A transcript of the operation report is shown in Figure 6. The patient was discharged on January 12th 1952, with GOS 3. The surgeon inquired about the patient's recovery a few years later; the patient reported in a letter dated May 14th 1957 that he had fully recovered and was working as a logger. The patient died due to a massive SAH 20 years after the initial bleeding, on December 29th 1971 at the age of 38 years.

2.8.2.2. Developments in neurosurgery

The first neurosurgical operation in Finland was performed by Professor Snellman after his return from Karolinska Institute in September 1935.[165] The first cerebral angiographies were performed in 1936.[178,287] At that time, cerebral angiographies required a surgical exposure of the carotid artery and were considered risky for the patient. The introduction of the percutaneous carotid puncture technique in 1948 gradually increased the annual number of these procedures, from about 20 in 1947 to over 150 in 1949.[165] Finally, in the 1970s, Seldinger's percutaneous transfemoral route,[267] originally introduced in the mid-1950s became more common in Helsinki. With catheter angiography, the rate of complications decreased and the accuracy of diagnosis increased. During the 1990s DSA as the preferred diagnostic tool for intracranial aneurysms in SAH patients was displaced by a less invasive method, CTA.[120]

```
4.1.52. Craniotomia explorativa (Novoc.) Prof. Snellman - Tola - Karatau - Sis. Laina.
       Vasemmasta frontaaliaukaesta sisään. Erittäin voimakas pingoitus vähenee
       jonkinverran vasemman etusarviopunktion jälkeen. Tämänjälkeen lähdetään tun-
       keutumaan syvyyteen vasemman otsalohkon etupintaa pitkin. Erikoisena piirtee-
       nä huomataan, että arachnoidea aivojen pinnalla jonkinverran samea. Liquoria ei
       ole laisinkaan frontaalilohkon etupinnalla eikä cisternoissa edessä, joten
       exploratio on erittäin vaikeaa. Ilmeisesti synnynnäisinä anomalioina todetaan
       myöskin kaksi erittäin voimkasta laskimoa, jotka kulkevat vasemman frontaal lohkon
       etu-lateraalipinnalla sagittaalisuunnassa. Syvyyteen päästään aina fissura
       Sylviin alkuun asti mitään hematomaa tai sellaisen jätteitä löytämittä.
       Koska missään ei todeta liquoria, tilan arvellaan johtuvan blokadista bulbuksen
       seudussa, joka estää liquorikulun convexiteetille. Tyypillinen kerroksittainen
       sulku. Ihoon silkkiä ja haavaan kumiputki.
```

FIGURE 6.
Transcript of the operation report of the first pediatric aneurysm surgery in Finland on January 4th 1952. Translation of the report (original in Finnish):

4th January 1952. Craniotomia explorativa (Novoc.) Prof. Snellman-Tola-Karatau-Nurse Laina.

Entry through a left-sided frontal opening. Distension is very strong but reduces to some extent after frontal left-sided ventricular punction. After this the deeper entry is through the anterior surface of left frontal lobe. It is noticed that the arachnoid on the surface of the brain is opaque to some extent. CSF is not evident on the anterior surface of the frontal lobe or in the cisterns, making the exploration extremely difficult. Apparently, as a congenital anomaly there are two strong veins passing on the anterior-lateral surface of the frontal lobe in sagittal direction. The beginning of Sylvian Fissure is reached without finding hematoma or anything suggesting to it. Because CSF is not noted, it is assumed that there is a blockade around bulbus thus preventing the passage of CSF to the convexity. Typical closure in layers. Skin is closed with silk and a rubber tube is inserted to the wound.

The two World Wars have had a major impact on the development of neurosurgery in Finland. During World War II the Red Cross Hospital served as the War Hospital. The large number of head injuries increased the need for neurosurgical skills, and many foreign volunteer surgeons worked at the hospital. Two years after the end of the war in 1947, Aarno Snellman was appointed the first Professor in Neurosurgery in Finland, and the era of neurosurgery in Finland had officially started. However, in the early years the neurosurgical resources were limited.

From the 1930s paramedics, diagnostics, medical treatment, surgical equipment, and surgical skills in the field of neurosurgery have developed enormously. SAH was diagnosed by lumbar puncture at the Department of Neurosurgery in Helsinki until the first computed tomography (CT) scan became available in 1977 (J. Hernesniemi, personal communication).[164] In the early years, aneurysms were ligated with linen or silk thread ligature (Figure 7) or silver clips, until spring clips became available in the 1960s.[151] The hospital's operative records show that wrapping, trapping, and proximal occlusions were frequently used. The use of the Crutchfield® clamp continued until the late 1970s.

FIGURE 7.

Ligating a ruptured right-sided internal carotid artery (ICA) bifurcation aneurysm in an 18-year-old girl with a linen thread, as illustrated by Professor af Björkesten in 1955 (A), with preoperative (B) and postoperative angiography (C). A control angiography in 2011, 56 years after the initial treatment showed the ICA aneurysm and a de novo aneurysm at the right posterior communicating artery (PCoA) (D). The patient had a new SAH from the left-sided PCoA 25 years after the initial SAH.
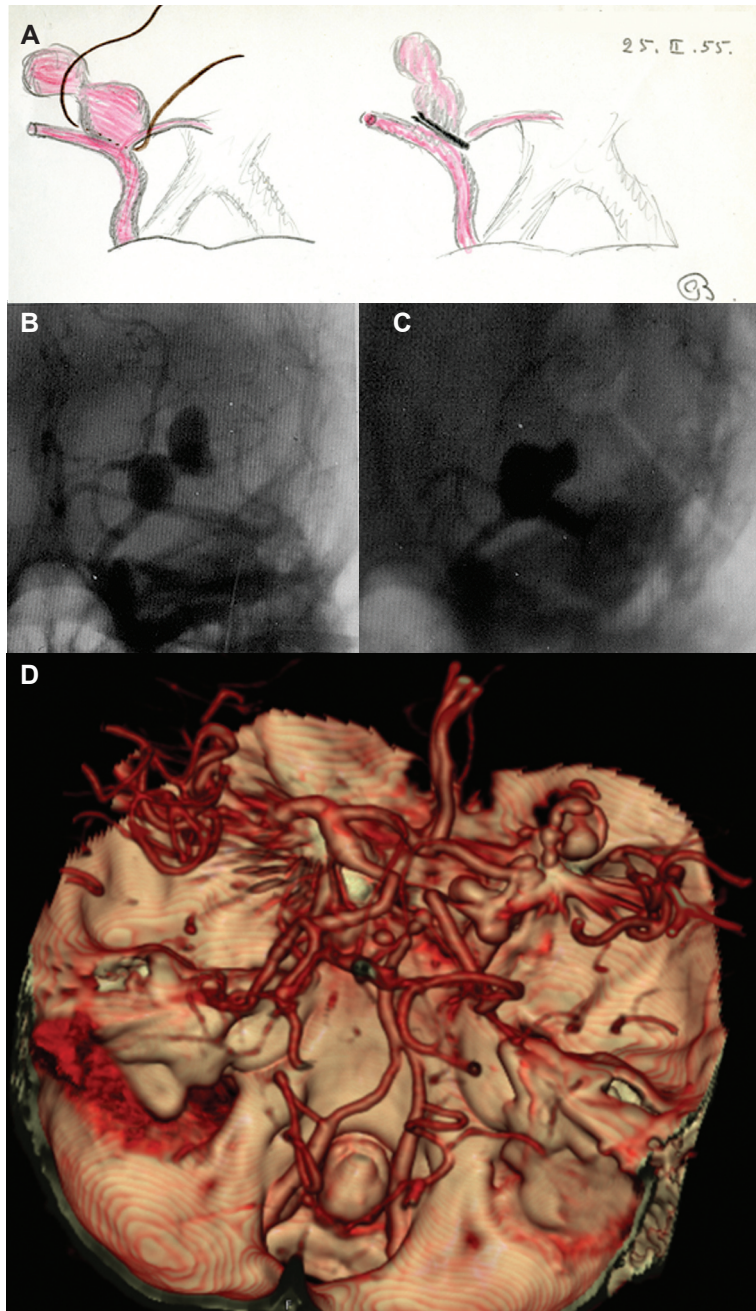
Introduction of the operating microscope initiated the era of microsurgery.[330] A Turkish born neurosurgeon Davut Tovi from Umeå, Sweden, demonstrated the use of an operating microscope in the operating room in Helsinki in January 1975.[164] The first operating microscope became available in Helsinki in 1975.[164] It was introduced into clinical practice by senior neurosurgeons no thorough training in its use. Professor Juha Hernesniemi operated on his first aneurysm in 1976, and has since then operated on nearly 4000 aneurysms, all under the microscope.[165]

Together with advances in surgical equipment, medical treatment has taken great strides forward. Progress in neuroanesthesia has had an impact on intensive care management of neurosurgical patients. Active secondary prevention with invasive patient monitoring has superseded the formerly more passive "wait and see"-approach.[165] The calcium channel antagonist nimodipine was introduced in the late 1980s and has been routinely used in Helsinki ever since.[338] Also the timing of surgery after SAH has changed from late to early.[58,338] The treatment of unruptured aneurysms in Helsinki began in the 1980s. Due to these advances and improved management of patients with SAH, a slight decrease in the case-fatality rate of SAH during the last three decades has been reported.[90] Initial bleeding from a ruptured aneurysm is fatal in 12-15% of cases before the patient reaches the hospital,[90,93,211,222,262] and another 15% will not recover from the initial bleed. The proportion of patients with SAH who will profit from new medical and surgical advances is, therefore, not high.[90] Nevertheless, the proportion of patients who remain independent has increased and the quality of life of survivors is significantly better.[58,176]

Today, up to 3200 neurosurgical operations, including about 300 aneurysm patients, are performed yearly at the Department of Neurosurgery in Helsinki. It is the largest neurosurgical center in Finland, with a catchment area of nearly 1.8 million people.

3. Aims of the study

1.   To clarify the special characteristics of pediatric cerebral aneurysms

2.   To perform a long-term clinical and angiographic follow-up of patients with cerebral aneurysm in childhood and to identify risk factors for developing new aneurysms and new SAH

3.   To assess long-term excess-mortality and to evaluate factors affecting morbidity and mortality of pediatric patients with cerebral aneurysms

4. Materials and methods

This study is based on the data from the pediatric patients admitted to the Department of Neurosurgery, HUCH, between 1937 and 2009. All patients aged 18 years or younger, excluding those with AVM-related aneurysms or vein of Galen malformations, were included. Some of this patient material has been previously published, in 1981 and 1989. [80,81]

4.1. Publication I:

Long-term outcome

4.1.1.Patients

In publication I, a retrospective analysis of 114 pediatric (≤ 18 years) intracranial aneurysm patients admitted to the Department of Neurosurgery, HUCH, between 1937 and 2009 was performed. Hospital records and available radiological examinations were analyzed. The diagnosis of SAH was assessed if there were signs of bleeding either in lumbar puncture or CT, or if there was a clear history of sudden severe headache, and a bleeding could not be ruled out. Initial Hunt & Hess classifications (all patients) and the Fisher grade[54] (when CT available; n=9) were used. Aneurysm(s) were diagnosed by conventional angiography (n=113) and/or CT-angiography (n=3) and/or MR-angiography (n=5). Postoperative occlusion status was verified by conventional angiography (n=72) or CT-angiography (n=2). In cases where the original angiographies were not available (earlier years of our series), the reports of the neuroradiologist were analyzed. GOS was used to assess clinical outcome.[108]

4.1.2. Follow-up

The latest clinical outcome was obtained by a new follow-up, a written questionnaire (see Appendix II). The questionnaire had questions about patients' general health and underlying medical condition, detailed neurological symptoms, smoking habits and previous smoking, education and employment, diagnosis of new cerebral aneurysms or hemorrhagias, family history of aneurysms, diagnosis of connective tissue disorders, family history of connective tissue disorders, and current medication. Outcome was defined by using GOS and mRS, and patients were asked about activities of daily living and degree of independence in daily activities.

4.1.3. Statistical methods

Statistical analyses were performed by using commercial SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). The Pearson $\chi2$ –test and Linear-by-Linear Association tests were used when appropriate. A probability value < 0.05 was considered statistically significant.

4.2. Publication II:

Long-term excess mortality

4.2.1. Patients

In contrast to publication I, in publication II patients with traumatic aneurysms (n=10) and foreign patients (n=2) were excluded. Data collected retrospectively were in concordance with the data collection in publication I. Aneurysm treatment methods were categorized as active (i.e. surgical or endovascular) or conservative. The aneurysms in the conservatively treated category were not subject to any surgical or endovascular treatments (or treatment attempts) during the entire follow-up. An aneurysm was considered partially occluded if there was any filling in the postoperative angiograms.

4.2.2. Data collection

during follow-up

Patients were followed from diagnosis until death or the end of the year 2010. The vital status of patients (deceased or alive) at the end of the year 2010 was obtained from the Finnish Population Register Center. Two patients had moved abroad and were lost to long-term follow-up. Autopsy reports for patients who died during hospitalization were available. Statistics Finland provided the death certificates of all deceased patients (n=23). Death certificates contain the dates of death and the main cause of death, immediate cause of death, and intermediate stages as well as a short description of the fatal events. Statistics Finland also provided comparable data on the general Finnish population regarding expected survival. Death was considered aneurysm-related if it was attributable to the aneurysm or its treatment or to late sequelae of aneurysm-associated morbidity, e.g. pneumonia in a bedridden patient paralyzed by the initial SAH.

4.2.3. Statistical methods

Relative survival ratios (RSRs) were calculated compared with the matched (gender, age, calendar time) catchment population. RSRs provided a measure of excess mortality irrespective of whether this mortality was directly or indirectly attributable to the aneurysm itself. The RSR is a ratio of the observed survival proportion of patients to the expected one in a comparable reference population.[44] The expected survival was derived using Hakulinen's method[77,78] from that of the comparable general population of Finland matched with respect to age, sex, and calendar time based on data from Statistics Finland. The confidence intervals (CIs) were constructed on the log cumulative hazard scale and the variance of the observed survival proportion was estimated using "Greenwood's method".[70,118]

RSRs and CIs were determined from one year after the admission to Department of Neurosurgery, HUCH, using R environment for statistical computing and graphics.[293]

The Pearson $\chi 2$ –test and Student's t-test were used to find associations between different patient and aneurysm characteristics when appropriate. Statistical analyses were performed using a commercial software (IBM SPSS Inc., version 19.0, Chicago, IL, USA). A probability value < 0.05 was considered statistically significant.

4.3. Publication III: De novo- and recurrent aneurysms

4.3.1. Patients

In concordance with publication II, foreign patients and patients with traumatic aneurysms were excluded.

4.3.2. Follow-up

The long-term follow-up studies with cerebral angiographies were carried out at twenty referral hospitals in Finland during 1978-2012. The data were collected from these referring hospitals with the permission of the National Institute for Health and Welfare. All medical records from all specialties from other hospitals were evaluated. The new radiological studies were re-analyzed by a radiologist. Death certificates (Statistics Finland) and autopsy reports for the deceased patients were reviewed.

4.3.3. Statistical methods

The Pearson χ2 –test and Mann-Whitney U-test were used when appropriate. Unconditional binary logistic regression analysis with a stepwise forward elimination procedure was used to calculate odds ratios (ORs) and 95% CIs of independent risk factors associated with new aneurysm formation. Annual rates of formation of de novo and recurrent aneurysms and a new SAH were calculated by dividing the number of new clinical or angiographic findings by the number of patient follow-up years assuming a linear risk throughout the follow-up period. Cumulative rate of new SAH was estimated using the Kaplan-Meier product-limit method, and the resulting curves were compared using the log-rank test. The Cox proportional hazards model with a forward stepwise regression procedure was used to determine independent risk factors and relative risks (hazard ratio) for a new SAH. Tested risk factors were age at onset, gender, duration of follow-up, current or previous smoking, rupture status of the initial aneurysm, family history for intracranial aneurysms, presence of multiple aneurysms initially, and antihypertensive medication. Statistical analysis was performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). Probability value < 0.05 was considered statistically significant.

4.4. Ethical aspects

The study protocol was approved by the ethics committee of HUCH. Written informed consent was obtained from all patients participating in the new follow-up study in publication I. Death certificates were obtained with permission of Statistics Finland. Long-term follow-up patient records and angiographies were obtained from the referring hospitals with permission of the National Institute for Health and Welfare.

5. Results

5.1. Incidence of pediatric aneurysms

During 1937-2009 altogether 114 pediatric patients (1.3% of all 8996 aneurysm patients treated during this time period) with intracranial aneurysms were treated at the Department of Neurosurgery, HUCH. The proportion of these patients has diminished over the last decades (Figure 8).

5.2. Patient characteristics

The patient populations in the three parts of this study are overlapping (Table 8).

5.2.1. Age and gender

The mean age of patients was 14.5 years (median 16.1 yrs, range 3 months -18 yrs) (Table 8 and Figure 9). At the time of diagnosis, 14 patients were younger than 10 years, including four patients with traumatic aneurysms. The majority of the patients were boys (3:2).

5.2.2. Predisposing factors

In our series, no classical systemic collagenous vasculopathies were diagnosed. However, ten patients were diagnosed with a predisposing factor for intracranial aneurysms (Table 9). One 6-year-old boy had ADPKD and another (a 6-year-old boy) had tuberous sclerosis complex together with aortic stenosis. Four patients had congenital heart diseases; three patients (14- and 17-year-old boys and a 15-year-old girl) had coarctation of the aorta and one patient (a 16-year-old boy) a hypoplastic aortic wall. All of the heart diseases were undiagnosed and untreated at the time of SAH, resulting in hypertension on admission. Ten patients had a recent history of high-energy head trauma.

One patient had a family history of aneurysms in first-degree relatives at the time of admission and 13 were reported later (new follow-up; questionnaire) was available for 64 of 74 patients), yielding a total of 14 (12 %) patients with a family history of aneurysms. One patient had a history of alcohol abuse (a 17-year-old boy), and altogether 10 patients were smokers (seven boys and three girls, aged 15-18 years).
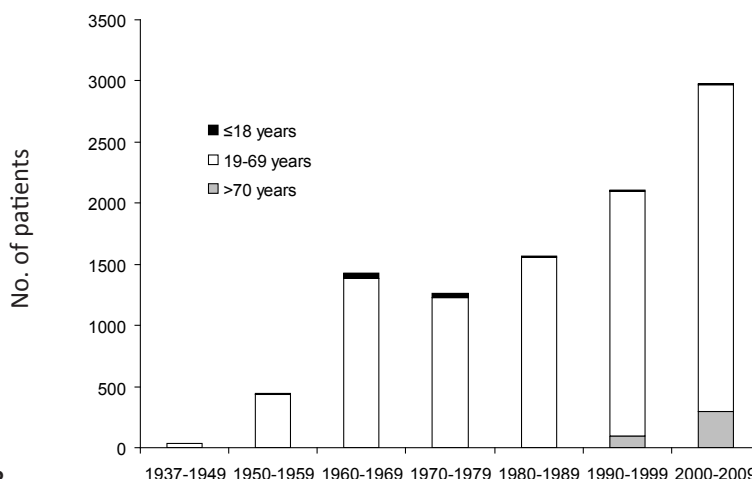
FIGURE 8.
Proportion of pediatric cerebral aneurysm patients of all aneurysm patients admitted to the Department of Neurosurgery during 1937-2009.

	Study I	Study II	Study I
No. of patients	114	102 (88 1-year-survivors)	59
Gender			
Boys (%)	69 (61%)	53 (60%)	36 (61%)
Girls (%)	45 (39%)	35 (40%)	23 (39%)
Age			
Mean(years)	14.5	15.0	16.0
Aneurysms			
Ruptured (%)	89 (78%)	77 (88%)	52 (88%)
Unruptured (%)	25 (22%)	11 (12%)	7 (12%)
Follow-up			
Mean (years)	24.8	26.8	34.0
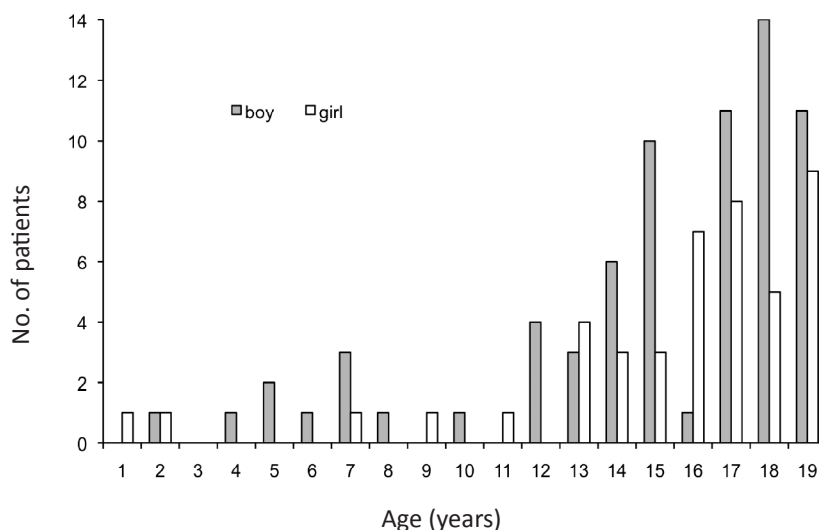
FIGURE 9.
Gender and age distribution in 114 children with intracranial aneurysms.

