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INTRACRANIAL ANEURYSMS IN PATIENTS WITH KAWASAKI DISEASE OR THORACIC AORTIC ANEURYSMS

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To my loved ones

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ABSTRACT

Saccular intracranial aneurysm (sIA) is the most common type of IAs and characterized by outpoching sac with a neck arising from the cerebral artery wall. Pathophysiology of IAs are still poorly understood. Fusiform IA is a focal circumferential dilatation of the cerebral artery and unlike sIAs, do not have aneurysm neck, which make their treatment more complex compared to sIAs. The primary goal in the study I and II were to evaluate if Kawasaki disease (KD) is associated with increased risk for IAs (I) and white matter hyperintensities (WMH) (II), in the study III if sIAs are related with increased risk for thoracic aortic aneurysms (TAA) or dilatations (TAD), and in the study IV was to evaluate outcomes of flow diverter stent (FD) treatment of the ruptured posterior circulation fusiform IAs.

In the study (I and II) 40 adults with a history of KD in a childhood were screened with brain Magnetic Resonance Imaging and Angiography for IAs and brain WMHs. No IAs were found in KD patients, which is significantly under the prevalence of 10% (95% CI, 0%-8.8%, $p = 0.03$) that is the recommended limit for IA screening. In the study (II), we found that Kawasaki disease is related with increased WMH burden compared to age- and sex-matched migraine controls. Our study suggests that KD is not associated with IAs, but instead is associated with increased WMH burden, indicating long-term cerebrovascular involvement of KD.

In the study (III) we retrospectively reviewed 411 patients with sIAs and available imaging studies (computed tomography or magnetic resonance imaging) of all thoracic aortic segments for TADs and TAAs. The prevalence of TADs and TAAs were 18% and 8%. Rheumatic disease and alcohol abuse were significant risk factors for TADs/TAAs. Our results suggests that sIAs might be associated with increased risk for TAAs and TADs.

In the study (IV) five patients with ruptured posterior circulation fusiform aneurysms and treated with a FD were reviewed rertrospectively. We found that FD is a feasible treatment option for ruptured fusiform posterior circulation IAs, with a high aneurysm occlusion rate (100% at 6-months) and 80% of patients had a good outcome. However, FD treatment carries a significant risk for complications and should be considered only when other treatment options are not available.

KEYWORDS: intracranial aneurysm, flow diverter, fusiform aneurysm, Kawasaki disease, vasculitis, aortic aneurysm

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Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Sakkulaarinen aivovaltimoaneurysma (sIA) on yleisin aivoaneurysmatyyppi. SIA on aivovaltimoiden seinämästä työntyvä paikallinen pullistuma, joka yhdistyy aivovaltimon seinämään kaulalla. Fusiforminen IA on aivovaltimon paikallinen laajentuma ja toisin kuin sIA:ssa, fusiformisessa IA:ssa ei ole erillistä kaulaa, joka tekee hoidosta haastavaa. IA:ien syntymisen patofysiologia tunnetaan huonosti. Tutkimuksien (I) ja (II) tavoitteena oli selvittää, onko lapsuuden Kawasakin taudilla yhteyttä suurentuneeseen riskiin vuotamattomille IA:lle ja aivojen valkean aineen muutoksille. Tutkimuksen (III) tavoitteena oli selvittää ovatko sIA:t yhteydessä suurentuneeseen riskiin torakaaliaortan aneurysmille (TAA) tai dilataatioille (TAD). Tutkimuksen (IV) tarkoituksena oli selvittää flow diverter stenttihoidon (FD) tuloksia vuotaneiden takaverenkierron fusiformisten IA:ien hoidossa.