5.3. Aneurysm characteristics

5.3.1 Presentation

In 89 (78%) of a total of 114 patients, the aneurysm presented as SAH (Table 10). The diagnosis of SAH was based on lumbar puncture, CT, operative findings, or clinical assessment. The most common circumstances during which the aneurysm ruptured are presented in Table 11. Fisher classification was available for nine patients (Table 12).

The majority of patients were in a good neurological state on admission (Table 13). Up untill the 1980s, SAH-patients were typically first treated with bed rest and operations were performed 2-3 weeks later. Later Hunt & Hess scores were better than the initial ones; however, two patients died due to rebleedings during this waiting period. There was no correlation with the initial Hunt & Hess grades and the time period of treatment. Early radiographic vasospasm was diagnosed in 20 (23%) of 89 SAH-patients. In almost 30% of the cases, there was a delay in the diagnosis of SAH (Table 14).

TABLE 9.
Predisposing factors for intracranial aneurysms. ADPKD=autosomal dominant polycystic kidney disease.

Predisposing factor	No. of patients	Mean age (yrs)
Aortic coarctation	3	15
ADPKD	1	6
Congenital heart disease	1	16
Tuberosis sclerosis•	1	6
Trauma	10	12

•Patient also had aortic stenosis

TABLE 10.
Diagnosis of subarachnoid hemorrhage on admission (n=89). CSF= cerebrospinal fluid, CT=computed tomography.

	No.of patients	%
Bloody CSF	77	87
At operation	2	2
Clinically•	1	1
Positive CT	9	10
	89	100

•Clear history of sudden severe headache, and a bleeding was not ruled out.

TABLE 11.
Most common circumstances (≥ three patients) during which an aneurysm ruptured.

	No. of patients
Walking, standing, or sitting	13
Swimming	6
Sleeping	6
Heavy lifting	6
Skating or skiing	5
Cycling	4
Running	3

TABLE 12.
Fisher classification of patients with subarachnoid hemorrhage and initial computed tomography (n=10).
ICH=intracerebral hemorrhage,
IVH=intraventricular hemorrhage.

	No. of patients
No blood•	1
< 1 mm	1
> 1 mm	0
IVH/ICH	8

•Positive lumbar puncture

TABLE 13.
Initial and preoperative Hunt & Hess classification.

Hunt &Hess	Initial		Preoperative	
	No. of patients	%	No. of patients	%
0	12	11	6	11
1	6	5	40	51
2	57	49	19	23
3	20	18	8	10
4	10	9	2	3
5	9	8	2	3
	114	100	77	100

TABLE 14.
Reasons for delay in diagnosis of aneurysm.

Reason for delay	No. of patients	%
No delay	80	70
Patients or relatives	10	9
Primary physician	5	4
Local/Central hospital delay	4	3
University hospital	3	3
Other	12	10
	114	100

5.3.2. Location, size, number, and etiology

The 114 patients were initially diagnosed with 121 aneurysms, with 13 patients having multiple aneurysms initially; 11 patients (10%) had two, one patient (1%) had three, and another patient (1%) had four aneurysms. In the 34-year follow-up, the total number of aneurysms was 157, including 11 recurrent and 25 de novo aneurysms. The most common location for the initial aneurysm was the ICA bifurcation, whereas for de novo aneurysms ICA bifurcation, PCoA, and MCA bifurcation were equally common (Table 15, Figure 10). The aneurysms were of medium size (Table 16), and no statistically significant difference existed between size and rupture status of the aneurysms. The majority of aneurysms were saccular (Table 17). No infectious aneurysms were present in our series.
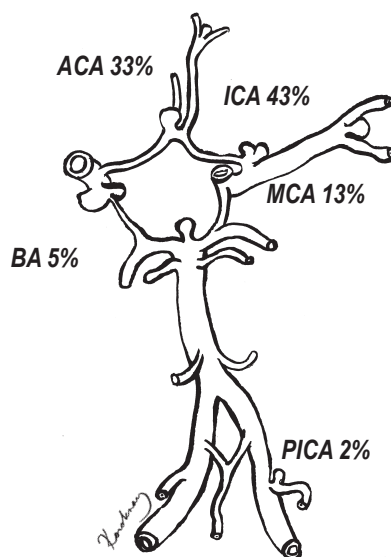
FIGURE 10.
Location of initial aneurysms with proportions in pediatric aneurysm patients in this series.
ACA = anterior cocerebral artery, BA = basilar artery, ICA = internal cerebral artery, MCA = middle cerebral artery, PICA = posterior inferior cerebellar artery.

TABLE 15.
Location of aneurysms. A1 = first segment of anterior cerebral artery, ACA=anterior cerebral artery AChA=anterior choroidal artery, ACoA=anterior communicating artery, MCA=middle cerebral artery, ICA=internal carotid artery, PCA=posterior cerebral artery, PCoA=posterior communicating artery, PICA=posterior inferior cerebral artery, SCA=superior cerebellar artery.

Location		Initial Aneurysms (%)	New aneurysms (%)
ICA		56 (43%)	15 (42%)
	Bifurcation	36 (28%)	7 (19%)
	Cavernous	9 (7%)	-
	PCoA	5 (4%)	7 (19%)
	Ophthalmic	3 (2%)	1 (3%)
	AChA	3 (2%)	-
ACA		43 (33%)	8 (22%)
	ACoA	32 (25%)	5 (14%)
	Pericallosal	7 (5%)	-
	A1	3 (2%)	3 (8%)
	Anterior others	1 (1%)	-
MCA		17 (13%)	10 (28%)
	Main trunk	6 (5%)	1 (3%)
	Bifurcation	6 (5%)	7 (19%)
	Peripheral	5 (4%)	-
Basilar		7 (5%)	2 (6%)
PCA		4 (3%)	-
	PCoA	2 (2%)	-
	Posterior others	2 (2%)	-
SCA		-	2 (6%)
PICA		2 (2%)	1 (3%)
Vertebral		1 (1%)	-
		121	36

5.3.3. Vasospasm and hydrocephalus

Early radiographic vasospasm was diagnosed in 20 (23%) of 88 SAH patients (general five, local 15). One SAH-patient died before an angiography was performed. Early vasospasm was diagnosed from the first conventional diagnostic angiography, most often performed soon after admission, a median of nine days after the SAH. Postoperatively, altogether three patients had symptomatic angiographic vasospasm. Two patients had focal deficits, and one patient had deterioration of consciousness. In addition to these, asymptomatic radiographic vasospasm was diagnosed in 29 patients (36%) after surgery. Postoperative angiography was performed a median of 15 days after the SAH.

No correlation existed between early and postoperative vasospasm. The existence of early or postoperative vasospasm also showed no correlation with gender or age of the patient, location or size of the aneurysm, or initial Hunt & Hess grade. Patients with early vasospasm had poorer outcome at both discharge and long-term follow-up. Postoperative vasospasm correlated with outcome only at long-term follow-up. There was no mortality related to vasospasm in this patient series.

Treatment for postoperative vasospasm was classical triple-H, i.e. hypervolemia, hypertension, and hemodilution. Nimodipine was used since 1989.[338] No angioplasties were performed on these patients.

Early hydrocephalus was diagnosed in four of the 89 SAH patients. Two of these patients had an EVD before operation and one had a ventriculostomy via the lamina terminalis during the aneurysm operation.[169] The fourth patient was managed by observation. Three patients had a shunt operation, but in one of them the shunt was removed due to infection. Of these 89 SAH-patients, two (2%) had permanent shunts, both with a posterior circulation aneurysm. Only one patient with an unruptured aneurysm had a shunt; this patient had a giant fusiform basilar aneurysm causing hydrocephalus. None of the patients with traumatic aneurysms developed symptomatic or radiographic hydrocephalus.

TABLE 16.
Sizes of aneurysms.

	Mean size (mm)	Median size (mm	Range (mm)
Initial aneurysm			
Ruptured (n=89)	9	9	2-50
Unruptured (n=32)	21	5	2-55
New aneurysm			
Ruptured (n=7)	11	11	6-15
Unruptured (n=29)	6	3	1-28

TABLE 17.
Etiology of aneurysms.

	No. of aneurysms (%)
Saccular	99 (63%)
Fusiform	12 (8%)
Traumatic	10 (6%)
De Novo•	25 (16%)
Recurrent	11 (7%)
	157 (100%)

•All of the de novo aneurysms were saccular in shape.

5.4. Treatment of pediatric aneurysms

5.4.1. Ruptured aneurysms

The majority of the ruptured aneurysms were actively treated, whereas in the early years of our series, unruptured aneurysms were treated conservatively (Table 18). Reasons for conservative treatment were poor neurological status on admission, technical difficulties during the 1950s and 1960s and family reluctance for operative treatment. The proportion of conservative treatment was highest during the earlier years in our series (p<0.05).

Surgical techniques included a variety of methods (Table 19), with clipping of the aneurysm being the most common. Intraoperative aneurysm rupture occurred in 17 operations. Re-operation was required in 10 patients, mainly due to incomplete occlusion of the aneurysm in the postoperative angiography. For one patient, a decompressive craniectomy was performed for massive brain edema after proximal artery occlusion.

TABLE 19.
Detailed information on surgical treatment. EC-IC=extracranial-intracranial, ELANA= Excimer laser-assisted nonocclusive anastomosis.

	No. of Aneurysms (%)	
	Ruptured aneurysms	Unruptured aneurysms
Clipping	58	4
Proximal occlusion	6	-
intracranial	2	-
extracranial	4	1
Wrapping	3	-
Trapping	1	-
By-Pass	-	-
EC-IC	-	1
ELANA	-	4
Explorative	2	-

TABLE 18.
Treatment methods.

	No. of Aneurysms (%)	
	Ruptured aneurysms	Unruptured aneurysms
Surgery	70 (85%)	10 (24%)
Endovascular	2 (2%)	-
Conservative	10 (12%)	31 (76%)

54

The surgical approach for anterior circulation aneurysms has traditionally been pterional; however, in recent years, it has been a modification of this approach, mainly lateral supraorbital. [83]

Endovascular treatment

The treatment of aneurysms was purely endovascular for only two patients. A 15-year-old girl had a large ruptured basilar tip aneurysm and was referred to another neurosurgical institute for GDC-embolization because at that time this particular method was not available at our department.

A 3-year-old boy with a gunshot wound to the head and zygoma presented with massive epitaxes three years after the initial trauma, which had been treated conservatively (Figure 11). A traumatic ICA aneurysm was diagnosed and successfully coiled. One de novo aneurysm diagnosed 37 years later was coiled at another hospital. Two more patients are waiting for a stent-assisted coiling of their newly detected unruptured de novo aneurysms.
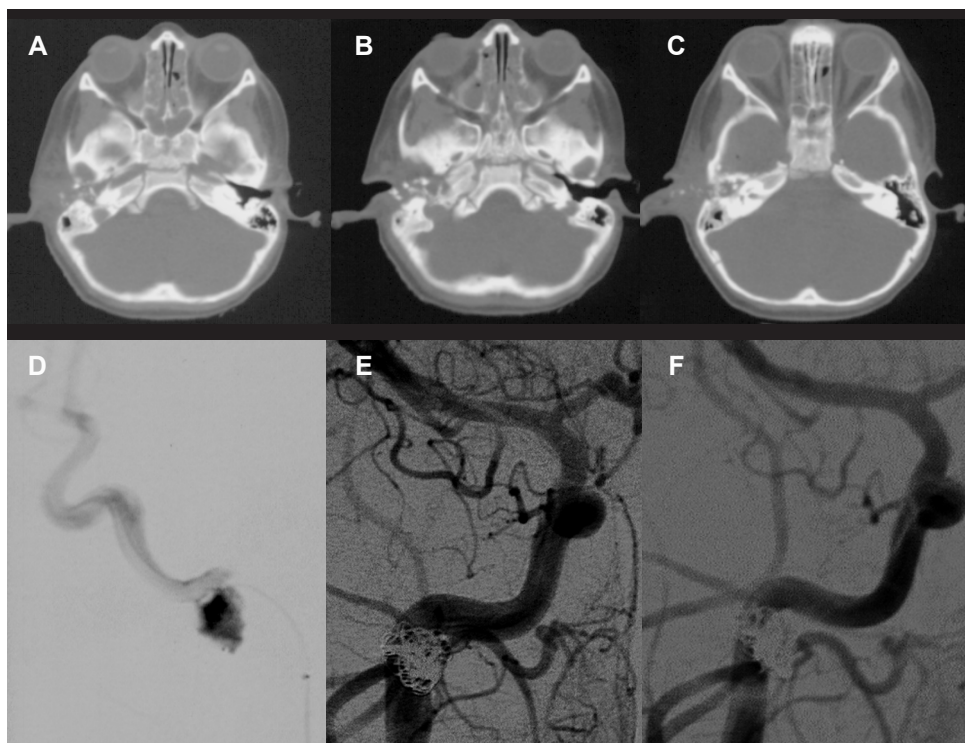
FIGURE 11.
A 3-year-old boy had a gunshot wound in the right ear and carotid canal (A-C). Three years later, the patient had massive epitaxes. Angiography showed a traumatic aneurysm in the right cavernous internal carotid artery (D). The aneurysm was successfully coiled (E). Control angiography five years after coiling and eight years after the initial trauma showed an occluded aneurysm (F).

Conservative treatment

Of the 130 aneurysms in publication I, 37 were treated conservatively mainly because of poor neurologic condition on admission, limited surgical techniques, or parental refusal of an operation. Seven of the 18 patients who survived the initial bleeding had rebleedings, with five (28%) of them being lethal. The first rebleeding was not lethal in any of these patients. There was no correlation between the time of treatment (decade), gender, or age of the patient, location or size of the aneurysm, or initial Hunt & Hess grade and the number of rebleedings. Moreover, no correlation existed between outcome at discharge and rebleedings. Two of the primarily conservatively treated patients were later surgically treated.

Eight (44%) of the 18 conservatively treated SAH patients had a good clinical outcome, i.e. GOS 4-5, at the end of 2010. A favorable long-term outcome among the conservatively treated patients did not correlate with age or gender of the patient, location or size of the aneurysm.

5.4.2. Unruptured aneurysms

During the earlier years unruptured aneurysms were not systematically surgically treated. Figure 12 presents a 13-year-old girl who had been diagnosed with epilepsy two years earlier, with no initial imaging of the brain. Seizures became more frequent and head magnetic resonance imaging (MRI) and MRA were performed, showing a left giant middle cerebral artery (MCA) aneurysm, which was successfully treated. At the 5-year follow-up, the patient was asymptomatic and the anti-epileptic medication was withdrawn. No new aneurysms were diagnosed in the follow-up MRA.

One 17-year old girl had a giant unruptured left vertebral artery aneurysm that presented with cranial nerve deficits and ataxia. The an-

eurysm was treated with a Crutchfield® instrument. The clamp was closed on 1st postoperative day. A few hours after closing of the clamp, the patient developed right hemiplegia and swallowing difficulties and became stuporous. The clamp was opened and the symptoms resolved. However, after opening of the clamp, the patient had a sudden severe headache and lost consciousness. SAH was diagnosed by lumbar puncture. The patient had respiratory arrest and died. Autopsy verified that the giant left vertebral aneurysm had ruptured and resulted in massive SAH and hydrocephalus.

5.4.3. Traumatic aneurysms

Ten patients had traumatic aneurysms. Four of these patients had primary trauma surgery, craniotomy for subdural and epidural hematomas, EVD for intracranial pressure (ICP) control, and occlusion of a CSF-fistula. All of the traumatic aneurysms were diagnosed from the primary angiographies. Three patients died due to primary head trauma. Two patients had SAH 14 days and 20 days after the trauma, and in both cases the ruptured aneurysms were treated microsurgically. A patient case with a gunshot wound and a traumatic cavernous ICA aneurysm is presented in Figure 11.

5.4.4. Extent of aneurysm occlusion

Postoperatively, conventional angiography (n=72), or CT-angiography (n=2) was performed to verify the exclusion quality in operatively treated patients. Postoperative studies were unavailable for 10 patients. These 10 patients consisted of three patients with extracranial proximal artery occlusion in the neck, three patients with wrapped aneurysms, two patients whose surgery was limited to the exploratory stage, and two patients with clipped aneurysms.
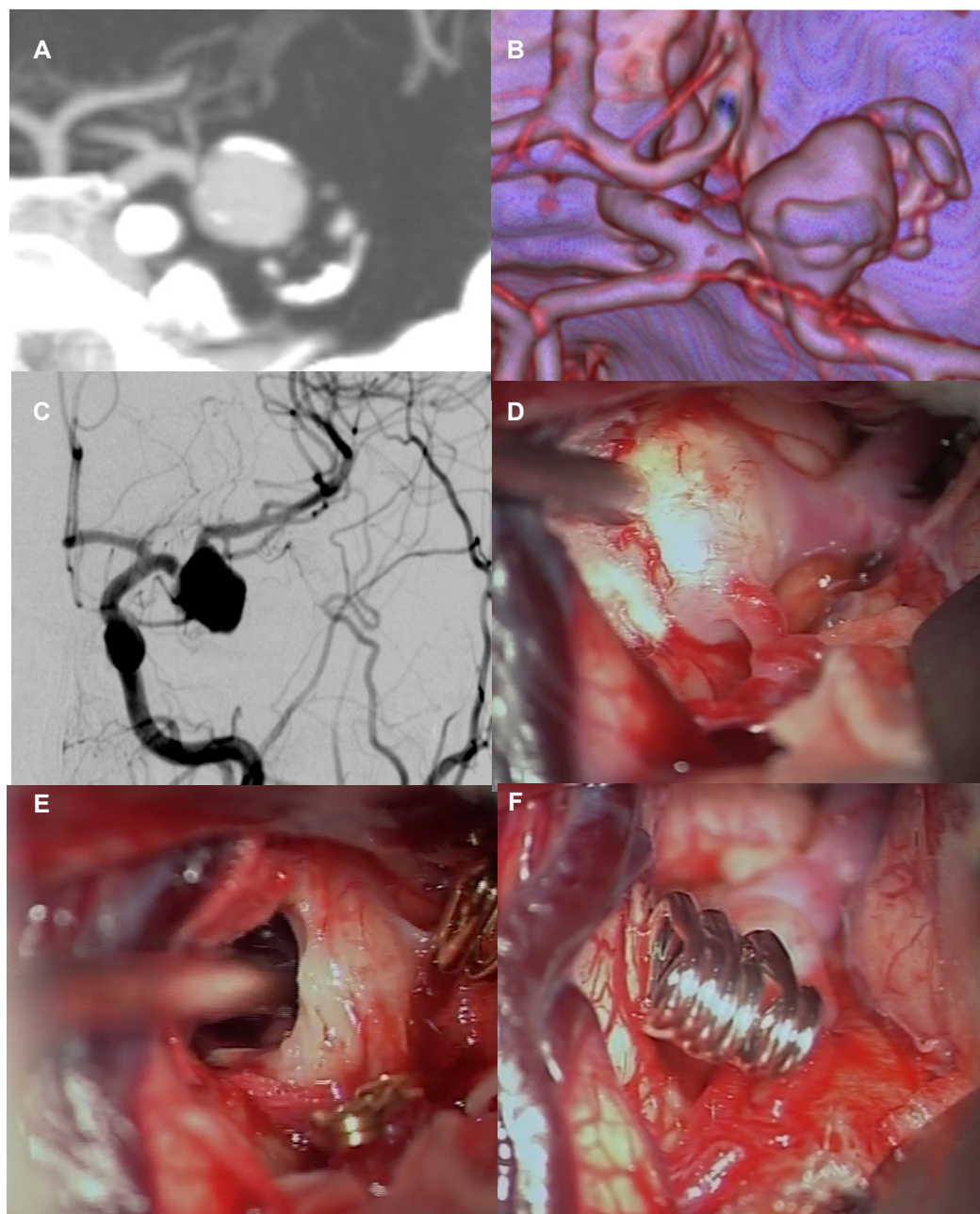
FIGURE 12.
Giant left middle cerebral artery (MCA) bifurcation aneurysm in a 13-year-old girl presenting with epileptic seizures; computed tomography angiograhy (CTA), 3-D CTA and digital subtraction angiography (A-C). Aneurysm dome exposed (D). Temporary clips and decompressing the aneurysm with suction (E). Occlusion with three aneurysm clips (F).