Tutkimuksissa (I ja II) 40:lle lapsuudessa Kawasakin taudin sairastaneelle potilaalle suoritettiin aivojen ja aivoverisuonten magneettikuvaus IA:ien, sekä WMH muutosten seulomiseksi. Valkean aineen muutosten määrää verrattiin ikä- ja sukupuolivakioituihin verrokkeihin (migreenipotilaat). Kawasakin taudin sairastaneilla potilailla ei todettu IA:a ja prevalenssi oli merkittävästi alle suositellun IA:en seulontarajan 10 % (95 % CI 0 %-8.8 %, p= 0.03). Sen sijaan Kawasakin taudin sairastaneilla henkilöillä oli merkittävästi enemmän valkean aineen muutoksia verrokkeihin nähden, viitaten siihen, että Kawasakin taudilla voi olla myös aivoverisuoniin kohdistuvia vaikutuksia.

Tutkimuksessa (III) analysoimme retrospektiivisesti 411 sIA potilasta, joilla oli kuvannettu rinta-aortta tietokonetomografialla tai magneettikuvauksella. TAD:n ja TAA:n prevalenssi oli 18 % ja 8 %. Reumasairaus ja alkoholin väärinkäyttö lisäsivät merkittävästi riskiä TAD:lle/TAA:lle. SIA:iin saattaa liittyä suurentunut riski TAD:lle/TAA:lle.

Tutkimuksessa (IV) analysoimme retrospektiivisesti viisi potilasta, joiden vuotanut aivojen takaverenkierron fusiforminen IA oli hoidettu FD:llä. Aneurysmien hoitotulokset olivat hyviä FD:llä ja 80 % potilaista toipuivat hyvin. FD hoitoon liittyy kuitenkin merkittäviä komplikaatioriskejä ja FD hoitoa tulisi miettiä vuotaneissa aneurysmissa vain, jos muut hoitovaihtoehdot katsotaan mahdottomiksi.

AVAINSANAT: aivovaltimoaneurysma, flow diverter, fusiforminen aneurysma, Kawasakin tauti, vaskuliitti, aortta-aneurysma

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Abbreviations

ANCA	Anti-Neutrophilic Cytoplasmic Autoantibody
EVD	External Ventricular Drainage
FD	Flow Diverter-stent
FLAIR	Fluid-attuenuated inversion recovery
FRED	Flow Re-Direction Endoluminal Device System
GCS	Glasgow Coma Scale
HH	Hunt and Hess
IA	Intracranial Aneurysm
ICAM-1	Intercellular adhesion molecule 1
ICH	Intracerebral Hemorrhage
IL-1	Interleukin-1 family
IL-6	Interleukin-6 family
IPST	Intraprocedural Stent Thrombosis
KD	Kawasaki disease
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
OKM	O'Kelly Marotta grading scale
PKD1	Polycystic Kidney Disease 1 Gene
PKD2	Polycystic Kidney Disease 2 Gene
PCA	Posterior Cerebral Artery
PICA	Posterior Inferior Cerebellar Artery
rIA	Ruptured Intracranial Aneurysm
SAH	Subarachnoid Hemorrhage
SCA	Superior Cerebellar Artery
sIA	Saccular Intracranial Aneurysm
TAA	Thoracic Aortic Aneurysm
TAD	Thoracic Aortic Dilation
TNF-alpha	Tumor Necrosis Factor-alpha
UIA	Unruptured Intracranial Aneurysm
VCAM	Vascular cell adhesion molecule 1
VPS	Ventriculoperitoneal shunt

WMH	White Matter Hyperintesity
WEB	Woven Endobrigde

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Laukka D, Rahi M, Parkkola R, Vahlberg T, Rintala A, Salo E, Rinne J. Unlikely association between Kawasaki disease and intracranial aneurysms: a prospective cohort study. *J Neurosurg Pediatr*, 2019, 5: 537-659

II Laukka D, Parkkola R, Hirvonen J, Ylikotila P, Vahlberg T, Salo E, Kivelev J, Rinne J, Rahi M. Brain white matter hyperintensities in Kawasaki disease: A case-control study. *Front Neurosci*. 2022, 18, 1 6: 995480.

III Laukka D, Pan E, Fordell T, Alpay K, Rahi M, Hirvonen J, Rinne J, Gunn J. Prevalence of thoracic aortic aneurysms and dilatations in patients with intracranial aneurysms. *J Vasc Surg*, 2019, 6: 1801-1808.