Postoperatively, 68% of the aneurysms were completely occluded, 10% were partially occluded, and 11% were open. Half of the patients with completely open aneurysms had a fatal re-bleeding, at a median of 64 days (range 4 days-19 yrs). There was a statistically significant correlation between aneurysm exclusion quality and time of treatment (decade); in later years, the completeness of aneurysm closure was higher.

One conservatively treated patient had a control angiography four months after SAH of a left distal MCA aneurysm. The aneurysm had totally thrombosed in the control angiography.

5.5. Short-term outcome

The mean duration of hospital stay was 15 days (median 12 days, range 0-46 days). Nine patients died during hospitalization, with causes of death being severe SAH (n=4), rebleeding before treatment (n=2), treatment complication (i.e. main vessel occlusion) (n=2), and bleeding after treatment (n=1). During the first year after SAH two conservatively treated patients died due to rebleedings, at one month and at ten months after primary bleedings. Two patients died due to rebleedings after operative treatment two and three months after initial bleeding; one of these patients had a totally open wrapped ACoA aneurysm and the other a by partially closed (by clipping) ICA bifurcation aneurysm. There were no deaths associated with vasospasm. All deaths during the first year after admission to the Department of Neurosurgery were aneurysm- or treatment-related. Two of these patients had unruptured aneurysms. The overall mortality during the first year after SAH was 13%. Of all the deaths during the follow-up period, 41% occurred during the first year after diagnosis.

At discharge, 73 (64%) patients had a favorable outcome (GOS>3), 24 (21%) were dependent, and 3 (3%) were in vegetative state. Fourteen patients (12%) had died. The outcome of patients at discharge correlated with patients'

age, i.e. younger patients had poorer outcome. Unfavorable outcome correlated also with the initial Hunt & Hess grade and early vasospasm. However, the outcome of patients at discharge did not correlate with year of treatment, gender of patient, location, size, or rupture status of aneurysm, treatment method, or completeness of aneurysm closure.

5.6. Long-term outcome

The majority (n=49) of the surgically treated patients had a 2-month clinical follow-up at our out patient department, with a mean follow-up time of 66 days (range 14-118 days). A new follow-up was organized using a written questionnaire, which was sent to all 74 patients who were alive according to the national population registry; 64 (86%) patients responded. Two patients were lost to follow-up due to their moving abroad. One patient declined to participate and seven did not reply to the letters. Eventually, the total coverage was 104 patients (91%), with a mean follow-up time of 24.8 years (median 29.6 yrs, range 0-55.8 yrs). At the last follow-up, 71 (62%) of the patients had recovered well (GOS>3), 3 (3%) were dependent, and 40 (35%) had died. Cause of late disability was SAH or treatment related in 77 %.

The most common neurological deficits were memory deficit in 21 patients (32%) and cranial nerve deficit in 12 patients (18%). Forty-three patients (67%) reported having no neurological deficits. Neurological deficits were associated with partially occluded and totally open aneurysms. A total of 94% of patients not having any neurological deficits had a closed aneurysm, compared with 70% of patients reporting a neurological deficit.

Long-term outcome correlated with aneurysm location, with anterior circulation aneurysms being associated with more favorable outcomes. The good neurologic condition of the patient on admission, i.e. initial Hunt & Hess grade, correlated with favorable outcome.

Both early and postoperative vasospasms were associated with a poorer long-term outcome. A favorable outcome did not correlate more strongly with surgical or endovascular treatment than with conservative treatment. However, there was a statistically significant correlation of long-term outcome with completeness of aneurysm closure; patients with totally occluded aneurysms had better long-term outcome. The size of the aneurysm and the age or gender of the patient were not correlated with long-term outcome.

At the end of 2010, the mean age of patients who had survived (n=74) was 49 years (range 11-73 yrs). Seventeen patients (27%) had medication for hypertension and 12 patients (19%) for epilepsy (Table 20). The majority (n=41/64, 64 %) of the patients were former or current smokers. At the time of the last follow-up, 27 patients (42%) were current smokers,

with 29.7 mean years of smoking (range 5-51 yrs). There were 14 ex-smokers (22%) , with 16.2 mean years of smoking (range 2-40 yrs).

The majority (n=58, 91%) of the patients lived at home independently without assistance, and none of the patients were permanently hospitalized (Table 21). Most of the patients considered that the aneurysm and its possible treatment had no effect on their success at school or career selection. At the end of follow-up majority of the patients were working or studying, and 8% had retired due to aneurysm-related reasons (Table 22).

TABLE 20.
Detailed information on the general health condition of patients at the end of 2010.

	No. of Patients (%)
Hypertension	18 (27%)
Epilepsy	13 (20%)
Cardiac disease	11 (17%)
Arteriosclerosis	10 (15%)
Diabetes	7 (11%)
Tumor‡	5 (8%)
Respiratory disease	3 (5%)
Rheumatic disease	2 (3%)
Kidney disease	2 (3%)
Hypothyreosis	2 (3%)
Coagulopathy•	1 (2%)
	66

‡Breast cancer, colon cancer, uterine tumor, benign soft tissue tumor, benign breast tumor
•von Willebrandt disease

TABLE 21.
Living arrangements of patients at the last follow-up.

	No. of Patients (%)
Home	60 (91%)
Home-assisted	4 (6%)
Nursing home	2 (3%)
Hospital	-
	66

TABLE 22.
Working ability of patients at the end of 2010.

	No. of Patients (%)
Working/studying	42 (64%)
Retared	16 (24%)
Due to age	5 (8%)
Due to aneurysm	5 (8%)
Due to other illnessess	6 (9%)
Modified work/studies	8 (12%)
	66

5.7. Long-term mortality and excess mortality

5.7.1. Long-term mortality

Ruptured aneurysms and aneurysm-related deaths

Four patients died due to rebleeding during conservative treatment, two of whom were first-year survivors, dying at one and a half years and five years after the initial bleedings, respectively. Two postoperatively totally open aneurysms had lethal rebleedings at three years (MCA aneurysm with clipping) and 20 years (MCA aneurysm and explorative craniotomy) after initial bleedings. One patient with a totally occluded aneurysm died due to massive SAH 11 years later. This bleeding was due to recurrent aneurysm verified at autopsy. Three patients died due to bleedings from de novo aneurysms at 11, 30, and 33 years after initial bleedings. All of these patients had fully recovered from the initial bleedings.

Unruptured aneurysms

Only one death was observed in patients with unruptured aneurysms after surviving the first year after diagnosis. A 17-year-old patient had multiple giant fusiform aneurysms. At the time of diagnosis, all of the aneurysms were unruptured. One of the aneurysms was giant thrombosed basilar artery aneurysm, which had caused cerebellar and pontine infarctions on presentation, and four months later bled. The patient recovered reasonably well from the infarcts and SAH (GOS 4). An ELANA by-pass operation was performed due to right-sided giant ICA aneurysm without immediate complications. The patient was found dead at home three months later. Autopsy revealed high blood alcohol level, but no clear evidence of aneurysm-related death.

Ruptured aneurysms and aneurysm-unrelated deaths

In the long-term follow-up, one cardiovascular death was observed at 37 years after the treatment of a ruptured aneurysm. There were two cancer-related deaths, one leukemia and one prostate cancer, at 29 years and 40 years after SAH, respectively. One patient died due to pancreatitis and septicemia 19 years after SAH.

For three patients, the actual cause of death was uncertain/unconfirmed. One patient had moved abroad later and died, but no death certificate or autopsy report was available. Another patient was found dead at home and no autopsy was performed. This death was classified as cardiovascular on the death certificate; however, an aneurysm-related death can not be excluded. The third patient died due to massive intracerebral hematoma and intraventricular bleeding, but no angiography or autopsy was performed to identify the etiology of the bleeding. This patient had a ruptured aneurysm that was surgically totally occluded 40 years earlier. The causes of deaths of these three patients were classified as unknown and aneurysm-unrelated.
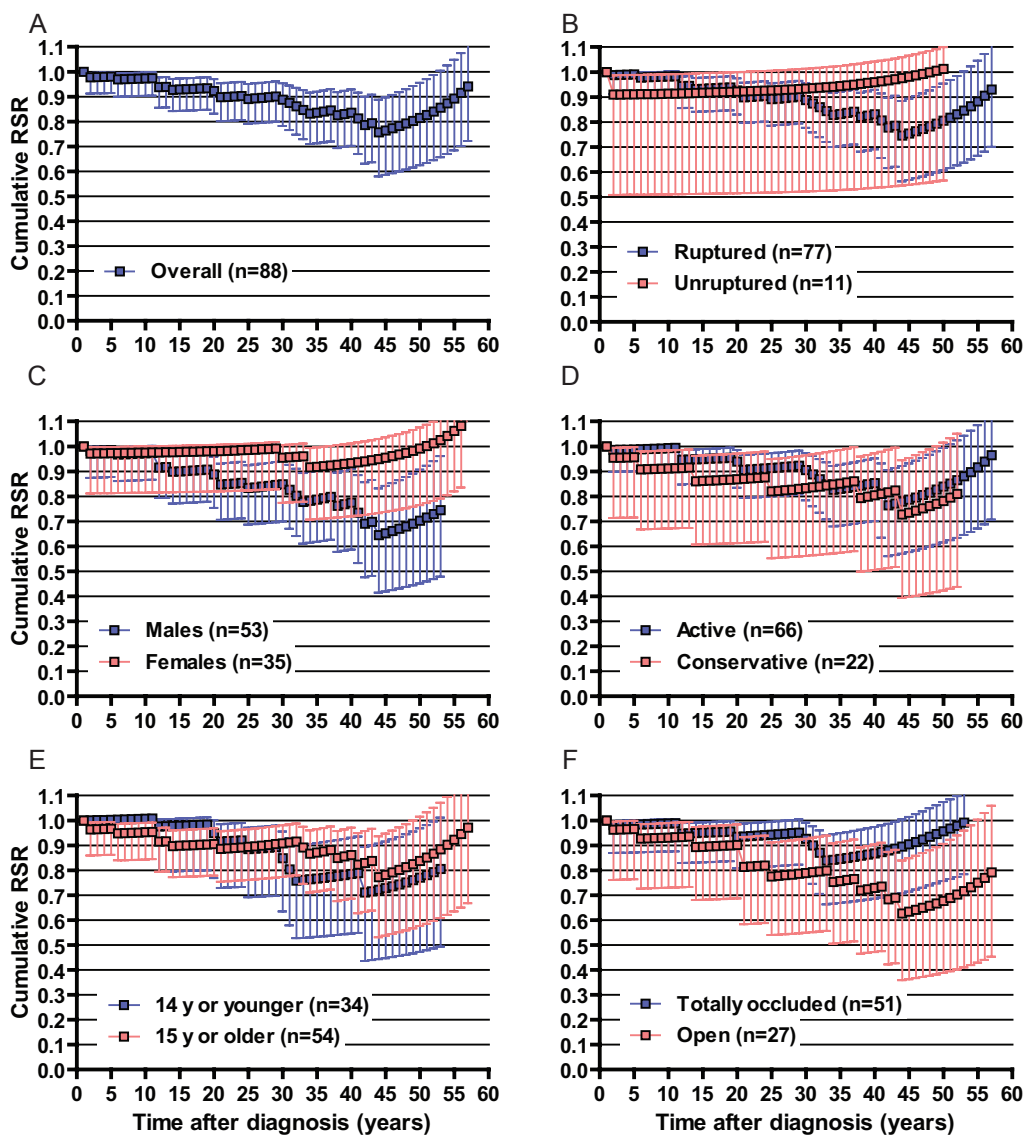
5.7.2. Long-term excess mortality

Long-term excess mortality was estimated in the one-year survival pediatric aneurysm patients compared with the matched Finnish population. The overall cumulative RSRs in one-year survivors (n=88) after diagnosis of an intracranial aneurysm were 0.90 (95% CI 0.80-0.95) and 0.81 (95% CI 0.67-0.91) at 20 and 40 years after the diagnosis, respectively (Table 23 and Figure 13A). Patients with a ruptured aneurysm (n=77) had significant excess mortality, in contrast to patients with unruptured aneurysms (n=11) (Table 23 , Figure 13B). Males (n=53) faired worse, with excess mortality of 15% and 27% at 20 and 40 years, respectively, compared with the corresponding figures for females (n=35) of 2% and 6% (Table 23, Figure 13C). There was excess mortality in patients with single (n=77)

TABLE 23.
Cumulative survival ratios and corresponding 95% confidence intervals, stratified by age, gender, number of aneurysms, rupture status of the index aneurysm, treatment method, and aneurysm status after treatment. N/A = not available.

	Cumulative relative survival ratios (95% CI)			
	at 5 years	at 10 years	at 20 years	at 40 years
	0.97 (0.90-0.99)	**0.97 (0.90-1.00)**	**0.90 (0.80-0.95)**	**0.81 (0.67-0.91)**
Age (years)				
0-14	1.00 (N/A)	1.01 (N/A)	0.92 (0.73-0.99)	0.79 (0.55-0.93)
15-18	0.95(0.84-0.99)	0.95 (0.84-0.99)	0.89 (0.75-0.96)	0.82 (0.62-0.94)
Gender				
Boy	0.97 (0.86-1.00)	0.97 (0.87-1.00)	0.85 (0.71-0.93)	0.73 (0.53-0.88)
Girl	0.97 (0.81-1.00)	0.97 (0.82-1.00)	0.98 (0.82-0.95	0.94 (0.72-1.01)
No. of aneurysms				
Single	0.98 (0.90-1.00)	0.98 (0.91-1.00)	0.90 (0.80-0.96)	0.83 (0.68-0.94)
Multiple	0.91 (0.51-1.0)	0.92 (0.51-1.00)	0.84 (0.46-0.98)	0.66 (0.26-0.93)
Rupture status of aneurysm				
Ruptured	0.98 (0.90-1.00)	0.98 (0.91-1.00)	0.90 (0.80-0.96	0.80 (0.65-0.91)
Unruptured	0.91 (0.51-0.99)	0.91 (0.51-0.99)	0.92 (0.51-1.00)	0.96 (0.54-1.05)
Treatment				
Surgical or endovascular	0.99 (0.90-1.00)	0.99 (0.91-1.00)	0.91 (0.79-0.97)	0.81 (0.63-0.93)
Conservative	0.91 (0.67-0.98)	0.91 (0.67-0.98)	0.87 (0.61-0.99)	0.80 (0.51-0.97)
Aneurysm status after treatment				
Totally occluded	0.98 (0.87-1.00)	0.99 (0.88-1.00)	0.94 (0.81-0.99)	0.87 (0.67-0.98)
Partially occluded	1.00 (N/A)	1.01 (N/A)	1.02 (N/A)	0.83 (0.14-1.01)
Open	0.93 (0.73-0.98)	0.93 (0.73-0.99)	0.81 (0.58-0.93)	0.73 (0.47-0.90)

FIGURE 13.

Excess mortality of one-year survival of pediatric aneurysm patients compared with the matched Finnish population. Overall cumulative relative survival ratios (RSRs) in one-year survivors (n=88) after diagnosis of an intracranial aneurysm (A). Cumulative RSR of 77 patients with ruptured aneurysms and 11 patients with unruptured aneurysms (B), 53 males and 35 females (C), 66 patients with actively treated aneurysms and 22 patients with conservatively treated aneurysms (D), 34 patients were aged 14 years or less and 54 patients 15 years or more at diagnosis (E), and 51 patients with totally occluded aneurysms and 27 with open aneurysms. Error bars, 95% confidence intervals.

and multiple (n=11) aneurysms. The type of treatment, i.e. active (n=66) versus conservative (n=22), did not affect the long-term excess mortality, in contrast to the aneurysm occlusion status, which was a significant factor (Table 23, Figure 13D and F). Younger patients (14 years or younger) tended to have greater excess mortality than patients 15 years or older at the time of diagnosis (Table 23, Figure 13E). No difference existed between saccular (n=81) and fusiform (n=7) aneurysms in survival; however, the low number of fusiform aneurysms should be noted. There were no aneurysm-related deaths among patients with unruptured aneurysms in the long-term follow-up after surviving the first year after diagnosis. Cumulative survival ratios and corresponding 95% confidence intervals stratified by age, gender, number of aneurysms, rupture status of the index aneurysm, treatment method, aneurysm status after treatment are presented in Table 23.

5.8. Long-term angiographic follow-up

5.8.1. Recurrent SAH and new aneurysms

Of the one-year-SAH-survivors (n=77), angiographic follow-up (CTA n=33, MRA n=13 and/or DSA n=13) was available in 56 patients (73%) and/or neuropathological autopsy in three patients (4%) (total, 59 patients (77%)). The median follow-up was 34.0 years (mean 32.5 yrs, range 4-56 yrs). During this time a total of 23 patients (44%) with a previous SAH (n=52) had de novo and/or recurrent aneurysms; there were 25 de novo-aneurysms and 10 recurrent aneurysms, and eight patients (33%) had multiple new aneurysms. The median times for diagnosis of symptomatic and asymptomatic aneurysms were 19.9 years (mean 19.9 yrs, range 11-33 yrs) and 36.0 years (mean 37 yrs, range 26-47 yrs), respectively, in patients with previous SAH. Thus, patients with symptomatic new aneurysms were younger (median 33 yrs, range 22-50 yrs) than patients with asymptomatic aneurysms (median 50 yrs, range 40-62 yrs). Eight (27%) of all de novo/recurrent aneurysms presented with SAH, with an early mortality of 57%. There were no de novo aneurysms in patients with previous unruptured aneurysms; however, one patient had a symptomatic, but unruptured recurrent aneurysm (Fig-
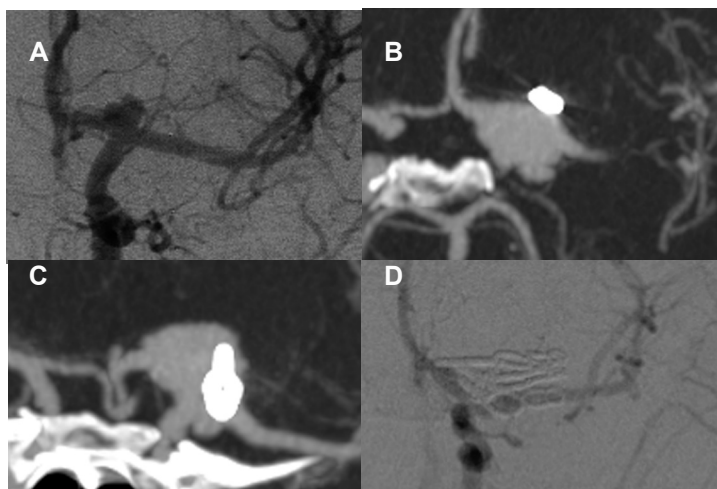
FIGURE 14.
A 16-year-old girl with seizures was diagnosed with an unruptured internal cerebral artery bifurcation aneurysm (A) that was clipped. Six years later seizures severed with angiography revealing a large recurrent aneurysm (B and C). The recurrent aneurysm was succesfully clipped (D).

ure 14). Asymptomatic growth of an untreated aneurysm was diagnosed in three patients (5%). Spontaneous thrombosis was diagnosed in three patients (5%). Thirty-five patients (59%) were former (n=11, 19%) or current (n=24, 41%) smokers, and 26 (44%) had a diagnosis of hypertension. Six of the eight patients with multiple aneurysms were current (n=5) or former (n=1) smokers. Of the de novo aneurysms, 24% were located on the ipsilateral side to the initial aneurysm. Symptomatic aneurysms were larger than asymptomatic ones, with median sizes of 15.0 mm (mean 14.8 mm, range 6-28 mm) and 3.0 mm (mean 6.2 mm, range 1-14 mm), respectively (p>0.05).

Of the original 102 patients, 34 had died by the end of 2010. Of them, four had died due to a SAH from a de novo aneurysm. Five patients had a new aneurysm located in posterior circulation, but only two of them had had a four-vessel angiography initially. One patient had verified aneurysmal SAH, intraventricular hemorrhage (IVH), and large midline frontal hematoma around a previously totally clipped ACA aneurysm. No angiography was performed and the autopsy report did not specify whether the new ruptured aneurysm was de novo or recurrent.

5.8.2. Annual rates and risk factors

During 1935 person-years of follow-up the annual rate of hemorrhage (n=7) was 0.4% and development of de novo or recurrent aneurysm (n=36) was 1.9%. In patients with previous SAH (1766 person-years of follow-up), the corresponding rates were 0.5% and 2%. Separate annual rates for de novo (n=25) and recurrent (n=11) aneurysms were 1.3% and 0.6%, respectively, for all the patients. The only statistically significant risk factor for new aneurysm formation was current or previous smoking (OR 3.39; 95% CI 1.02 to 11.29; p=0.047). For patients with ruptured aneurysm in the childhood the risk was even higher; OR 4.92; 95% CI, 1.32 to 18.39 (p=0.018). Hypertension, gender, age of the patient initially, initial number of aneurysms, initially ruptured aneurysm, family history for aneurysms, or previous parent artery occlusion had no statistically significant effect on new angiographic findings. None of the acknowledged risk factors had a statistically significant role in occurence of a new SAH; however, smoking seemed to have an impact, although it did not quite reach statistical significance (p=0.077). Kaplan-Meier statistical analysis on survival of a new SAH is presented in Figure 15.
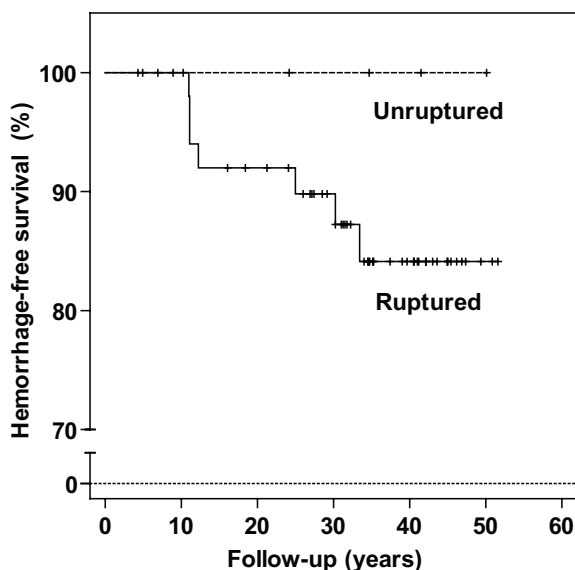
FIGURE 15.
Kaplan Meier survival analysis on a new SAH.

5.8.3. Treatment of new aneurysms

All symptomatic new aneurysms were treated actively at three of the five University Hospitals in Finland during 1989-2011, except for four patients dying soon after SAH. All of the patients with a new asymptomatic aneurysm have been referred to a consultation with a local neurosurgeon (Figure 16).

FIGURE 16.
A 59-year-old female had three new left-sided asymptomatic aneurysms (recurrent posterior communicating artery (PCoA) aneurysm 6 mm, de novo internal cerebral artery (ICA)-ophthalmic aneurysm 3 mm, and de novo superior cerebellar artery aneurysm 3 mm) 41 years after successful clipping of a ruptured left PCoA aneurysm. Two of the aneurysms (PCoA and ICA-ophthalmic) were treated successfully with stent-assisted coiling (A and B), with antiplatelet medications started afterwards. Two months after coiling, the patient sustained a large spontaneous intracranial hematoma (C and D) which was operated on. At the last follow-up, the patient had severe dysphasia and hemiparesis (GOS 3).

6. Discussion

This study presents a single-center consecutive series of pediatric patients with intracerebral aneurysms together with a literature review. To date, this is the largest reported series on these rare patients. Descriptive data for these patients are presented. The clinical long-term follow-up data with later co-morbidities, neurological outcome, and educational status and employment are presented over a mean follow-up time of 25 years. The long-term risk of these patients harboring de novo and recurrent aneurysms, possibly leading to SAH, and factors affecting this risk are assessed. Excess mortality and contributing factors are determined.

Age and gender

In our study, there was a male predominance (61%) for aneurysm formation, consistent with the literature review. Among adults, the majority of aneurysm patients are females. However, a meta-analysis study found that the incidence of SAH was significantly higher in men than in women in the age group 25–45 years, while in the age group 55–85 years, the incidence was significantly higher in women.[37]

Predisposing factors

The main risk factors for aneurysm formation and rupture in the adult population are hypertension, smoking, excessive alcohol abuse, previous aneurysm rupture, and female gender. In our series there were seven patients (6%) with a known predisposing factor. Three patients had aortic coarctations with hypertension, and all were operated on later. One patient had AD-PKD. One patient had a hypoplastic aortic wall. There was one patient with tuberous sclerosis complex and multiple giant fusiform aneurysms. Intracranial vascular lesions are very rare in tuberous sclerosis, and seldom are intracranial aneurysms reported in these patients.[96,111,271]

Beltramello et al.[9] suggested that intracranial aneurysm can be added to the nonprimary diagnostic features for the clinical diagnosis of tuberous sclerosis complex; however, a recent paper did not recommend routinely screening for vascular lesions in these patients.[248]

In a recent publication by Sanai et al.,[250] the proportion of significant comorbid disease was as high as 28%, contrary to our series. Our series was collected over a long period, and in the early years possible underlying connective tissue disorders may have gone unnoticed. However, when studying the medical records and written questionnaire no indication emerged of connective tissue disorders in the patients later in life.

There were altogether 14 patients with a positive family history, i.e. a first-degree relative(s) had a diagnosis of an intracranial aneurysm. According to our results in pediatric patients, there is no tendency for increased family history of cerebral aneurysms compared with adults.[240]

Presentation

Most aneurysms (78%) in this series were ruptured. Despite a clear delay in the diagnosis of an aneurysm after classical symptoms of SAH, the majority of the patients were in good condition on admission. Surprisingly, the neurologic condition of patients on admission was not significantly better during the modern era, as would be expected due to major advances in emergency care and neurointensive care.

Aneurysm characteristics and etiology

Most aneurysms (89%) were located in the anterior circulation, especially in the ICA and ACoA. This is in good agreement with the literature review on pediatric aneurysm patients, thus differing from location in adults (see Figure 1). Also, the patients in our series had a lower frequency (12%) of multiple aneurysms than adult patients (about 30%). The

mean sizes of ruptured aneurysms (9 mm) and unruptured aneurysms (21 mm) were slightly larger than those reported in the adult population in Finland (7 mm).[100] The proportion of giant aneurysms was slightly higher (12%) than that in the adult population (5%).[161] In our series, there were 10 patients with traumatic aneurysms. Seven of these 10 aneurysms were located in the distal branches of either the ACA or MCA. These patients were younger than those with spontaneous aneurysms. In three patients, the aneurysms bled later, at a mean of 4 weeks. The major causes for high-energy trauma were motor vehicle accidents in the 1950s, 1960s and 1970s. Nowadays, angiography is not used as the primary imaging method in trauma cases so asymptomatic traumatic aneurysms may remain hidden. Furthermore, children may have a greater tendency for traumatic aneurysms than adults. As previously stated by Yazbak et al.,[333] the formation of a traumatic aneurysm should be considered in a patient with a history of head injury with new neurological symptoms. No mycotic aneurysms were present in our series.

Conservative treatment

A large proportion of conservatively treated patients (44%) with a ruptured aneurysm in childhood have a good long-term outcome. This is surprising, especially when taking into account ongoing smoking among these patients. However, almost one-third of patients had died due to re-bleedings without the proper follow-up imaging recommended today. The incidence of rebleedings was not associated with any specific factor in patients or in aneurysms among the conservatively treated patients.

Microsurgical versus endovascular treatment

Debate over the two treatment modalities, microsurgical and endovascular, is ongoing. A recent paper found microsurgery to be more efficacious and durable, especially when con-

sidering the long life expectancy of children.[250] Another study promotes endovascular treatment over surgery.[2] Sanai et al.[249] found that the number of de novo aneurysms was considerably higher in the endovascularly treated patients, thus suspecting that the coiling procedure itself harms the previously somewhat fragile vessel wall, predisposing to aneurysm formation. In our series, the majority of the patients were microsurgically treated, even during the last 20 years, when endovascular treatment has been available. This is partly because of our vast experience in microsurgery. Due to the small number of endovascularly treated patients in our series, no statistical comparison between the two treatment methods could be performed.

Outcome

The fact that classical connective tissue disorders were not diagnosed in our series led us to suspect that these patients have some systemic vascular disorders that would predispose them in the future to cardiac diseases or other cerebrovascular events. This, however, was not the case, with the exception of de novo aneurysms. The incidence of hypertension, hypercholesterolemia, stroke, etc., was no higher than in the age-matched Finnish population. Also there was no increase in the incidence of autoimmune disorders.

In our series, the proportion of current smokers was over three-fold that of the general population in Finland.[279] In addition, there was a long history of smoking among these patients.

The two most significant factors associated with a favorable long-term outcome were aneurysm location in the anterior circulation and complete aneurysm closure. Furthermore, good neurologic condition of the patient on admission and absence of early and postoperative vasospasm correlated with a good outcome. In our series, the timing of the first angiography was relatively late, i.e. nine days after SAH, compared with the modern practice.

The treatment method had no correlation with the outcome, mainly due to inefficient completeness of aneurysm closure during the early years. Incomplete aneurysm closure, by contrast, was associated with neurological deficits. It is noteworthy that although one-third of patients in our series had a neurologic deficit they managed well in their lives and most of them considered that the aneurysm and its treatment had not affected their lives with regard to education, career, or social activities.

It is reasonable to assume that children have an overall better recovery potential than adults for cerebral assaults as well as for many other diseases. Comorbidities, such as underlying atherosclerosis, hypertension, and diabetes, are virtually non-existent or have a very short duration in children. In addition to the initial hemorrhage, rebleeding and vasospasm are the leading causes of morbidity and mortality in SAH patients. In our series, no patients died due to vasospasm, and among pediatric patients the incidence of delayed cerebral ischemia has been reported to be low,[207,216,225] possibly due to capable leptomeningeal collateral circulation.[159]

In our series, one-third of patients reported neurological deficits, with slight hemiparesis and cranial nerve deficits being most common. However, even though patients might lack major motor neurological deficits, they may have impaired memory. Memory deficit was the most common deficit reported. Patients were also able to classify the memory deficit as aneurysm–related or unrelated. In an SAH patient study with adult patients, Hackett et al.[75] found that good-outcome patients may have high-level deficits in memory and other cognitive functions, which became obvious in neuropsychological examination. In our series, no neuropsychological tests were carried out. However, level of education was determined together with employment status and line of work.

Search for predisposing factors

In this study, only a minority of the children had classical predisposing systemic connective disease. When dealing with a child with an intracranial aneurysm, recognition of an underlying systemic connective tissue disorder may be of considerable importance, although marked phenotypic heterogeneity often complicates the diagnosis of these disorders.[257] Abdominal ultrasound to exclude polycystic kidneys is an inexpensive examination with excellent availability and precision. For every child with an intracranial aneurysm and high blood pressure, aortic coarctation and other cardiac disorders in addition to secondary etiologies for hypertension should be excluded. Furthermore, as pointed out by Schievink et al.,[257] the association of certain neurovascular anomalies with systemic connective tissue disorders and recognition of their basic molecular defect may offer clues to the etiology and pathogenesis of these neurovascular diseases in general.

New aneurysms

In our series, almost 40% of the patients developed new aneurysms over the long follow-up (mean 34 years). The only risk factor found was smoking, which among patients with previously ruptured aneurysms raised the OR to 5. There were no de novo aneurysms among patients with unruptured aneurysms. However, the number of patients with unruptured aneurysms was small, which might have had an impact on this finding. In our risk factor study, however, a ruptured aneurysm status was not an independent risk factor for new aneurysm formation.

Previously, annual rates of up to 2.6% for de novo aneurysms and 3.5% for recurrent aneurysms among pediatric patients have been reported;[117] these are high relative to our study (1.3% and 0.6%, respectively). However, the patient inclusion criteria differ markedly; in the study from Barrow Neurological Institute

(BNI)[117] also AVM-related aneurysm patients and patients with iatrogenic, traumatic, and infectious aneurysms were enrolled. Our results are in concordance with adult aneurysm patient studies, where the annual rate for de novo aneurysms has varied between 1.8% and 4%[20,36,113] and the rate for annual recurrent aneurysm formation after clipping has ranged from 0.06% to 0.5%.[36,302,323] In our series, the annual risk of developing de novo aneurysms was threefold that of deleloping recurrent aneurysms, in concordance with previous studies in adult aneurysm patients.[36,302]

There has been wide variation in the rate of hemorrhage from a de novo or recurrent aneurysm, one adult study found no recurrent SAHs despite de novo aneurysms,[46] whereas another[36] reported rates that were almost fivefold (1.9%) those of our series with pediatric patients. The annual rupture rate in our series (0.4%) is consistent with earlier pediatric studies (0.6%).[117] It should be noted that in Finnish patients the risk of an aneurysm rupture is two- to threefold that in other populations. In our study, eight patients (14%) experienced a new SAH. The early mortality from an SAH from a de novo aneurysm was high (57%) relative to recent literature.[20]

Risk factors for new aneurysm and new SAH

In our series, the majority of patients were current or previous smokers, and half of them had hypertension, both known risk factors for aneurysm formation, growth, and rupture.[116,228,295,320] However, the only statistically significant factor for recurrent or de novo aneurysm formation was smoking, with an OR of almost 5 in patients with previously ruptured aneurysms. The impact of a patient initially harboring multiple aneurysms, female gender, or family history of intracranial aneurysms was not significant for later developing new aneurysms, contrary to results in the literature.[8,20,36,130] Moreover, the rupture status of the previous aneurysm or

the age of the patient initially were not risk factors. There were no de novo aneurysms in patients with previous unruptured aneurysms in our series (n=7), even though in studies with adult aneurysm patients de novo rates of up to 1.06% have been reported.[116]

In a study from San Fransisco,[250] 19% of endovascularly treated patients had de novo aneurysms, in contrast to 6% in the microsurgically treated patients. In our series, the only endovascularly treated patient had no new findings in a follow-up MRA 16 years after the SAH. Ligation of the proximal major vessel and especially ICA ligations have been reported to be associated with symptomatic ACoA de novo aneurysms due to hemodynamic changes.[42] In our series, there were two patients with previous proximal artery ligation, and one of them had a ruptured de novo ACoA aneurysm.

None of the common acknowledged risk factors for recurrent SAH had a statistically significant role in new SAH in our series; however, smoking seemed to have some impact, although it failed to reach statistical significance (p=0.077). The annual rupture rate of a previously unruptured aneurysm in a Finnish patient with another ruptured aneurysm is about 1.3%.[115]

When and whom to follow-up?

In recent years, intracranial aneurysms have been speculated to some extent be an embodiment of a systemic vascular disease and aneurysm formation to be more a continuous process than a single unfortunate incident. There has been debate over screening for new aneurysms among adult SAH patients.[255] There are risks in preventively treating unruptured aneurysms (ISUIA), and even if diagnosed, not all aneurysms are treated. Although screening is an important preventative strategy in high-risk individuals, it has been associated with considerable psychosocial effects.[322] The knowledge of having an aneurysm has been observed to have some effect on the quality of life. However, even

in these cases, the possibility to reduce the risk factors (e.g. smoking and hypertension) for aneurysm growth and rupture is valuable. Cigarette smoking after a history of a ruptured aneurysm carries an especially high risk for the development of a new aneurysm.[255]

Among pediatric patients, the risk for a new aneurysm is high, particularly considering the long life expectancy of a child. This should overcome the psychological burden of screening. Of course, eventually, patients decide themselves whether they wish to participate in follow-up.

Among SAH adult patients, debate exists about screening for asymptomatic new aneurysms.[112] However, in children, intracerebral aneurysms should be regarded as "*a potentially chronic progressive condition,*" as stated by Hetts et al.[87] Most of the angiographic follow-up studies among pediatric aneurysm patients recommend strict surveillance,[87,117] tailored depending on the chosen treatment modality.[250] In our series, the earliest symptomatic recurrent aneurysm was found at 6 years after the initial treatment, and the first de novo –aneurysms at 11 years after SAH, in concordance with reported adult series.[302,335] In children, long-term angiographic follow-up studies are scare. However, one pediatric series reported recurrent and de novo aneurysms at a very short-term interval of 5 months,[117] another at 5 years.[87] Among adult series, a short-term angiographic follow-up at 3- to 5-year intervals was recommended in patients under 50-years of age with hypertension.[295] Another study suggested follow-up imaging for female patients at 10 years after the initial aneurysm.[228] Our study indicate that all pediatric aneurysm patients should have follow-up imaging regardless of the absence of possible risk factors such as smoking, hypertension, female gender, and previously ruptured aneurysm. In young patients, for whom a life-long angiographic follow-up is recommended, MRA, as the safest method, is the preferred imaging modality.

In our study, MRA was the first-line screening method to detect new aneurysms in the long-term angiographic follow-up. CTA was performed on patients with a contraindication for MRI, main reason for this being MRI-incompatible, old aneurysm clip. DSA as an additional study was carried out when planning endovascular treatment of a de novo or recurrent aneurysm or preoperatively in complex cases. Our department has considerable experience with CTA, and CTA is currently the preferred angiographic imaging method in SAH patients.[120]

Treatment of de novo and recurrent aneurysms

Treatment of previously treated recurrent aneurysms is complex. Due to the prior treatment, the procedure-related complication rates are higher in reoperations than in the initial treatment.[89] In recent years, advanced endovascular techniques have become more frequent in the treatment of previously clipped residual and recurrent aneurysms. The choice of treatment method in these complex and demanding cases should be discussed by a multidisciplinary team of skilled neurosurgeons and neurointerventionists.[117,249]

Statistical analysis

We performed the excess mortality study by focusing on survival. Some previous studies have focused on the mortality rate and expected deaths by using standardized mortality ratio. Recent population-based studies on excess mortality among SAH patients have been carried out by two different methods: either the Ederer II method[45] or the Hakulinen method.[77] The Hakulinen method is optimal under informative censoring when the relative survival is constant across the ages. Eventhoug in our series, the range of patients' age was very narrow and the risk for informative censoring low, the Hakulinen method[77] was chosen. For comparison, we also analyzed the data using the Ederer II method, and obtained comparable results (data not shown).

7. Conclusions

Intracranial aneurysms in children are rare, constituting 1-2% of all aneurysm patients. In our series of 114 patients, the majority of the patients were boys. Most aneurysms were ruptured. Of the aneurysms, 89 % were located in the anterior circulation, the ICA bifurcation being the most frequent location. The mean size of aneurysms was 11 mm. Most patients had a good recovery; factors correlating with a favourable long-term outcome were good neurologic condition of the patient on admission, aneurysm location in the anterior circulation, complete aneurysm closure, and absence of vasospasm. In our series, the connective tissue disorders common to pediatric aneurysm patients were lacking. There was no increased family history of aneurysms in these patients compared with adult aneurysm patients.

There was a significant long-term excess mortality in pediatric patients with aneurysm even decades after successful treatment of ruptured aneurysm, being most significant in males. However, there was no increased long-term excess mortality in patients with unruptured aneurysms. The causes of death were mainly aneurysm-related, i.e. rebleedings from incompletely treated aneurysms, seizures, and de novo and recurrent aneurysms.

There was a high risk for de novo and recurrent aneurysm formation in our series, up to 41%. The cumulative risk of new SAH 40 years after the initial diagnosis was 15%. Current and previous smoking were independent risk factors for de novo and recurrent aneurysm formation, especially in patients with a previously ruptured aneurysm. Therefore, cessation of smoking is essential.

Our results emphasize the importance of angiographically verified complete occlusion of aneurysms, followed by a life-long angiographic follow-up in children with intracranial aneurysms.

7.1. Recommendations for treatment and follow-up

Ruptured and unruptured aneurysms in children should be treated by an experienced microvascular or endovascular neurosurgeon. Patients with unruptured, asymptomatic aneurysms should have a consultation with a neurosurgeon, and the aneurysm should be actively treated; in very selected cases, close observation is might be sufficient. Special attention should be paid to the complete closure of the aneurysm. Microsurgical treatment of the aneurysm is preferred to endovascular treatment.