IV Laukka D, Rautio R, Rahi M, Rinne J. Acute Treatment of Ruptured Fusiform Posterior Circulation Posterior Cerebral, Superior Cerebellar, and Posterior Inferior Cerebellar Artery Aneurysms With FRED Flow Diverter: Report of 5 Cases. *Operative Neurosurgery (Hagerstown)*, 2019, 5: 549-556.

1 Introduction

Subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysm (rIA) accounts 5% of all stroke types (Feiqin et al., 2009). Unlike ischemic stroke, SAH is affecting mainly in the working age population and diagnosed in 8/100 000 persons per year (Etminan et al 2019). Up to 40% of patients with dies during 12-months after the acute SAH (Korja et al., 2013) and only one-third of survivors are able to return back to work (Buunk et al., 2019). For these reasons SAH carries high costs for society (Meretoja et al., 2011)

Prevalence of unruptured intracranial aneurysms (UIA) is 3% in the general population (Vlak et al., 2011), meaning that about 100 000 persons carries UIA in the Finnish population. Most of the UIAs are found incidentally (Bos et al., 2016) and only a portion of UIAs rupture during the lifetime (Hackenberg et al., 2018). Pathophysiology of UIAs and rIAs are poorly understood, but local hemodynamic stress and IA wall inflammation plays important role in IA formation and rupture (Chalouhi et al., 2012). Smoking, increasing age, female sex, hypertension, positive family history of intracranial aneurysms, certain connective tissue disorders, and polycystic kidney disease are known risk factors for IAs (Thompson et al., 2015). Because most of the UIAs are asymptomatic before the devastating bleeding and on the other hand, only a small portion of UIAs rupture, it is important to gather better understanding from the pathophysiology of IA formation and rupture.

In general, IAs can be treated with neurosurgical or endovascular treatment (Zhao et al., 2018). Ruptured IAs should be treated in the first days after the SAH to prevent rebleeding (Connolly et al., 2012). Saccular IAs (sIA) can usually be treated with conventional neurosurgical ligation or endovascular treatment. More rare type of IAs are fusiform IAs, which are local spindle shaped dilatations of cerebral artery and accounts only <10% of all IAs. Because fusiform IAs do not have aneurysm neck, their treatment differs from sIAs and conventional endovascular coiling or ligation of fusiform IAs is hard or impossible to implement. Surgical treatment of fusiform IAs usually needs trapping of the proximal artery with or without bypass, which is technically challenging with a high risk of morbidity and mortality. (Barletta et al., 2018)

This book presents four different studies. In the first (I) study we investigated prospectively if childhood Kawasaki disease is related to IAs in the later adulthood and in the second (II) study we investigated if Kawasaki disease is associated with increased risk for white matter hyperintensities. In the third (III) study we investigated retrospectively if IAs are related to thoracic aortic aneurysms. In the fourth (IV) study we investigated retrospectively outcome and treatment results of flow diverter stents in the ruptured posterior circulation fusiform IAs. Because these three different studies deal with treatment and ideas of aneurysm pathophysiology this book review extensively pathophysiology, risk factors and treatment of sIAs to understand the basic ideas behind the study thesis. Fusiform IAs are reviewed in the separate chapters, because they differ from sIAs by their risk factors, outcomes and treatment.