A child diagnosed with an intracranial aneurysm should be evaluated for possible co-morbidities predisposing to intracranial aneurysms (Figure 17). A life-long angiographic follow-up at 3- to 5-year intervals, preferably with MRA, is mandatory for all of these patients.
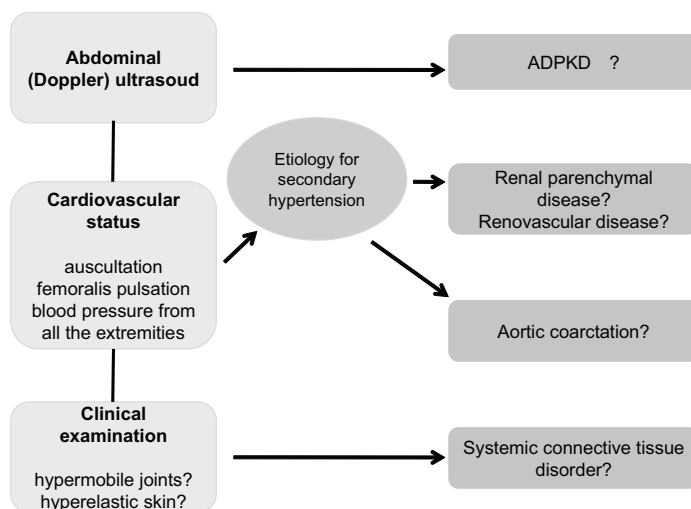
FIGURE 17.
Primary screening for systemic predisposing conditions in a child with an intracranial aneurysm. ADPKD = autosomal dominant polycystic kidney disease.

Acknowledgments

In Helsinki, November 2012

APPENDIX I

HUNT & HESS Scale[97]

Grade	Signs and symptoms after subarachnoid hemorrhage	Survival
1	Asymptomatic or minimal headache and slight neck stiffness	70%
2	Moderate to severe headache; neck stiffness, no neurologic deficit except cranial nerve palsy	60%
3	Drowsy, minimal neurological deficit	50%
4	Stuporous; moderate to severe hemiparesis, decerebrate rigidity	20%
5	Deep coma, moribund, decerebrate rigidity	10%

FISHER Scale[54]

Grade	Appearance of hemorrhage on computed tomography
1	None evident
2	Less than 1 mm thick
3	More than 1 mm thick
4	Intraventricular or parenhcymal hematoma

APPENDIX II

WRITTEN QUESTIONARY

1. Do you have some symptoms or permanent deficiencies, such as paralysis, vision problems, or memory problems, after the diagnosis and/or treatment of the aneurysm?

☐ yes ☐ no

2. If you answered yes, could you please be more specific? You may also describe your deficiencies in your own words.

Paralysis of a hand and/or leg	☐ yes ☐ no
Vision problem	☐ yes ☐ no
Visual field deficit	☐ yes ☐ no
Double vision	☐ yes ☐ no
Hearing problem	☐ yes ☐ no
Difficulty in sense of smell	☐ yes ☐ no
Facial paralysis	☐ yes ☐ no
Swallowing difficulty	☐ yes ☐ no
Memory difficulty	☐ yes ☐ no
Balance difficulty	☐ yes ☐ no
Concentration difficulty	☐ yes ☐ no
Speech production and /or comprehension difficulties	☐ yes ☐ no

3.　　Do you smoke?　　　　☐ yes ☐ no　　How long have you smoked?_____
　　　Have you previously smoked?　☐ yes ☐ no
　　　How long did you smoke before cessation?_____

4. Have you had imaging of your brain during the follow-up?

☐ yes ☐ no

　If you answered yes, please specify when and where?_____

5. Have you had a diagnosis of a new aneurysm or new cerebral hemorrhage after the initial diagnosis?　☐ yes ☐ no

　If you answered yes, please specify when and where?_____

6. Do you have a close family member (parent, sibling, offspring) who has been screened for an intracranial aneurysm?

☐ yes ☐ no

7. Do you have a close family member (parent, sibling, offspring) who has been diagnosed with an intracranial aneurysm or a cerebral hemorrhage?

☐ yes ☐ no

8. Do you have a diagnosis of a long-term illness?

Heart disease	☐ yes ☐ no
Coronary disease/infarction	☐ yes ☐ no
Hypertension	☐ yes ☐ no
Blood disease/Bleeding disorder	☐ yes ☐ no
Lung disease	☐ yes ☐ no
Kidney disease	☐ yes ☐ no
Diabetes	☐ yes ☐ no
Immune deficiency	☐ yes ☐ no
Cerebrovascular disorder	☐ yes ☐ no
Epilepsy	☐ yes ☐ no
Tumor (where)	☐ yes ☐ no
Other illness (please specify)	☐ yes ☐ no
Aortic coarctation	☐ yes ☐ no

9. Have you been diagnosed with a rare connective tissue disorder?

Marfan syndrome	☐ yes ☐ no
Osteogenesis imperfecta	☐ yes ☐ no
Ehlers-Danlos syndrome	☐ yes ☐ no
Pseudoxantoma elasticum	☐ yes ☐ no
Polycystic kidney disease	☐ yes ☐ no
Neurofibromatosis	☐ yes ☐ no
Other connective tissue disorder (please specify)	☐ yes ☐ no

10. Do you have a close family member (parent, sibling, offspring) who has been diagnosed with a rare connective tissue disorder?

☐ yes ☐ no

11. Do You have continous medication?   ☐ yes ☐ no
If yes, could you please list your medication(s).

12. How would you describe your current capability? Usual daily activities include dressing and dining. You may also describe your capability in your own words.

☐   I have no symptoms.
☐   I have no significant disability. I am able to carry out all usual activities without
         assistance, despite some symptoms (e.g. headache, vertigo).
☐   I have slight disability (e.g. slight weakness in the arm, dysphasia). I am able
         to look after my own affairs without assistance, but am unable to carry out all
         previous activities.
☐   I have moderate disability. I require some help, but am able to walk unassisted.
☐   I have moderately severe disability. I am unable to attend to my bodily needs
         without assistance and am unable to walk unassisted.
☐   I have severe disability. I require constant nursing care and attention. I am bedridden.

13. Do you have impaired functional capacity? If yes, is it due to intracranial aneurysm or to something else?

☐   My functional capacity is impaired for reasons related to intracranial aneurysm.
☐   My functional capacity is impaired for reasons other than intracranial aneurysm.
☐   My functional capacity is not impaired.

14. What is your education and profession? Did the aneurysm or its treatment have any impact on your profession or social life?

15. Comments/questions?

APPENDIX II

WRITTEN QUESTIONARY (in Finnish)

1. Onko teille jäänyt aneurysman diagnosoinnin ja mahdollisen leikkauksen jälkeen jotain pysyviä puutosoireita, kuten halvausoireita, näköongelmia tai muistiongelmia?

☐ kyllä ☐ ei

2. Jos vastasitte edelliseen kysymykseen kyllä, tarkentaisitteko? Voitte kuvata myös omin sanoin puutosoireitanne.

Käden ja/tai jalan halvausoire	☐ kyllä ☐ ei
Näön heikentyminen	☐ kyllä ☐ ei
Näkökenttäpuutos	☐ kyllä ☐ ei
Kaksoiskuvien näkeminen	☐ kyllä ☐ ei
Kuulon heikentyminen	☐ kyllä ☐ ei
Hajuaistin heikentyminen	☐ kyllä ☐ ei
Kasvohermohalvaus	☐ kyllä ☐ ei
Nielemisvaikeus	☐ kyllä ☐ ei
Muistiongelma	☐ kyllä ☐ ei
Tasapainon heikentyminen	☐ kyllä ☐ ei
Keskittymiskyvyn heikentyminen	☐ kyllä ☐ ei
Puheen tuottamisen ja/tai ymmärtämisen vaikeus	☐ kyllä ☐ ei

3. Tupakoitteko?   ☐ kyllä ☐ ei   Kuinka kauan olette tupakoinut?_____
   Oletteko aiemmin tupakoinut?   ☐ kyllä ☐ ei
   Kuinka kauan tupakoitte ennen tupakoinnin lopettamista?_____

4.Onko seuranta-aikana aivojanne kuvattu?

☐ kyllä ☐ ei

Jos vastasitte kyllä, niin kirjoittakaa missä ja milloin?_____

5. Onko teillä seuranta-aikana todettu uusia aivovaltimopullistumia tai aivoverenvuotoja?

☐ kyllä ☐ ei

Jos vastasitte kyllä, niin kirjoittakaa missä ja milloin?_____

6.Onko lähisukulaisianne (vanhemmat, sisarukset, omat lapset) kuvattu mahdollisten aivovalti-mopullistumien löytämiseksi?

☐ kyllä ☐ ei

7. Onko lähisukulaisillanne (vanhemmat, sisarukset, omat lapset) todettu aivovaltimopullis-tumia tai aivoverenvuotoja?

☐ kyllä ☐ ei

8. Onko teillä todettu jokin pitkäaikaissairaus?

Sydänvika	☐ kyllä ☐ ei
Sepelvaltimotauti/infarkti	☐ kyllä ☐ ei
Verenpainetauti	☐ kyllä ☐ ei
Verenvuoto-/verisairaus	☐ kyllä ☐ ei
Keuhkosairaus	☐ kyllä ☐ ei
Munuaissairaus	☐ kyllä ☐ ei
Sokeritauti	☐ kyllä ☐ ei
Immuunikato	☐ kyllä ☐ ei
Aivoverenkierron häiriö	☐ kyllä ☐ ei
Epilepsia	☐ kyllä ☐ ei
Kasvain (missä)	☐ kyllä ☐ ei
Muu sairaus (kuvatkaa)	☐ kyllä ☐ ei
Aortan ahtauma (koarktaatio)	☐ kyllä ☐ ei

9. Onko teillä todettu jokin harvinainen sidekudossairaus?

Marfanin oireyhtymä	☐ kyllä ☐ ei
Synnynnäinen luustonhaurastumistauti (Osteogenesis imperfecta)	☐ kyllä ☐ ei
Ehlers-Danlos oireyhtymä	☐ kyllä ☐ ei
Pseudoxantoma elasticum	☐ kyllä ☐ ei
Monirakkulainen munuaissairaus (Polycystic kidney disease)	☐ kyllä ☐ ei
Neurofibromatoosi	☐ kyllä ☐ ei
Muu sidekudossairaus (kuvatkaa)	☐ kyllä ☐ ei

10. Onko lähisukulaisillanne (vanhemmat, sisarukset, omat lapset) todettu jokin kohdassa 9 mainituista sairauksista?

☐ kyllä ☐ ei

11. Onko teillä säännöllistä lääkitystä?   ☐ kyllä ☐ ei

Jos vastasitte kyllä, voisitteko kirjoittaa listan lääkkeistänne.

12. Kuinka kuvaisitte tämänhetkistä toimintakykyänne? Päivittäistoiminnoilla tarkoitetaan mm. pukeutumista ja ruokailua. Tarvittaessa voitte kuvata toimintakykyänne omin sanoin.

☐   Olen oireeton.
☐   Minulla on oireita (esim. päänsärkyä, huimausta), mutta ei vammaa. Oireistani huoli-
         matta selviydyn päivittäisistä toiminnoistani omatoimisesti ilman apua.
☐   Olen lievästi vammautunut (esim. lievä käden halvaus, puhevaikeus). Vammastani
         huolimatta selviydyn päivittäisistä toiminnoistani omatoimisesti ilman apua.
☐   Olen kohtalaisesti vammautunut. Tarvitsen apua päivittäisissä toiminnoissa, mutta
         pystyn kävelemään ilman apua.
☐   Olen kohtalaisen vakavasti vammautunut. Tarvitsen huomattavasti apua päivittäisissä
         toiminnoissani. En pysty kävelemään ilman apua.
☐   Olen vakavasti vammautunut vuodepotilas. Tarvitsen ympärivuorokautista sairaan-
         hoitoa.

13. Johtuuko mahdollinen alentunut toimintakykynne aivovaltimoaneurysmasta, vaiko muusta sairaudesta?

☐   Toimintakykyni on alentunut aivoaneurysmasta johtuvista syistä.
☐   Toimintakykyni on alentunut muista sairauksista johtuen.
☐   Toimintakykyni ei ole alentunut.

14. Mikä on koulutuksenne ja ammattinne? Oliko aneurysmalla tai sen hoidolla vaikutusta ammatinvalintaanne tai elämäänne muuten?

15. Kommentteja/kysymyksiä?

References

1. Aeron G, Abruzzo TA and Jones BV. Clinical and imaging features of intracranial arterial aneurysms in the pediatric population. Radiographics 2012; 32:667-681.

2. Agid R, Souza MP, Reintamm G, Armstrong D, Dirks P and TerBrugge KG. The role of endovascular treatment for pediatric aneurysms. Child's Nervous System 2005; 21:1030-1036.

3. Allison JW, Davis PC, Sato Y, James CA, Haque SS, Angtuaco EJ and Glasier CM. Intracranial aneurysms in infants and children. Pediatric Radiology 1998; 28:223-229.

4. Amin-Hanjani S, Alaraj A and Charbel FT. Flow replacement bypass for aneurysms: decision-making using intraoperative blood flow measurements. Acta Neurochirurgica 2010; 152:1021-1032.

5. Arambepola PK, McEvoy SD and Bulsara KR. De novo aneurysm formation after carotid artery occlusion for cerebral aneurysms. Skull base 2010; 20:405-408.

6. Asari S, Nakamura S, Yamada O, Beck H and Sugatani H. Traumatic aneurysm of peripheral cerebral arteries. Report of two cases. Journal of Neurosurgery 1977; 46:795-803.

7. Ashwal S. *The Founders of Child Neurology*. Norman Publishing, San Fransisco, USA. 1990.

8. Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). Epidemiology of aneurysmal subarachnoid hemorrhage in Australia and New Zealand: incidence and case fatality from the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). Stroke 2000; 31:1843-1850.

9. Beltramello A, Puppini G, Bricolo A, Andreis IA, el-Dalati G, Longa L, Polidoro S, Zavarise G and Marradi P. Does the tuberous sclerosis complex include intracranial aneurysms? A case report with a review of the literature. Pediatric radiology 1999; 29:206-211.

10. Benoit BG and Wortzman G. Traumatic cerebral aneurysms. Clinical features and natural history. Journal of Neurology, Neurosurgery, and Psychiatry 1973; 36:127-138.

11. Berenstein A, Flamm ES and Kupersmith MJ. Unruptured intracranial aneurysms. The New England Journal of Medicine 1999; 340:1439-1440.

12. Beridze N and Frishman WH. Vascular Ehlers-Danlos syndrome: pathophysiology, diagnosis, and prevention and treatment of its complications. Cardiology in Review 2012; 20:4-7.

13. Bolar N, Van Laer L and Loeys BL. Marfan syndrome: from gene to therapy. Current Opinion in Pediatrics 2012; 24:498-504

14. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. Stroke 1986; 17:831-835.

15. Briganti F, Cirillo S, Caranci F, Esposito F and Maiuri F. Development of "de novo" aneurysms following endovascular procedures. Neuroradiology 2002; 44:604-609.

16. Brilstra EH, Rinkel GJ, Klijn CJ, van der Zwan A, Algra A, Lo RT and Tulleken CA. Excimer laser-assisted bypass in aneurysm treatment: short-term outcomes. Journal of Neurosurgery 2002; 97:1029-1035.

17. Brisman JL, Song JK and Newell DW. Cerebral aneurysms. The New England Journal of Medicine 2006; 355:928-939.

18. Brown H. Kenneth Till. Lancet 2008; 372:1216.

19. Brozici M, van der Zwan A and Hillen B. Anatomy and functionality of leptomeningeal anastomoses: a review. Stroke 2003; 34:2750-2762.

20. Bruneau M, Rynkowski M, Smida-Rynkowska K, Brotchi J, De Witte O and Lubicz B. Long-term follow-up survey reveals a high yield, up to 30% of patients presenting newly detected aneurysms more than 10 years after ruptured intracranial aneurysms clipping. Neurosurgical Review 2011; 34:485-496.

21. Buckingham MJ, Crone KR, Ball WS, Tomsick TA, Berger TS and Tew JM, Jr. Traumatic intracranial aneurysms in childhood: two cases and a review of the literature. Neurosurgery 1988; 22:398-408.

22. Buis DR, van Ouwerkerk WJ, Takahata H and Vandertop WP. Intracranial aneurysms in children under 1 year of age: a systematic review of the literature. Child's Nervous System 2006; 22:1395-1409.

23. Burger IM, Murphy KJ, Jordan LC, Tamargo RJ and Gailloud P. Safety of cerebral digital subtraction angiography in children: complication rate analysis in 241 consecutive diagnostic angiograms. Stroke 2006; 37:2535-2539.

24. Campbell M. Incidence of cardiac malformations at birth and later, and neonatal mortality. British Heart Journal 1973; 35:189-200.

25. Chapman AB, Rubinstein D, Hughes R, Stears JC, Earnest MP, Johnson AM, Gabow PA and Kaehny WD. Intracranial aneurysms in autosomal dominant polycystic kidney disease. The New England Journal of Medicine 1992; 327:916-920.

26. Chassaing N, Martin L, Calvas P, Le Bert M and Hovnanian A. Pseudoxanthoma elasticum: a clinical, pathophysiological and genetic update including 11 novel ABCC6 mutations. Journal of Medical Genetics 2005; 42:881-892.

27. Cheong JJ, Ghinea N and van Gelder JM. Estimating the annual rate of de novo multiple aneurysms: three statistical approaches. Neurosurgical Focus 2004; 17:E8.

28. Chmayssani M, Rebeiz JG, Rebeiz TJ, Batjer HH and Bendok BR. Relationship of growth to aneurysm rupture in asymptomatic aneurysms </= 7 mm: a systematic analysis of the literature. Neurosurgery 2011; 68:1164-1171.

29. Chowdhary A, Spence AM, Sales L, Rostomily RC, Rockhill JK and Silbergeld DL. Radiation associated tumors following therapeutic cranial radiation. Surgical Neurology International 2012; 3:48.

30. Ciceri EF, Cuccarini V, Chiapparini L, Saletti V and Valvassori L. Paediatric stroke: review of the literature and possible treatment options, including endovascular approach. Stroke Research and Treatment 2011; 2011:781612.

31. Clare CE and Barrow DL. Infectious intracranial aneurysms. Neurosurgery Clinics of North America 1992; 3:551-566.

32. Cohnen M, Wittsack HJ, Assadi S, Muskalla K, Ringelstein A, Poll LW, Saleh A and Modder U. Radiation exposure of patients in comprehensive computed tomography of the head in acute stroke. AJNR American Journal of Neuroradiology 2006; 27:1741-1745.

33. Consortium on Polycystic Kidney Disease. Polycystic kidney disease: the complete structure of the PKD1 gene and its protein. The International Polycystic Kidney Disease Consortium. Cell 1995; 81:289-298.

34. Conway JE, Hutchins GM and TamaRGO RJ. Lack of evidence for an association between neurofibromatosis type I and intracranial aneurysms: autopsy study and review of the literature. Stroke 2001; 32:2481-2485.

35. Dashti R, Hernesniemi J, Niemelä M, Rinne J, Porras M, Lehecka M, Shen H, Albayrak BS, Lehto H, Koroknay-Pál P, de Oliveira RS, Perra G, Ronkainen A, Koivisto T and Jääskeläinen JE. Microneurosurgical management of middle cerebral artery bifurcation aneurysms. Surgical Neurology 2007; 67:441-456.

36. David CA, Vishteh AG, Spetzler RF, Lemole M, Lawton MT and Partovi S. Late angiographic follow-up review of surgically treated aneurysms. Journal of Neurosurgery 1999; 91:396-401.

37. de Rooij NK, Linn FH, van der Plas JA, Algra A and Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. Journal of Neurology, Neurosurgery, and Psychiatry 2007; 78:1365-1372.

38. Derdeyn CP, Cross DT, 3rd, Moran CJ, Brown GW, Pilgram TK, Diringer MN, Grubb RL, Jr., Rich KM, Chicoine MR and Dacey RG, Jr. Postprocedure ischemic events after treatment of intracranial aneurysms with Guglielmi detachable coils. Journal of Neurosurgery 2002; 96:837-843.

39. Doyle DM and Einhorn LH. Delayed effects of whole brain radiotherapy in germ cell tumor patients with central nervous system metastases. International Journal of Radiation Oncology, Biology, Physics 2008; 70:1361-1364.

40. Drake CG, Peerles SJ and Hernesniemi JA. *Surgery of Vertebrobasilar Aneurysms*. Springer-Verlag, Wien, Austria. 1996.

41. Dubrovsky T, Curless R, Scott G, Chaneles M, Post MJ, Altman N, Petito CK, Start D and Wood C. Cerebral aneurysmal arteriopathy in childhood AIDS. Neurology 1998; 51:560-565.

42. Dyste GN and Beck DW. De novo aneurysm formation following carotid ligation: case report and review of the literature. Neurosurgery 1989; 24:88-92.

43. Eddleman C, Nikas D, Shaibani A, Khan P, Dipatri AJ, Jr. and Tomita T. HydroCoil embolization of a ruptured infectious aneurysm in a pediatric patient: case report and review of the literature. Child's Nervous System 2007; 23:707-712.

44. Ederer F, Axtell LM and Cutler SJ. The relative survival rate: a statistical methodology. National Cancer Institute Monograph 1961; 6:101-121.

45. Ederer F and Heise H: Instructions to IBM 650 programmers in processing survival computations. Methodotological notes nro 10. in: End Results Evaluation Section.Bethesda, MD: National Cancer Institute, 1959

46. Edner G and Almqvist H. The Stockholm 20-year follow-up of aneurysmal subarachnoid hemorrhage outcome. Neurosurgery 2007; 60:1017-1023.

47. Ellis MJ, Cheshier S, Sharma S, Armstrong D, Hawkins C, Bouffet E, Rutka JT and Taylor MD. Intracerebral malignant peripheral nerve sheath tumor in a child with neurofibromatosis Type 1 and middle cerebral artery aneurysm treated with endovascular coil embolization. Journal of Neurosurgery Pediatrics 2011; 8:346-352.

48. Farrell B, Godwin J, Richards S and Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. Journal of Neurology, Neurosurgery, and Psychiatry 1991; 54:1044-1054.

49. FEIGIN VL, LAWES CM, BENNETT DA AND ANDERSON CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurology 2003; 2:43-53.

50. FEIGIN VL, RINKEL GJ, LAWES CM, ALGRA A, BENNETT DA, VAN GIJN J AND ANDERSON CS. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke 2005; 36:2773-2780.

51. FINDLAY JM. *Cerebral vasospasm*. In: Winn HR (ed.); Youmans Neurological Surgery. Elsevier Saunders, Philadelphia, USA. 2011, Vol. 4.

52. FINLAY HM, WHITTAKER P AND CANHAM PB. Collagen organization in the branching region of human brain arteries. Stroke 1998; 29:1595-1601.

53. FISHER C AND ROSSMANN JS. Effect of non-newtonian behavior on hemodynamics of cerebral aneurysms. Journal of Biomechanical Engineering 2009; 131:091004.

54. FISHER CM, ROBERSON GH AND OJEMANN RG. Cerebral vasospasm with ruptured saccular aneurysm--the clinical manifestations. Neurosurgery 1977; 1:245-248.

55. FLEISCHER AS, PATTON JM AND TINDALL GT. Cerebral aneurysms of traumatic origin. Surgical Neurology 1975; 4:233-239.

56. FODSTAD H. Tranexamic acid (AMCA) in aneurysmal subarachnoid haemorrhage. Journal of Clinical Pathology Supplement 1980; 14:68-73.

57. FOGELHOLM R. Subarachnoid hemorrhage in middle-Finland: incidence, early prognosis and indications for neurosurgical treatment. Stroke 1981; 12:296-301.

58. FOGELHOLM R, HERNESNIEMI J AND VAPALAHTI M. Impact of early surgery on outcome after aneurysmal subarachnoid hemorrhage. A population-based study. Stroke 1993; 24:1649-1654.

59. FRAZEE JG, CAHAN LD AND WINTER J. Bacterial intracranial aneurysms. Journal of Neurosurgery 1980; 53:633-641.

60. FRÖSEN J, PIIPPO A, PAETAU A, KANGASNIEMI M, NIEMELÄ M, HERNESNIEMI J AND JÄÄSKELÄINEN J. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. Stroke 2004; 35:2287-2293.

61. FUJIWARA S, FUJII K AND FUKUI M. De novo aneurysm formation and aneurysm growth following therapeutic carotid occlusion for intracranial internal carotid artery (ICA) aneurysms. Acta Neurochirurgica 1993; 120:20-25.

62. GAÁL EI, SALO P, KRISTIANSSON K, REHNSTRÖM K, KETTUNEN J, SARIN AP, NIEMELÄ M, JULA A, RAITAKARI OT, LEHTIMÄKI T, ERIKSSON JG, WIDEN E, GUNEL M, KURKI M, VON UND ZU FRAUNBERG M, JÄÄSKELÄINEN JE, HERNESNIEMI J, JÄRVELIN MR, POUTA A, NEWTON-CHEH C, SALOMAA V, PALOTIE A AND PEROLA M. Intracranial aneurysm risk locus 5q23.2 is associated with elevated systolic blood pressure. PLoS genetics 2012; 8:e1002563.

63. GERMAIN DP AND HERRERA-GUZMAN Y. Vascular Ehlers-Danlos syndrome. Annales de Genetique 2004; 47:1-9.

64. GEROSA M, LICATA C, FIORE DL AND IRACI G. Intracranial aneurysms of childhood. Child's Brain 1980; 6:295-302.

65. GEWIRTZ RJ, BRODERICK RW, BAUMANN RJ AND STEVENS JL. Fusiform P1 segment artery aneurysm in a pediatric patient: technical case report. Pediatric Neurosurgery 1998; 29:218-221.

66. Glennie D, Connolly BL and Gordon C. Entrance skin dose measured with MOSFETs in children undergoing interventional radiology procedures. Pediatric Radiology 2008; 38:1180-1187.

67. Goedee HS, Depauw PR, vd Zwam B and Temmink AH. Superficial temporal artery-middle cerebral artery bypass surgery in a pediatric giant intracranial aneurysm presenting as migraine-like episodes. Child's Nervous System 2009; 25:257-261.

68. Gonzales-Portillo GA and Valdivia JM. Uncommon presentation of pediatric ruptured intracranial aneurysm after radiotherapy for retinoblastoma. Case report. Surgical Neurology 2006; 65:391-396.

69. Gralla J, Brekenfeld C, Schmidli J, Caversaccio M, Do DD and Schroth G. Internal carotid artery aneurysm with life-threatening hemorrhages in a pediatric patient: endovascular treatment options. Journal of Endovascular Therapy 2004; 11:734-738.

70. Greenwood M: The error of sampling of the survivorship Table, vol 33 of report on the public health and medical subjects. His majesty's Stationery Office, London: 1926.

71. Grosso S, Mostardini R, Venturi C, Bracco S, Casasco A, Berardi R and Balestri P. Recurrent torticollis caused by dissecting vertebral artery aneurysm in a pediatric patient: results of endovascular treatment by use of coil embolization: case report. Neurosurgery 2002; 50:204-208.

72. Grzyska U, Freitag J and Zeumer H. Selective cerebral intraarterial DSA. Complication rate and control of risk factors. Neuroradiology 1990; 32:296-299.

73. Guglielmi G, Vinuela F, Dion J and Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. Journal of Neurosurgery 1991; 75:8-14.

74. Guglielmi G, Vinuela F, Sepetka I and Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results. Journal of Neurosurgery 1991; 75:1-7.

75. Hackett ML and Anderson CS. Health outcomes 1 year after subarachnoid hemorrhage: An international population-based study. The Australian Cooperative Research on Subarachnoid Hemorrhage Study Group. Neurology 2000; 55:658-662.

76. Haddad FS, Haddad GF and Taha J. Traumatic intracranial aneurysms caused by missiles: their presentation and management. Neurosurgery 1991; 28:1-7.

77. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. Biometrics 1982; 38:933-942.

78. Hakulinen T, Seppä K and Lambert PC. Choosing the relative survival method for cancer survival estimation. European Journal of Cancer 2011; 47:2202-2210.

79. Heiskanen O. [Spina bifida]. Duodecim 1967; 83:862-868.

80. Heiskanen O. Ruptured intracranial arterial aneurysms of children and adolescents. Surgical and total management results. Child's Nervous System 1989; 5:66-70.

81. Heiskanen O and Vilkki J. Intracranial arterial aneurysms in children and adolescents. Acta Neurochirurgica 1981; 59:55-63.

82. Herman JM, Rekate HL and Spetzler RF. Pediatric intracranial aneurysms: simple and complex cases. Pediatric Neurosurgery 1991; 17:66-73.

83. Hernesniemi J, Ishii K, Niemelä M, Smrcka M, Kivipelto L, Fujiki M and Shen H. Lateral supraorbital approach as an alternative to the classical pterional approach. Acta Neurochirurgica Suppl 2005; 94:17-21.

84. Hernesniemi J, Tapaninaho A, Vapalahti M, Niskanen M, Kari A and Luukkonen M. Saccular aneurysms of the distal anterior cerebral artery and its branches. Neurosurgery 1992; 31:994-999.

85. Hernesniemi J, Vapalahti M, Niskanen M, Tapaninaho A, Kari A, Luukkonen M, Puranen M, Saari T and Rajpar M. One-year outcome in early aneurysm surgery: a 14 years experience. Acta Neurochirurgica 1993; 122:1-10.

86. Hetts SW, English JD, Dowd CF, Higashida RT, Scanlon JT and Halbach VV. Pediatric Intracranial Aneurysms: New and Enlarging Aneurysms after Index Aneurysm Treatment or Observation. AJNR American Journal of Neuroradiology 2011; 32:2017-2022.

87. Hetts SW, Narvid J, Sanai N, Lawton MT, Gupta N, Fullerton HJ, Dowd CF, Higashida RT and Halbach VV. Intracranial aneurysms in childhood: 27-year single-institution experience. AJNR American Journal of Neuroradiology 2009; 30:1315-1324.

88. Hillbom M and Kaste M. Does alcohol intoxication precipitate aneurysmal subarachnoid haemorrhage? Journal of Neurology, Neurosurgery, and Psychiatry 1981; 44:523-526.

89. Hoh BL, Carter BS, Putman CM and Ogilvy CS. Important factors for a combined neurovascular team to consider in selecting a treatment modality for patients with previously clipped residual and recurrent intracranial aneurysms. Neurosurgery 2003; 52:732-738; discussion 738-739.

90. Hop JW, Rinkel GJ, Algra A and van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke 1997; 28:660-664.

91. Horowitz MB, Kopitnik TA, Landreneau F, Ramnani DM, Rushing EJ, George E, Purdy PP and Samson DS. Multidisciplinary approach to traumatic intracranial aneurysms secondary to shotgun and handgun wounds. Surgical Neurology 1999; 51:31-41.

92. Huang J, McGirt MJ, Gailloud P and Tamargo RJ. Intracranial aneurysms in the pediatric population: case series and literature review. Surgical Neurology 2005; 63:424-432; discussion 432-423.

93. Huang J and van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis. Neurosurgery 2002; 51:1101-1105; discussion 1105-1107.

94. Humphreys RP. The modernization of pediatric neurosurgery. The Donald D. Matson Lecture 2003. Child's Nervous System 2004; 20:18-22.

95. Humpreys R: *The history of pediatric neurosurgery*. In: Albright AL, Pollack IF and Adelson PD, (eds): Principles and Practice of Pediatric Neurosurgery. Thieme Medical Publishers, New York, USA. 2008.

96. Hung PC, Wang HS, Chou ML and Wong AM. Tuberous sclerosis complex with multiple intracranial aneurysms in an infant. Pediatric Neurology 2008; 39:365-367.

97. Hunt WE and Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. Journal of Neurosurgery 1968; 28:14-20.

98. Huston J, 3rd, Torres VE, Sulivan PP, Offord KP and Wiebers DO. Value of magnetic resonance angiography for the detection of intracranial aneurysms in autosomal dominant polycystic kidney disease. Journal of the American Society of Nephrology 1993; 3:1871-1877.

99. Huttunen T, Riihinen A, Pukkala E, von und zu Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Hernesniemi J, Sankila R and Jääskeläinen JE. Increased relative risk of lung cancer in 2,904 patients with saccular intracranial aneurysm disease in eastern Finland. Neuroepidemiology 2012; 38:93-99.

100. Huttunen T, von und zu Fraunberg M, Frösen J, Lehecka M, Tromp G, Helin K, Koivisto T, Rinne J, Ronkainen A, Hernesniemi J and Jääskeläinen JE. Saccular intracranial aneurysm disease: distribution of site, size, and age suggests different etiologies for aneurysm formation and rupture in 316 familial and 1454 sporadic eastern Finnish patients. Neurosurgery 2010; 66:631-638; discussion 638.

101. Huttunen T, von und Zu Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Sankila R, Seppä K and Jääskeläinen JE. Long-term excess mortality of 244 familial and 1502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage compared with a matched Eastern Finnish catchment population. Neurosurgery 2011; 68:20-27.

102. Ibrahimi DM, Tamargo RJ and Ahn ES. Moyamoya disease in children. Child's Nervous System 2010; 26:1297-1308.

103. Inagawa T. Risk factors for the formation and rupture of intracranial saccular aneurysms in Shimane, Japan. World Neurosurgery 2010; 73:155-164.

104. International Study of Unruptured Intracranial Aneurysms Investigator (ISUIA). Unruptured intracranial aneurysms--risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. The New England Journal of Medicine 1998; 339:1725-1733.

105. Iob I, Scanarini M, Salar G and Ori C. Traumatic cerebral aneurysm in pediatric age. Case report. Journal of Neurosurgical Sciences 1983; 27:187-190.

106. Ishibashi T, Murayama Y, Urashima M, Saguchi T, Ebara M, Arakawa H, Irie K, Takao H and Abe T. Unruptured intracranial aneurysms: incidence of rupture and risk factors. Stroke 2009; 40:313-316.

107. Jane JA, Winn HR and Richardson AE. The natural history of intracranial aneurysms: rebleeding rates during the acute and long term period and implication for surgical management. Clinical Neurosurgery 1977; 24:176-184.

108. Jennett B and Bond M. Assessment of outcome after severe brain damage. Lancet 1975; 1:480-484.

109. Jordan LC. Assessment and treatment of stroke in children. Current treatment options in neurology 2008; 10:399-409.

110. Jordan LC, Johnston SC, Wu YW, Sidney S and Fullerton HJ. The importance of cerebral aneurysms in childhood hemorrhagic stroke: a population-based study. Stroke 2009; 40:400-405.

111. Jurkiewicz E and Jozwiak S. Giant intracranial aneurysm in a 9-year-old boy with tuberous sclerosis. Pediatric Radiology 2006; 36:463.

112. Juvela S. Risk of subarachnoid hemorrhage from a de novo aneurysm. Stroke 2001; 32:1933-1934.

113. Juvela S, Porras M and Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. Journal of Neurosurgery 1993; 79:174-182.

114. Juvela S, Porras M and Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. Journal of Neurosurgery 2000; 93:379-387.

115. Juvela S, Porras M and Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. Journal of Neurosurgery 2008; 108:1052-1060.

116. Juvela S, Poussa K and Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. Stroke 2001; 32:485-491.

117. Kakarla UK, Beres EJ, Ponce FA, Chang SW, Deshmukh VR, Bambakidis NC, Zabramski JM and Spetzler RF. Microsurgical Treatment of Pediatric Intracranial Aneurysms: Long-term Angiographic and Clinical Outcomes. Neurosurgery 2010; 67:237-250.

118. Kalbfleisch JD and Prentice RL. *The Statistical Analysis of the Failure Time Data*. John Wiley and Sons, New York, USA. 2002.

119. Kale SP, Edgell RC, Alshekhlee A, Haghighi AB, Sweeny J, Felton J, Kitchener J, Vora N, Bieneman BK, Cruz-Flores S and Abdulrauf S. Age-Associated Vasospasm in Aneurysmal Subarachnoid Hemorrhage. Journal of Stroke and Cerebrovascular Diseases 2011 [epub].

120. Kangasniemi M, Mäkelä T, Koskinen S, Porras M, Poussa K and Hernesniemi J. Detection of intracranial aneurysms with two-dimensional and three-dimensional multislice helical computed tomographic angiography. Neurosurgery 2004; 54:336-340.

121. Kannoth S and Thomas SV. Intracranial microbial aneurysm (infectious aneurysm): current options for diagnosis and management. Neurocritical Care 2009; 11:120-129.

122. Karamanakos PN, von Und Zu Fraunberg M, Bendel S, Huttunen T, Kurki M, Hernesniemi J, Ronkainen A, Rinne J, Jääskeläinen JE and Koivisto T. Risk Factors for Three Phases of 12-Month Mortality in 1657 Patients from a Defined Population After Acute Aneurysmal Subarachnoid Hemorrhage. World Neurosurgery 2011 [epub].

123. Kassell NF and Torner JC. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. Neurosurgery 1983; 13:479-481.

124. Kassell NF, Torner JC, Haley EC, Jr., Jane JA, Adams HP and Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. Journal of Neurosurgery 1990; 73:18-36.

125. Kato T, Hattori H, Yorifuji T, Tashiro Y and Nakahata T. Intracranial aneurysms in Ehlers-Danlos syndrome type IV in early childhood. Pediatric neurology 2001; 25:336-339.

126. Katritsis D, Kaiktsis L, Chaniotis A, Pantos J, Efstathopoulos EP and Marmarelis V. Wall shear stress: theoretical considerations and methods of measurement. Progress in Cardiovascular Diseases 2007; 49:307-329.

127. Kauhtio J and Törmä T. Subtotal hemisphrectomy for intractable convulsive seizures. Annales paediatriae Fenniae 1961; 7:67-78.

128. Kieck CF and de Villiers JC. Vascular lesions due to transcranial stab wounds. Journal of Neurosurgery 1984; 60:42-46.

129. Kimura H, Hosoda K, Hara Y and Kohmura E. A very unusual case of fibromuscular dysplasia with multiple aneurysms of the vertebral artery and posterior inferior cerebellar artery. Journal of Neurosurgery 2008; 109:1108-1112.

130. King JT, Jr. Epidemiology of aneurysmal subarachnoid hemorrhage. Neuroimaging clinics of North America 1997; 7:659-668.

131. Knol DS, van Gijn J, Kruitwagen CL and Rinkel GJ. Size of third and fourth ventricle in obstructive and communicating acute hydrocephalus after aneurysmal subarachnoid hemorrhage. Journal of Neurology 2011; 258:44-49.

132. Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J and Vapalahti M. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. Stroke 2000; 31:2369-2377.

133. Korja M, Silventoinen K, McCarron P, Zdravkovic S, Skytthe A, Haapanen A, de Faire U, Pedersen NL, Christensen K, Koskenvuo M and Kaprio J. Genetic epidemiology of spontaneous subarachnoid hemorrhage: Nordic Twin Study. Stroke 2010; 41:2458-2462.

134. Krings T, Geibprasert S and terBrugge KG. Pathomechanisms and treatment of pediatric aneurysms. Child's Nervous System 2010; 26:1309-1318.

135. Krishna H, Wani AA, Behari S, Banerji D, Chhabra DK and Jain VK. Intracranial aneurysms in patients 18 years of age or under, are they different from aneurysms in adult population? Acta Neurochirurgica 2005; 147:469-476.

136. Kulcsar Z, Ugron A, Marosfoi M, Berentei Z, Paal G and Szikora I. Hemodynamics of cerebral aneurysm initiation: the role of wall shear stress and spatial wall shear stress gradient. AJNR American Journal of Neuroradiology 2011; 32:587-594.

137. Kumar M and Kitchen ND. Infective and traumatic aneurysms. Neurosurgery Clinics of North America 1998; 9:577-586.

138. Kung DK, Abel TJ, Madhavan KH, Dalyai RT, Dlouhy BJ, Liu W, Jabbour PM and Hasan DM. Treatment of endovascular coil and stent migration using the merci retriever: report of three cases. Case reports in Medicine 2012; 2012:242101.

139. Kuo I, Long T, Nguyen N, Chaudry B, Karp M and Sanossian N. Ruptured intracranial mycotic aneurysm in infective endocarditis: a natural history. Case Reports in Medicine 2010 [epub].

140. Kure K, Park YD, Kim TS, Lyman WD, Lantos G, Lee S, Cho S, Belman AL, Weidenheim KM and Dickson DW. Immunohistochemical localization of an HIV epitope in cerebral aneurysmal arteriopathy in pediatric acquired immunodeficiency syndrome (AIDS). Pediatric pathology / affiliated with the International Paediatric Pathology Association 1989; 9:655-667.

141. Kwon JH, Sung SK, Song YJ, Choi HJ, Huh JT and Kim HD. Predisposing factors related to shunt-dependent chronic hydrocephalus after aneurysmal subarachnoid hemorrhage. Journal of Korean Neurosurgical Society 2008; 43:177-181.

142. Lai HP, Cheng KM, Yu SC, Au Yeung KM, Cheung YL, Chan CM, Poon WS and Lui WM. Size, location, and multiplicity of ruptured intracranial aneurysms in the Hong Kong Chinese population with subarachnoid haemorrhage. Hong Kong Medical Journal 2009; 15:262-266.