Kawasaki disease is a vasculitis that affects in the small- and medium size arteries and occurs usually in childhood. One of the complications of Kawasaki disease is coronary artery aneurysms, which develops in around 23% of patients without treatment. (Cohen et al., 2016) Vasculitis affects also cerebral arteries and found in around 38% of patients (Amano et al., 1980). There are few case reports of ruptured IA in young patients with Kawasaki disease (Tanaka et al., 2007, Ahn et al., 2010, Ishida et al., 2014), however it is unknown if Kawasaki disease is related with increased risk for IAs. White matter hyperintensities (WMH) are chronic ischemic lesions indicating cerebral small vessel disease that are associated with increased risk for stroke, dementia, death and psychiatric disorders (Wardlaw et al., 2016). Hypoperfusion, the blood-brain barrier dysfunction and inflammation are suggested pathophysiological mechanisms for WMHs (Alber et al., 2019). In the study I we hypothesized that Kawasaki disease could be a risk factor for UIAs, because Kawasaki disease affects also cerebral vessels (Ichiyama et al., 1998, Hikita et al., 2011) and Kawasaki disease is characterized by coronary artery aneurysms (Kato et al., 1996) and more rarely peripheral arterial aneurysms (Zhao et al., 2019). In the study II we hypothesized that Kawasaki disease could be related to increased risk for WMHs.

Aortic aneurysms and intracranial aneurysms shares similar comorbidities and genetic risk factors (van't Hof et al., 2016). Around 10% of patients with aortic aneurysms have concomitant IAs (Kuzmik et al., 2009; Rouchaud et al., 2016). Current belief is that abdominal aortic aneurysms and thoracic aortic aneurysms have different pathophysiological background. Abdominal aortic aneurysms are related to atherosclerosis while genetic factors are more involved in thoracic aortic aneurysms. (Isselbacher 2005) Presence of thoracic aortic aneurysms in patients with IA is poorly studied and previous studies has focused on ascending or descending thoracic aorta, neglecting the aortic arch. In the study III we investigated the prevalence of thoracic aortic aneurysms and dilatations in patients with IAs. We hypothesized that

possible overlapping of genetic risk factors between IAs and aortic aneurysms could be involved especially in the thoracic aortic region

Flow diverter stents (FD) are new endovascular treatment option for IAs that are difficult to treat surgically or with conventional endovascular treatment like coiling. Currently, the FDA have approved treatment of UIAs that locate in the carotid artery proximal to ophthalmic artery. However, there are number of publications of off-label use of FD in the treatment of IAs. (Limbucci et al., 2020) FD requires dual antiplatelet therapy to prevent stent thrombosis that could potentially cause brain infarction. In the acute setting of SAH, dual antiplatelet could cause serious problems, because some of the SAH patients may need neurosurgical procedures and dual antiplatelet therapy could predispose major hemorrhagic surgical complications. However, without treatment of ruptured IA there are major risk of rebleeding and mortality. There are lack of studies investigating FD treatment of ruptured posterior circulation fusiform IAs, without treatment there are 70% risk of rebleeding and 50% risk of mortality (Mizutani et al., 1995). Ruptured posterior circulation fusiform IAs are usually demanding or sometimes impossible to treat with conventional endovascular or neurosurgical treatment. For these reasons we carried out a study IV, where we investigated retrospectively outcomes of the FD treatment in the patients with a ruptured posterior circulation fusiform IAs which were not suitable for other treatment options.

2 Review of the Literature

2.1 Saccular intracranial aneurysms

Saccular intracranial aneurysms (sIA) are outpouching sacs which arise from the wall of the cerebral artery. Portion which locate between the sac and cerebral artery wall is called aneurysm neck. SIAs usually locates in the cerebral artery bifurcations (Brisman et al., 2006). See **Figure 1 (A)**. Another rare type of IAs is fusiform IA, which is circumferential dilatation of the cerebral artery and unlike sIAs, do not have aneurysm neck. See **Figure 1 (B)**.

When the IA rupture it causes bleeding in to the subarachnoid space and is called subarachnoid hemorrhage. See **Figure 2**.