143. Laitinen L. *Craniosynostosis; premature fusion of the cranial sutures: an experimental, clinical and histological investigation with particular reference to the pathogenesis and etiology of the disease.* Annales Paediatriae Fenniae, Supplementum, Helsinki, Finland. 1956.

144. Laitinen L. [Medical defects in the cerebral arteries of newborn infants]. Nordisk Medicin 1961; 65:137-139.

145. Laitinen L. [Arterial Aneurysm with Subarachnoid Hemorrhage in Children]. Nordisk Medicin 1964; 71:329-333.

146. Laitinen L and Miettinen P. Unilateral coloboma nervi optici combined with a homolateral block of aquaeductus monro; a case report. Annales Paediatriae Fenniae 1954; 1:133-136.

147. Laitinen L, Miettinen P and Sulamaa M. Ophthalmological observations in craniosynostosis. Acta Ophthalmologica 1956; 34:121-132.

148. Laitinen L and Sulamaa M. Craniosynostosis; symptoms and results of treatment. Annales Paediatriae Fenniae 1954; 1:283-296.

149. Laitinen L and Sulamaa M. Some results of operative treatment for craniosynostosis. Acta Paediatrica Supplementum 1955; 44:132-133.

150. Laitinen L and Sulamaa M. Craniosynostosis; symptoms, treatment and results of treatment. II. Annales Paediatriae Fenniae 1956; 2:1-8.

151. Laitinen L and Troupp H. Reliability of partial ligation in the treatment of intracranial arterial aneurysm. Acta Neurologica Scandinavica 1961; 37:62-66.

152. Laitinen LV. Short-term results of stereotaxic treatment for infantile cerebral palsy. Confinia Neurologica 1965; 26:258-263.

153. Laitinen LV. My 50 years of interest in stereotactic and functional neurosurgery. Stereotactic and Functional Neurosurgery 2001; 77:7-10.

154. Laitinen LV. Personal memories of the history of stereotactic neurosurgery. Neurosurgery 2004; 55:1420-1429.

155. Lam CH, Montes J, Farmer JP, O'Gorman AM and Meagher-Villemure K. Traumatic aneurysm from shaken baby syndrome: case report. Neurosurgery 1996; 39:1252-1255.

156. Langer DJ and Vajkoczy P. ELANA: Excimer Laser-Assisted Nonocclusive Anastomosis for extracranial-to-intracranial and intracranial-to-intracranial bypass: a review. Skull base 2005; 15:191-205.

157. Lansen TA, Kasoff SS and Arguelles JH. Giant pediatric aneurysm treated with ligation of the middle cerebral artery with the Drake tourniquet and extracranial-intracranial bypass. Neurosurgery 1989; 25:81-85.

158. LaRovere KL, Brett MS, Tasker RC, Strauss KJ and Burns JP. Head computed tomography scanning during pediatric neurocritical care: diagnostic yield and the utility of portable studies. Neurocritical Care 2012; 16:251-257.

159. Lasjaunias P, Wuppalapati S, Alvarez H, Rodesch G and Ozanne A. Intracranial aneurysms in children aged under 15 years: review of 59 consecutive children with 75 aneurysms. Child's Nervous System 2005; 21:437-450.

160. Laughlin S, Terbrugge KG, Willinsky RA, Armstrong DC, Montanera WJ and Humphreys RP. Endovascular management of paediatric intracranial aneurysms. Interventional Neuroradiology1997; 3:205-214.

161. Lawton MT and Spetzler RF. Surgical management of giant intracranial aneurysms: experience with 171 patients. Clinical Neurosurgery 1995; 42:245-266.

162. Lee JY, Kwon BJ, Kang HS and Wang KC. Subarachnoid hemorrhage from a dissecting aneurysm of the posterior cerebral artery in a child : rebleeding after stent-assisted coiling followed by stent-within-stent technique. Journal of Korean Neurosurgical Society 2011; 49:134-138.

163. Leffers AM and Wagner A. Neurologic complications of cerebral angiography. A retrospective study of complication rate and patient risk factors. Acta Radiologica 2000; 41:204-210.

164. Lehecka M. *Distal anterior cerebral artery aneurysms*. University of Helsinki, Helsinki, Finland. 2009.

165. Lehecka M, Laakso A and Hernesniemi J. Helsinki Microneurosurgery Basics and Tricks. Auesculap AG, Helsinki, Finland. 2011.

166. Lehecka M, Lehto H, Niemelä M, Juvela S, Dashti R, Koivisto T, Ronkainen A, Rinne J, Jääskeläinen JE and Hernesniemi JA. Distal anterior cerebral artery aneurysms: treatment and outcome analysis of 501 patients. Neurosurgery 2008; 62:590-601.

167. Lehecka M, Niemelä M, Seppänen J, Lehto H, Koivisto T, Ronkainen A, Rinne J, Sankila R, Jääskeläinen J and Hernesniemi J. No long-term excess mortality in 280 patients with ruptured distal anterior cerebral artery aneurysms. Neurosurgery 2007; 60:235-240.

168. Lehecka M, Porras M, Dashti R, Niemelä M and Hernesniemi JA. Anatomic features of distal anterior cerebral artery aneurysms: a detailed angiographic analysis of 101 patients. Neurosurgery 2008; 63:219-228.

169. Lehto H, Dashti R, Karatas A, Niemelä M and Hernesniemi JA. Third ventriculostomy through the fenestrated lamina terminalis during microneurosurgical clipping of intracranial aneurysms: an alternative to conventional ventriculostomy. Neurosurgery 2009; 64:430-434.

170. Levine NB, Tanaka T, Jones BV and Crone KR. Minimally invasive management of a traumatic artery aneurysm resulting from shaken baby syndrome. Pediatric neurosurgery 2004; 40:128-131.

171. Liang J, Bao Y, Zhang H, Wrede KH, Zhi X, Li M and Ling F. The clinical features and treatment of pediatric intracranial aneurysm. Child's Nervous System 2009; 25:317-324.

172. Liebeskind DS. Collateral circulation. Stroke 2003; 34:2279-2284.

173. Lindinger A, Schwedler G and Hense HW. Prevalence of congenital heart defects in newborns in Germany: Results of the first registration year of the PAN Study (July 2006 to June 2007). Klinische Padiatrie 2010; 222:321-326.

174. Lindvall P, Runnerstam M, Birgander R and Koskinen LO. The Fisher grading correlated to outcome in patients with subarachnoid haemorrhage. British Journal of Neurosurgery 2009; 23:188-192.

175. Liu JK and Couldwell WT. Intra-arterial papaverine infusions for the treatment of cerebral vasospasm induced by aneurysmal subarachnoid hemorrhage. Neurocritical Care 2005; 2:124-132.

176. Ljunggren B, Sonesson B, Saveland H and Brandt L. Cognitive impairment and adjustment in patients without neurological deficits after aneurysmal SAH and early operation. Journal of Neurosurgery 1985; 62:673-679.

177. Lord AS, Fernandez L, Schmidt JM, Mayer SA, Claassen J, Lee K, Connolly ES and Badjatia N. Effect of rebleeding on the course and incidence of vasospasm after subarachnoid hemorrhage. Neurology 2012; 78:31-37.

178. Louhimo I. [Lastenkirurgia Suomessa]. Duodecim 1992; 108:1511.

179. Lu J, Ji N, Yang Z and Zhao X. Prognosis and treatment of acute hydrocephalus following aneurysmal subarachnoid haemorrhage. Journal of Clinical Neuroscience 2012; 19:669-672.

180. Lv X, Jiang C, Li Y, Yang X and Wu Z. Endovascular treatment for pediatric intracranial aneurysms. Neuroradiology 2009; 51:749-754.

181. Lv X, Wu Z, Li Y, Jiang C, Yang X and Zhang J. Cerebral arteriovenous malformations associated with flow-related and circle of Willis aneurysms. World Neurosurgery 2011; 76:455-458.

182. Mahadevan A, Tagore R, Siddappa NB, Santosh V, Yasha TC, Ranga U, Chandramouli BA and Shankar SK. Giant serpentine aneurysm of vertebrobasilar artery mimicking dolichoectasia--an unusual complication of pediatric AIDS. Report of a case with review of the literature. Clinical Neuropathology 2008; 27:37-52.

183. Mahindu A, Koivisto T, Ronkainen A, Rinne J, Assaad N and Morgan MK. Similarities and differences in aneurysmal subarachnoid haemorrhage between eastern Finland and northern Sydney. Journal of Clinical Neuroscience 2008; 15:617-621.

184. Majamaa K. [Connective tissue and the origin of intracranial arterial aneurysms]. Duodecim 1997; 113:1757-1762.

185. Malecha MJ and Rubin R. Aneurysms of the carotid arteries associated with von Recklinghausen's neurofibromatosis. Pathology, Research and Practice 1992; 188:145-147.

186. Mallick AA and O'Callaghan FJ. Risk factors and treatment outcomes of childhood stroke. Expert Review of Neurotherapeutics 2010; 10:1331-1346.

187. Manninen AL, Isokangas JM, Karttunen A, Siniluoto T and Nieminen MT. A Comparison of Radiation Exposure between Diagnostic CTA and DSA Examinations of Cerebral and Cervicocerebral Vessels. AJNR American Journal of Neuroradiology 2012 [epub].

188. Manz HJ, Vester J and Lavenstein B. Dissecting aneurysm of cerebral arteries in childhood and adolescence. Case report and literature review of 20 cases. Virchows Archiv. A, Pathological Anatomy and Histopathology 1979; 384:325-335.

189. Matouk CC, Hanbidge A, Mandell DM, Terbrugge KG and Agid R. Osteogenesis imperfecta, multiple intra-abdominal arterial dissections and a ruptured dissecting-type intracranial aneurysm. Interventional Neuroradiology 2011; 17:371-375.

190. Maurice-Williams RS. Ruptured intracranial aneurysms: has the incidence of early rebleeding been over-estimated? Journal of Neurology, Neurosurgery, and Psychiatry 1982; 45:774-779.

191. Mayne R. Collagenous proteins of blood vessels. Arteriosclerosis 1986; 6:585-593.

192. McVerry F, Liebeskind DS and Muir KW. Systematic review of methods for assessing leptomeningeal collateral flow. AJNR American Journal of Neuroradiology 2012; 33:576-582.

193. Meyer FB, Sundt TM, Jr., Fode NC, Morgan MK, Forbes GS and Mellinger JF. Cerebral aneurysms in childhood and adolescence. Journal of Neurosurgery 1989; 70:420-425.

194. Miley JT, Rodriguez GJ and Qureshi AI. Traumatic Intracranial Aneurysm Formation following Closed Head Injury. Journal of Vascular and Interventional neurology 2008; 1:79-82.

195. Mitchell SC, Korones SB and Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. Circulation 1971; 43:323-332.

196. Mocco J, Ransom ER, Komotar RJ, Schmidt JM, Sciacca RR, Mayer SA and Connolly ES, Jr. Preoperative prediction of long-term outcome in poor-grade aneurysmal subarachnoid hemorrhage. Neurosurgery 2006; 59:529-538.

197. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J and Holman R. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002; 360:1267-1274.

198. Murayama Y, Nien YL, Duckwiler G, Gobin YP, Jahan R, Frazee J, Martin N and Vinuela F. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. Journal of Neurosurgery 2003; 98:959-966.

199. Newell DW, Elliott JP, Eskridge JM and Winn HR. Endovascular therapy for aneurysmal vasospasm. Critical Care Clinics 1999; 15:685-699.

200. Nishio A, Sakaguchi M, Murata K, Egashira M, Yamada T, Izuo M and Nakanishi N. Anterior communicating artery aneurysm in early childhood. Report of a case. Surgical Neurology 1991; 35:224-229.

201. Nomura S, Yamashita K, Kato S, Fujii Y, Uchida T, Urakawa M, Ito H and Takahashi M. Childhood subarachnoid hemorrhage associated with fibromuscular dysplasia. Child's Nervous System 2001; 17:419-422.

202. Nopajaroonsri C and Lurie AA. Venous aneurysm, arterial dysplasia, and near-fatal hemorrhages in neurofibromatosis type 1. Human Pathology 1996; 27:982-985.

203. O'Shaughnessy BA, Eddleman C, Bendok BR, Parkinson RJ, Awad IA and Batjer HH. Ruptured superior cerebellar artery aneurysm in a child with bilateral fibromuscular hyperplasia of the renal arteries: case report and review of the literature. Journal of Neurosurgery 2005; 102:338-341.

204. Oderich GS, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, Kalra M, Sullivan T and Gloviczki P. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. Journal of Vascular Surgery 2005; 42:98-106.

205. Olafsson E, Hauser WA and Gudmundsson G. A population-based study of prognosis of ruptured cerebral aneurysm: mortality and recurrence of subarachnoid hemorrhage. Neurology 1997; 48:1191-1195.

206. Ostbye T, Levy AR and Mayo NE. Hospitalization and case-fatality rates for subarachnoid hemorrhage in Canada from 1982 through 1991. The Canadian Collaborative Study Group of Stroke Hospitalizations. Stroke 1997; 28:793-798.

207. Ostergaard JR and Voldby B. Intracranial arterial aneurysms in children and adolescents. Journal of Neurosurgery 1983; 58:832-837.

208. Padua LM, Garcia LC, Rubira CJ and de Oliveira Carvalho PE. Stent placement versus surgery for coarctation of the thoracic aorta. Cochrane Database of Systematic reviews 2012; 5:CD008204.

209. Page LK. History of pediatric neurosurgery in the United States and Canada. Child's Nervous System 1991; 7:53-55.

210. Paiva WS, de Andrade AF, Amorim RL, Figueiredo EG and Teixeira MJ. Traumatic pseudoaneurysm of the middle meningeal artery causing an intracerebral hemorrhage. Case Reports in Medicine 2010; 2010:219572.

211. Pakarinen S. Incidence, aetiology, and prognosis of primary subarachnoid haemorrhage. A study based on 589 cases diagnosed in a defined urban population during a defined period. Acta Neurologica Scandinavica 1967; 43:Suppl 29:21-28.

212. Papaioannou TG and Stefanadis C. Vascular wall shear stress: basic principles and methods. Hellenic Journal of Cardiology 2005; 46:9-15.

213. Park DH, Kang SH, Lim DJ, Kwon TH, Park JY, Chung YG and Lee HK. Multiple intracranial aneurysms with intraventricular hemorrhage in a child with unilateral fibromuscular dysplasia of the renal artery. Pediatric Neurosurgery 2008; 44:486-489.

214. Parkinson D and West M. Traumatic intracranial aneurysms. Journal of Neurosurgery 1980; 52:11-20.

215. Pasqualin A, Mazza C, Cavazzani P, Scienza R and DaPian R. Intracranial aneurysms and subarachnoid hemorrhage in children and adolescents. Child's Nervous System 1986; 2:185-190.

216. Patel AN and Richardson AE. Ruptured intracranial aneurysms in the first two decades of life. A study of 58 patients. Journal of Neurosurgery 1971; 35:571-576.

217. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L and Berrington de Gonzalez A. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 2012; 380:499-505.

218. Petruzzellis M, De Blasi R, Lucivero V, Sancilio M, Prontera M, Tinelli A, Mezzapesa DM and Federico F. Cerebral aneurysms in a patient with osteogenesis imperfecta and exon 28 polymorphism of COL1A2. AJNR American Journal of Neuroradiology 2007; 28:397-398.

219. Piatt JH, Jr. and Clunie DA. Intracranial arterial aneurysm due to birth trauma. Case report. Journal of Neurosurgery 1992; 77:799-803.

220. Plomp AS, Hu X, de Jong PT and Bergen AA. Does autosomal dominant pseudoxanthoma elasticum exist? American Journal of Medical Genetics 2004; 126A:403-412.

221. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, Kasuya H, Wellman G, Keller E, Zauner A, Dorsch N, Clark J, Ono S, Kiris T, Leroux P and Zhang JH. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurological Research 2009; 31:151-158.

222. Pobereskin LH. Incidence and outcome of subarachnoid haemorrhage: a retrospective population based study. Journal of Neurology, Neurosurgery, and Psychiatry 2001; 70:340-343.

223. Prochazka V, Chmelova J, Cizek V, Skoloudik D and Hrbac T. Giant serpentine internal carotid artery aneurysm: endovascular parent artery occlusion. A pediatric case report. Interventional Neuroradiology 2007; 13:85-94.

224. Prockop DJ and Kivirikko KI. Collagens: molecular biology, diseases, and potentials for therapy. Annual Review of Biochemistry 1995; 64:403-434.

225. Proust F, Toussaint P, Garnieri J, Hannequin D, Legars D, Houtteville JP and Freger P. Pediatric cerebral aneurysms. Journal of Neurosurgery 2001; 94:733-739.

226. Pyeritz RE. Marfan syndrome: current and future clinical and genetic management of cardiovascular manifestations. Seminars in Thoracic and Cardiovascular Surgery 1993; 5:11-16.

227. Qureshi AI, Sung GY, Razumovsky AY, Lane K, Straw RN and Ulatowski JA. Early identification of patients at risk for symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. Critical Care Medicine 2000; 28:984-990.

228. Rahmah NN, Horiuchi T, Kusano Y, Sasaki T and Hongo K. De novo aneurysm: case reports and literature review. Neurosurgery 2011; 69:E761-766.

229. Raybaud C. Normal and abnormal embryology and development of the intracranial vascular system. Neurosurgery Clinics of North America 2010; 21:399-426.

230. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, Lamoureux J, Chagnon M and Roy D. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. Stroke 2003; 34:1398-1403.

231. Reig AS, Simon S and Mericle RA. Embolization of a giant pediatric, posttraumatic, skull base internal carotid artery aneurysm with a liquid embolic agent. Journal of Neurosurgery Pediatrics 2009; 4:449-452.

232. Rinkel GJ. Natural history, epidemiology and screening of unruptured intracranial aneurysms. Journal of Neuroradiology 2008; 35:99-103.

233. Rinkel GJ, Djibuti M, Algra A and van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998; 29:251-256.

234. Rinne J, Hernesniemi J, Niskanen M and Vapalahti M. Management outcome for multiple intracranial aneurysms. Neurosurgery 1995; 36:31-38.

235. Rinne J, Hernesniemi J, Niskanen M and Vapalahti M. Analysis of 561 patients with 690 middle cerebral artery aneurysms: anatomic and clinical features as correlated to management outcome. Neurosurgery 1996; 38:2-11.

236. Rinne J, Hernesniemi J, Puranen M and Saari T. Multiple intracranial aneurysms in a defined population: prospective angiographic and clinical study. Neurosurgery 1994; 35:803-808.

237. Rinne JK and Hernesniemi JA. De novo aneurysms: special multiple intracranial aneurysms. Neurosurgery 1993; 33:981-985.

238. Robinson RO. What, if any, is the appropriate neurological work-up for a child with autosomal dominant polycystic kidney disease and a family history of intra-cranial aneurysm? Pediatric Nephrology 1995; 9:158.

239. Romani R, Lehto H, Laakso A, Horcajadas A, Kivisaari R, Fraunberg M, Niemelä M, Rinne J and Hernesniemi J. Microsurgical technique for previously coiled aneurysms. Journal of neurosurgical sciences 2011; 55:139-150.

240. Ronkainen A, Hernesniemi J, Puranen M, Niemitukia L, Vanninen R, Ryynänen M, Kuivaniemi H and Tromp G. Familial intracranial aneurysms. Lancet 1997; 349:380-384.

241. Ronkainen A, Miettinen H, Karkola K, Papinaho S, Vanninen R, Puranen M and Hernesniemi J. Risk of harboring an unruptured intracranial aneurysm. Stroke 1998; 29:359-362.

242. Ronkainen A, Niskanen M, Rinne J, Koivisto T, Hernesniemi J and Vapalahti M. Evidence for excess long-term mortality after treated subarachnoid hemorrhage. Stroke 2001; 32:2850-2853.

243. Rosengart AJ, Schultheiss KE, Tolentino J and Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. Stroke 2007; 38:2315-2321.

244. Rosser TL, Vezina G and Packer RJ. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology 2005; 64:553-555.

245. Ruggieri PM, Poulos N, Masaryk TJ, Ross JS, Obuchowski NA, Awad IA, Braun WE, Nally J, Lewin JS and Modic MT. Occult intracranial aneurysms in polycystic kidney disease: screening with MR angiography. Radiology 1994; 191:33-39.

246. Ryttlefors M, Enblad P, Ronne-Engstrom E, Persson L, Ilodigwe D and Macdonald RL. Patient age and vasospasm after subarachnoid hemorrhage. Neurosurgery 2010; 67:911-917.