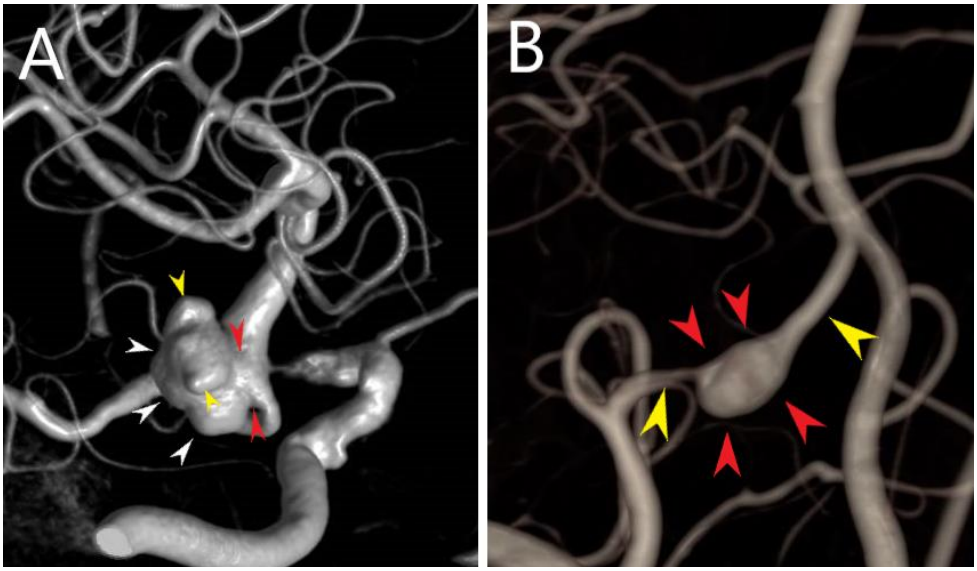


Figure 1. Saccular intracranial aneurysm (A) and fusiform intracranial aneurysm (B) in digital subtraction angiography 3D-reconstruction images. (A) Saccular intracranial aneurysm consisting of aneurysm neck (red arrows) and aneurysm sac/dome (white arrows). In deform aneurysms secondary pouches (yellow arrows) can be seen arising from the aneurysm sac. (B) Fusiform intracranial aneurysm (red arrows) which is a local circumferential dilation of the artery (yellow arrows). (Copyright Dan Laukka)

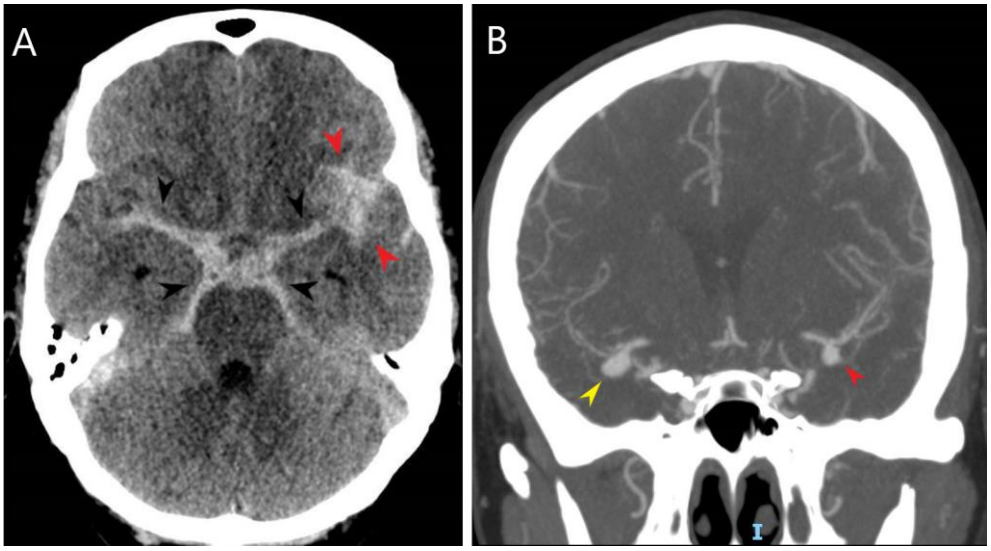


Figure 2. Subarachnoid hemorrhage (A) from left saccular intracranial aneurysm (B) (Copyright Dan Laukka). (A) Subarachnoid hemorrhage in the basal cisterns (black arrows) with a maximum bleeding on the patients left side (red arrows). (B) In this case there were two aneurysms, one in the right middle cerebral artery bifurcation (yellow arrow) and one in the left middle cerebral artery bifurcation (red arrow). Based on maximum bleeding site, left aneurysm were considered source of bleeding and treated first. (Copyright Dan Laukka)