247. Sabanci PA, Aras Y, Aydoseli A, Sencer S, Sencer A, Erguven M and Izgi N. A thrombosing, giant, distal posterior cerebral artery aneurysm in a newborn infant. Journal of Neurosurgery Pediatrics 2012; 10:50-55.

248. Salerno AE, Marsenic O, Meyers KE, Kaplan BS and Hellinger JC. Vascular involvement in tuberous sclerosis. Pediatric Nephrology 2010; 25:1555-1561.

249. Sanai N, Auguste KI and Lawton MT. Microsurgical management of pediatric intracranial aneurysms. Child's Nervous System 2010; 26:1319-1327.

250. Sanai N, Quinones-Hinojosa A, Gupta NM, Perry V, Sun PP, Wilson CB and Lawton MT. Pediatric intracranial aneurysms: durability of treatment following microsurgical and endovascular management. Journal of Neurosurgery 2006; 104:82-89.

251. Sarnat HB, Flores-Sarnat L and Pinter D. *Neuroembryology*. In: Winn HR, (ed.) Youmans Neurological Surgery. Elsevier Saunders, Philadelphia, USA. 2011, Vol. 1.

252. Sarti C, Tuomilehto J, Salomaa V, Sivenius J, Kaarsalo E, Narva EV, Salmi K and Torppa J. Epidemiology of subarachnoid hemorrhage in Finland from 1983 to 1985. Stroke 1991; 22:848-853.

253. Saveland H, Hillman J, Brandt L, Edner G, Jakobsson KE and Algers G. Overall outcome in aneurysmal subarachnoid hemorrhage. A prospective study from neurosurgical units in Sweden during a 1-year period. Journal of Neurosurgery 1992; 76:729-734.

254. Schievink WI. Genetics of intracranial aneurysms. Neurosurgery 1997; 40:651-662; discussion 662-653.

255. Schievink WI. Intracranial aneurysms. The New England Journal of Medicine 1997; 336:28-40.

256. Schievink WI, Link MJ, Piepgras DG and Spetzler RF. Intracranial aneurysm surgery in Ehlers-Danlos syndrome Type IV. Neurosurgery 2002; 51:607-611.

257. Schievink WI, Michels VV and Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders. A review. Stroke 1994; 25:889-903.

258. Schievink WI, Mokri B and Piepgras DG. Spontaneous dissections of cervicocephalic arteries in childhood and adolescence. Neurology 1994; 44:1607-1612.

259. Schievink WI, Mokri B, Piepgras DG and Gittenberger-de Groot AC. Intracranial aneurysms and cervicocephalic arterial dissections associated with congenital heart disease. Neurosurgery 1996; 39:685-689.

260. Schievink WI, Parisi JE, Piepgras DG and Michels VV. Intracranial aneurysms in Marfan's syndrome: an autopsy study. Neurosurgery 1997; 41:866-870.

261. Schievink WI, Riedinger M and Maya MM. Frequency of incidental intracranial aneurysms in neurofibromatosis type 1. American Journal of Medical Genetics 2005; 134A:45-48.

262. Schievink WI, Wijdicks EF, Parisi JE, Piepgras DG and Whisnant JP. Sudden death from aneurysmal subarachnoid hemorrhage. Neurology 1995; 45:871-874.

263. Schirmer CM and Malek AM. Critical influence of framing coil orientation on intra-aneurysmal and neck region hemodynamics in a sidewall aneurysm model. Neurosurgery 2010; 67:1692-1702.

264. Sedzimir CB, Jones EW, Hamilton D and Edwards R. Management of coarctation of aorta and bleeding intracranial aneurysm in paediatric cases. Neuropadiatrie 1973; 4:124-133.

265. Sedzimir CB and Robinson J. Intracranial hemorrhage in children and adolescents. Journal of Neurosurgery 1973; 38:269-281.

266. Sekhar LN and Heros RC. Origin, growth, and rupture of saccular aneurysms: a review. Neurosurgery 1981; 8:248-260.

267. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta Radiologica 1953; 39:368-376.

268. Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. Journal of Neurosurgery 1974; 41:125-145.

269. Sethi H, Moore A, Dervin J, Clifton A and MacSweeney JE. Hydrocephalus: comparison of clipping and embolization in aneurysm treatment. Journal of Neurosurgery 2000; 92:991-994.

270. Sharma BS, Sinha S, Mehta VS, Suri A, Gupta A and Mahapatra AK. Pediatric intracranial aneurysms-clinical characteristics and outcome of surgical treatment. Child's Nervous System 2007; 23:327-333.

271. Shelton JB, Ramakrishnaiah R, Glasier CM and Phillips PH. Cavernous sinus syndrome from an internal carotid artery aneurysm in an infant with tuberous sclerosis. Journal of the American Association for Pediatric Ophthalmology and Strabismus 2011; 15:389-391.

272. Shih P, Pinnaduwage T, Hu LS and Spetzler RF. A pediatric patient with a dissecting thrombotic anterior choroidal artery aneurysm: case report. Neurosurgery 2010; 67:E518.

273. Sivenius J, Tuomilehto J, Immonen-Räihä P, Kaarisalo M, Sarti C, Torppa J, Kuulasmaa K, Mahonen M, Lehtonen A and Salomaa V. Continuous 15-year decrease in incidence and mortality of stroke in Finland: the FINSTROKE study. Stroke 2004; 35:420-425.

274. Smith AB, Dillon WP, Lau BC, Gould R, Verdun FR, Lopez EB and Wintermark M. Radiation dose reduction strategy for CT protocols: successful implementation in neuroradiology section. Radiology 2008; 247:499-506.

275. Smith ER and Scott RM. Cavernous malformations. Neurosurgery Clinics of North America 2010; 21:483-490.

276. Smith ER and Scott RM. Spontaneous occlusion of the circle of Willis in children: pediatric moyamoya summary with proposed evidence-based practice guidelines. A review. Journal of Neurosurgery Pediatrics 2012; 9:353-360.

277. Snellman A. [Cerebral angiography as a diagnostic method.] Duodecim 1939; 55:26-46.

278. Songsaeng D, Srivatanakul K, Toulgoat F, Saliou G, Ozanne A and Lasjaunias P. Repair process in spontaneous intradural dissecting aneurysms in children: report of eight patients and review of the literature. Child's Nervous System 2009; 25:55-62.

279. Statistics Finland: Tobacco Statistics (e-publication). Helsinki, Finland. Statistics Finland 2010; http://www.stat.fi/til/tup/index_en.html.

280. Stegmayr B, Eriksson M and Asplund K. Declining mortality from subarachnoid hemorrhage: changes in incidence and case fatality from 1985 through 2000. Stroke 2004; 35:2059-2063.

281. Steiner RD, Pepin MG and Byers PH: Osteogenesis Imperfecta. in: Pagon RA, Bird TD, Dolan CR, Stephens K and Adam MP, (eds): GeneReviews.Seattle (WA);1993.

282. Stiefel MF, Heuer GG, Basil AK, Weigele JB, Sutton LN, Hurst RW and Storm PB. Endovascular and surgical treatment of ruptured cerebral aneurysms in pediatric patients. Neurosurgery 2008; 63:859-866.

283. Stieg PE and Friedlander R. Unruptured intracranial aneurysms. The New England Journal of Medicine 1999; 340:1442.

284. Storrs BB, Humphreys RP, Hendrick EB and Hoffman HJ. Intracranial aneurysms in the pediatric age-group. Child's Brain 1982; 9:358-361.

285. Streefkerk HJ, Bremmer JP and Tulleken CA. The ELANA technique: high flow revascularization of the brain. Acta Neurochirurgica Supplement 2005; 94:143-148.

286. Strouse JJ, Hulbert ML, DeBaun MR, Jordan LC and Casella JF. Primary hemorrhagic stroke in children with sickle cell disease is associated with recent transfusion and use of corticosteroids. Pediatrics 2006; 118:1916-1924.

287. Sulamaa M. *[Veitsellä ja sydämellä : kirurgin muistelmia.]* Weilin + Göös, Helsinki, Finland. 1971.

288. Sulamaa M and Vara P. An investigation into the occurrence of perinatal subdural haematoma; its diagnosis and treatment. Acta Obstetricia et Gynecologica Scandinavica 1952; 31:400-412.

289. Sungarian A, Rogg J and Duncan JA, 3rd. Pediatric intracranial aneurysm: a diagnostic dilemma solved with contrast-enhanced MR imaging. AJNR American Journal of Neuroradiology 2003; 24:370-372.

290. Swoboda NA, Armstrong DG, Smith J, Charkot E and Connolly BL. Pediatric patient surface doses in neuroangiography. Pediatric Radiology 2005; 35:859-866.

291. Tanaka S, Sagiuchi T and Kobayashi I. Ruptured pediatric posterior cerebral artery aneurysm 9 years after the onset of Kawasaki disease: a case report. Child's Nervous System 2007; 23:701-706.

292. Tapaninaho A, Hernesniemi J, Vapalahti M, Niskanen M, Kari A, Luukkonen M and Puranen M. Shunt-dependent hydrocephalus after subarachnoid haemorrhage and aneurysm surgery: timing of surgery is not a risk factor. Acta Neurochirurgica 1993; 123:118-124.

293. Team (R Development Core team). A language and environment for statistical computing, version 2.14.1. R Foundation for Statistical Computing, Vienna, Austria; 2011. http://www.R-project.org. Accessed March 13, 2012.

294. Teitelbaum GP, Larsen DW, Zelman V, Lysachev AG and Likhterman LB. A tribute to Dr. Fedor A. Serbinenko, founder of endovascular neurosurgery. Neurosurgery 2000; 46:462-470.

295. Tonn J, Hoffmann O, Hofmann E, Schlake HP, Sorensen N and Roosen K. "De novo" formation of intracranial aneurysms: who is at risk? Neuroradiology 1999; 41:674-679.

296. Torres VE, Harris PC and Pirson Y. Autosomal dominant polycystic kidney disease. Lancet 2007; 369:1287-1301.

297. Touze E, Oppenheim C, Trystram D, Nokam G, Pasquini M, Alamowitch S, Herve D, Garnier P, Mousseaux E and Plouin PF. Fibromuscular dysplasia of cervical and intracranial arteries. International Journal of Stroke 2010; 5:296-305.

298. Towbin RB, Ball WS and Kaufman RA. Pediatric case of the day. Abdominal aortic aneurysm in a patient with tuberous sclerosis. Radiographics 1987; 7:818-821.

299. Troupp H. Pathology, diagnosis, and treatment of supratentorial tumours in infancy and childhood. Annales Paediatriae Fenniae 1960; 6:21-33.

300. Troupp H and Heiskanen O. *[Mennyttä neurokirurgiaa etsimässä.]* Yliopistopaino, Helsinki, Finland. 2003.

301. Truwit CL. Embryology of the cerebral vasculature. Neuroimaging Clinics of North America 1994; 4:663-689.

302. Tsutsumi K, Ueki K, Morita A, Usui M and Kirino T. Risk of aneurysm recurrence in patients with clipped cerebral aneurysms: results of long-term follow-up angiography. Stroke 2001; 32:1191-1194.

303. Tulamo R, Frösen J, Junnikkala S, Paetau A, Kangasniemi M, Pelaez J, Hernesniemi J, Niemelä M and Meri S. Complement system becomes activated by the classical pathway in intracranial aneurysm walls. Laboratory Investigation 2010; 90:168-179.

304. Tulamo R, Frösen J, Junnikkala S, Paetau A, Pitkäniemi J, Kangasniemi M, Niemelä M, Jääskeläinen J, Jokitalo E, Karatas A, Hernesniemi J and Meri S. Complement activation associates with saccular cerebral artery aneurysm wall degeneration and rupture. Neurosurgery 2006; 59:1069-1076.

305. Tulamo R, Frösen J, Paetau A, Seitsonen S, Hernesniemi J, Niemelä M, Järvelä I and Meri S. Lack of complement inhibitors in the outer intracranial artery aneurysm wall associates with complement terminal pathway activation. The American Journal of Pathology 2010; 177:3224-3232.

306. Uitto J, Bercovitch L, Terry SF and Terry PF. Pseudoxanthoma elasticum: progress in diagnostics and research towards treatment : Summary of the 2010 PXE International Research Meeting. American Journal of Medical Genetics 2011; 155A:1517-1526.

307. Vaid VK, Kumar R, Kalra SK, Mahapatra AK and Jain VK. Pediatric intracranial aneurysms: an institutional experience. Pediatric Neurosurgery 2008; 44:296-301.

308. Vale FL, Bradley EL and Fisher WS, 3rd. The relationship of subarachnoid hemorrhage and the need for postoperative shunting. Journal of Neurosurgery 1997; 86:462-466.

309. Valencia AA, Guzman AM, Finol EA and Amon CH. Blood flow dynamics in saccular aneurysm models of the basilar artery. Journal of Biomechanical Engineering 2006; 128:516-526.

310. van Dijk FS, Cobben JM, Kariminejad A, Maugeri A, Nikkels PG, van Rijn RR and Pals G. Osteogenesis Imperfecta: A Review with Clinical Examples. Molecular Syndromology 2011; 2:1-20.

311. van Gijn J, Hijdra A, Wijdicks EF, Vermeulen M and van Crevel H. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery 1985; 63:355-362.

312. van Munster CE, von und zu Fraunberg M, Rinkel GJ, Rinne J, Koivisto T and Ronkainen A. Differences in aneurysm and patient characteristics between cohorts of Finnish and Dutch patients with subarachnoid hemorrhage: time trends between 1986 and 2005. Stroke 2008; 39:3166-3171.

313. Vapalahti PM, Schugk P, Tarkkanen L and af Björkesten G. Intracranial arterial aneurysm in a three-month-old infant. Case report. Journal of Neurosurgery 1969; 30:169-171.

314. Ventureyra EC and Higgins MJ. Traumatic intracranial aneurysms in childhood and adolescence. Case reports and review of the literature. Child's Nervous System 1994; 10:361-379.

315. Viljanto J and Salminen P. *[Suomen lastenkirurgiyhdistys. Sulamaa-seura ry 1973-1993.]* Kirjapaino Pika Oy, Turku, Finland. 1993.

316. Waaijer A, Prokop M, Velthuis BK, Bakker CJ, de Kort GA and van Leeuwen MS. Circle of Willis at CT angiography: dose reduction and image quality--reducing tube voltage and increasing tube current settings. Radiology 2007; 242:832-839.

317. WAN H AND LOCH MACDONALD R. Circulatory and vascular changes after aneurysmal subarachnoid hemorrhage. Journal of Neurosurgical Sciences 2011; 55:329-341.

318. WEIR B, GRACE M, HANSEN J AND ROTHBERG C. Time course of vasospasm in man. Journal of Neurosurgery 1978; 48:173-178.

319. WEIR B AND MACDONALD L, (eds.). *Intracranial aneurysms and subarachnoid hemorrhage: an overview.* McGraw-Hill, St Louis, USA. 1996

320. WERMER MJ, GREEBE P, ALGRA A AND RINKEL GJ. Incidence of recurrent subarachnoid hemorrhage after clipping for ruptured intracranial aneurysms. Stroke 2005; 36:2394-2399.

321. WERMER MJ, RINKEL GJ, GREEBE P, ALBRECHT KW, DIRVEN CM AND TULLEKEN CA. Late recurrence of subarachnoid hemorrhage after treatment for ruptured aneurysms: patient characteristics and outcomes. Neurosurgery 2005; 56:197-204.

322. WERMER MJ, VAN DER SCHAAF IC, VAN NUNEN P, BOSSUYT PM, ANDERSON CS AND RINKEL GJ. Psychosocial impact of screening for intracranial aneurysms in relatives with familial subarachnoid hemorrhage. Stroke 2005; 36:836-840.

323. WERMER MJ, VAN DER SCHAAF IC, VELTHUIS BK, ALGRA A, BUSKENS E AND RINKEL GJ. Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargement of existing aneurysms. Brain 2005; 128:2421-2429.

324. WIEBERS DO, WHISNANT JP, HUSTON J, 3RD, MEISSNER I, BROWN RD, JR., PIEPGRAS DG, FORBES GS, THIELEN K, NICHOLS D, O'FALLON WM, PEACOCK J, JAEGER L, KASSELL NF, KONGABLE-BECKMAN GL AND TORNER JC. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003; 362:103-110.

325. WILLEMSEN P, DE ROOVER D, KOCKX M AND GERARD Y. Mycotic common carotid artery aneurysm in an immunosuppressed pediatric patient: case report. Journal of Vascular Surgery 1997; 25:784-785.

326. WINSTON KR. Pediatric neurosurgery: pride and prejudice. Pediatric Neurosurgery 2000; 32:58-68.

327. WOO D, KHOURY J, HAVERBUSCH MM, SEKAR P, FLAHERTY ML, KLEINDORFER DO, KISSELA BM, MOOMAW CJ, DEKA R AND BRODERICK JP. Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. Neurology 2009; 72:69-72.

328. XU HW, YU SQ, MEI CL AND LI MH. Screening for intracranial aneurysm in 355 patients with autosomal-dominant polycystic kidney disease. Stroke 2011; 42:204-206.

329. YAMAUCHI-KAWAURA C, FUJII K, AOYAMA T, KOYAMA S AND YAMAUCHI M. Radiation dose evaluation in head and neck MDCT examinations with a 6-year-old child anthropomorphic phantom. Pediatric Radiology 2010; 40:1206-1214.

330. YASARGIL MG AND FOX JL. The microsurgical approach to intracranial aneurysms. Surgical Neurology 1975; 3:7-14.

331. Yasuno K, Bakircioglu M, Low SK, Bilguvar K, Gaál E, Ruigrok YM, Niemelä M, Hata A, Bijlenga P, Kasuya H, Jääskeläinen JE, Krex D, Auburger G, Simon M, Krischek B, Ozturk AK, Mane S, Rinkel GJ, Steinmetz H, Hernesniemi J, Schaller K, Zembutsu H, Inoue I, Palotie A, Cambien F, Nakamura Y, Lifton RP and Gunel M. Common variant near the endothelin receptor type A (EDNRA) gene is associated with intracranial aneurysm risk. Proceedings of the National Academy of Sciences of the United States of America 2011; 108:19707-19712.

332. Yasuno K, Bilguvar K, Bijlenga P, Low SK, Krischek B, Auburger G, Simon M, Krex D, Arlier Z, Nayak N, Ruigrok YM, Niemelä M, Tajima A, von und zu Fraunberg M, Doczi T, Wirjatijasa F, Hata A, Blasco J, Oszvald A, Kasuya H, Zilani G, Schoch B, Singh P, Stuer C, Risselada R, Beck J, Sola T, Ricciardi F, Aromaa A, Illig T, Schreiber S, van Duijn CM, van den Berg LH, Perret C, Proust C, Roder C, Ozturk AK, Gaál E, Berg D, Geisen C, Friedrich CM, Summers P, Frangi AF, State MW, Wichmann HE, Breteler MM, Wijmenga C, Mane S, Peltonen L, Elio V, Sturkenboom MC, Lawford P, Byrne J, Macho J, Sandalcioglu EI, Meyer B, Raabe A, Steinmetz H, Rufenacht D, Jääskeläinen JE, Hernesniemi J, Rinkel GJ, Zembutsu H, Inoue I, Palotie A, Cambien F, Nakamura Y, Lifton RP and Gunel M. Genome-wide association study of intracranial aneurysm identifies three new risk loci. Nature Genetics 2010; 42:420-425.

333. Yazbak PA, McComb JG and Raffel C. Pediatric traumatic intracranial aneurysms. Pediatric Neurosurgery 1995; 22:15-19.

334. Yin L, Ma CY, Li ZK, Wang DD and Bai CM. Predictors analysis of symptomatic cerebral vasospasm after subarachnoid hemorrhage. Acta Neurochirurgica Supplement 2011; 110:175-178.

335. Yoneoka Y, Takeda N, Akira I, Ibuchi Y, Kumagai T, Sugai T, Takeda KI and Ueda K. Ruptured de novo intracranial aneurysms. Acta Neurochirurgica 2004; 146:979-981.

336. Young WF and Pattisapu JV. Ruptured cerebral aneurysm in a 39-day-old infant. Clinical Neurology and Neurosurgery 2000; 102:140-143.

337. Zhang YJ, Barrow DL and Day AL. Extracranial-intracranial vein graft bypass for giant intracranial aneurysm surgery for pediatric patients: two technical case reports. Neurosurgery 2002; 50:663-668.

338. Öhman J and Heiskanen O. Effect of nimodipine on the outcome of patients after aneurysmal subarachnoid hemorrhage and surgery. Journal of Neurosurgery 1988; 69:683-686.