2.1.1 Epidemiology of unruptured and ruptured intracranial aneurysms

Prevalence of unruptured sIAs is about 3% in the general population around the world (Vlak et al., 2011). Most of the UIAs are asymptomatic and found incidentally for various reasons. As radiological imaging of the brain has become more affordable and more available, diagnosis of incidental UIAs are presumably increasing. Up to 30% of patients have more than one IAs (multiple IAs) (Rinne et al., 1994). Prevalence of UIAs increases with the age and are uncommon in <30 year old persons. Male to female ratio of UIAs is 1:1 until age 50, after which the ratio increases to 2:1 (Vlak et al., 2011).

About 80-90% of sIAs locate in the anterior circulation and rest in the posterior circulation. Typical places for unruptured sIAs are anterior communicating artery (16% of IAs), internal carotid artery (34% of IAs) and middle cerebral artery (36% of IAs). Only 7% of the sIAs locate in the basilar apex or superior cerebellar artery, 2% in the vertebrobasilar junction or vertebrobasilar-posterior inferior cerebellar artery junction and 6% in other locations. (Morita et al., 2012) Most common locations of ruptured sIAs are middle cerebral artery (32%), anterior communicating

atery (32%), posterior communicating artery (14%) and pericallosal artery (5%). (Korja et al., 2016)

Incidence of SAH from ruptured IA is about 10/100 000 in most of the countries (Etminan et al., 2019) including Finland (Korja et al., 2016). In the earlier reports incidence of SAH has been exceptionally high in Finland and Japan (De Rooji et al., 2007), but in Finland, incidence has been decreased to the similar level with other Nordic countries, possibly because of the decreasing smoking. (Korja et al., 2016) SAH is affecting mostly in working age people and the mean age for SAH is 55 years. SAH is a fatal disease, approximately 17% of patients die before hospital admission (Lindbohm et al., 2017) and 40% of patients die during the 12-months after the bleeding (Karamankos et al., 2012). Only one third of patients have good outcome after the SAH and can return back to work. (Passier et al., 2011) Psychiatric disorders are common in patients who recovers to independent life after SAH, ~70% of patients have experience of fatigue, around 30% anxiety and 20% depression (Huttunen J et al 2016). Risk of epilepsy is 13% after SAH (Huttunen J et al., 2015).

Most of the patients with SAH requires treatment in the intensive care unit, which equals with high costs. Total mean cost of intensive care unit treated SAH patient is 51 906 € in contrast to ischemic stroke 39 222€ (Raj et al., 2018).

2.1.2 Pathophysiology of saccular intracranial aneurysms

Pathophysiology of saccular intracranial aneurysms (sIA) is presented in **Figure 3.** Cerebral arteries are made of three layers, tunica intima, tunica media and adventitia. Tunica intima consists of endothelium which lines the vessel lumen and right under the endothelium there is a thin layer of elastic tissue called internal elastic lamina, which separates tunica intima from tunica media. Tunica media contains mainly smooth muscle cells and some collagen and elastin. Adventitia is made of fibroblasts, collagen and elastin. Unlike extracranial arteries, cerebral arteries do not have external elastic lamina. Larger cerebral arteries are surrounded by autonomic nerves and travels in the subarachnoid space. When larger arteries dive deeper in to the brain they are surrounded by astrocytes and pericytes which together with endothelium build so called blood brain barrier. (Iadecola 2004)

Pathophysiology of intracranial aneurysms formation, growth and rupture is yet poorly understood. However, evidence suggests that local hemodynamic stress and arterial wall inflammation has a crucial role in the formation and rupture of IAs. (Chalouhi et al., 2013)

Normal endothelium function is maintained by laminar flow and humoral response, which increases nitric oxide synthase activation and nitric oxide levels. Nitric oxide inhibits leukocyte and platelet adhesion, inhibits smooth muscle cell

migration, proliferation and contraction. In addition to hemodynamic stress, several other factors can cause endothelial dysfunction like oxidative stress, genetic risk factors, injury, infection, inflammation, cancer and thrombosis. (Gimbrone et al., 2016)

Local hemodynamic stress causes endothelial dysfunction, which leads to decreased endothelial nitric oxide synthase expression and activation of nuclear factor-κBn. Decreased levels of nitric oxide leads and activation of nuclear factor-κBn leads to increased expression of leukocyte adhesion molecules (VCAM-1, ICAM-1, E-selectin, P-selectin) and cytokines (monocyte chemoattractant protein-1, TNF-alpha, IL-1, IL-6), increased vasomotor tone and dysregulation of vascular smooth muscle cells. Because of cytokines and adhesion molecules, macrophages, T-cells, NK-cells and neutrophils infiltrates through the endothelium into the media layer. (Gimbrone et al., 2016)

Increased activation and secretion of matrix metalloproteinase 1, 2 and 9 are causing disruption of internal elastic lamina, apoptosis of vascular smooth muscle cells, abnormal collagen synthesis, fibrosis and dysfunctional remodeling of extracellular matrix that leads thinning and weakening of the aneurysm wall which eventually lead to IA rupture. (Frösen et al., 2019)

Macrophages have an essential role in the aneurysm formation and rupture. There are two different types of macrophages, type 1 and type 2. Type 1 macrophages are proinflammatory cells whereas type 2 macrophages have anti-inflammatory features. In the UIAs number of type 1 and type 2 cells are equal, but in the rIAs there are imbalance between these two cell types and type 1 macrophages are overrepresented. (Hasan et al., 2012)

2.1.3 Risk factors of unruptured intracranial aneurysms

Risk factors for unruptured intracranial aneurysms (UIA) can be divided in non-modifiable and modifiable risk factors. (Thompson et al. 2015)

Non-modifiable risk factors for UIAs are polycystic kidney disease, Ehlers-Danlos syndrome, female sex, age and positive family history of aneurysmal SAH or UIA. (Thompson et al. 2015)

The prevalence of UIAs in patients with polycystic kidney disease is ~10%, a prevalence that is around 4 times higher than in the general population. In this population prevalence of UIAs can reach up 23% if patient have family history of IAs or SAH. (Xu et al., 2010) PKD1 and PKD2 encodes polycystin-1 and polycystin-2 proteins which are present in smooth muscles and endothelial cells. PKD1 and/or PKD2 mutations are associated with autosomal dominant polycystic disease and could be also linked with intracranial aneurysms via vascular endothelium and smooth muscle defects. (Rossetti et al., 2003; Rossetti et al., 2013)

Microcephalic osteodysplastic primordial dwarfism is a rare genetic syndrome and up to 52% of patients have moymoya disease and/or intracranial aneurysms (Bober et al., 2010).

Prevalence of UIAs from ~9% (Ronkainen et al., 1997) have been reported in patients who have ≥2 first-degree relatives with a history of rIA or UIA. Although it is clear that IAs are associated with IA families, possible inheritance pattern and specific genetic risk factor are unclear. (Thompson et al. 2015)

Risk of UIAs increases with age (OR 1.02, p= 0.003) (Kang et al., 2015).

Smoking and hypertension are important modifiable risk factors of UIAs. Smoking together with hypertension have synergistic effect to the risk of UIAs (OR 8.3; CI 95%). Hypercholesterolemia and regular physical exercise seem to decrease the risk for UIAs (Vlak et al., 2013).

The risk of de novo aneurysms is low in patients with a history of previously diagnosed intracranial aneurysms. Only 2% of patients develop de novo aneurysms without difference between earlier diagnosis of rIA and UIA. Most of the de novo aneurysms (88.8%) develops only after 5-year follow-up. (Giordan et al., 2018).

2.1.4 Risk factors of intracranial aneurysm rupture

Modifiable risk factors for rIAs are cigarette smoking, high alcohol consumption (Juvela et al., 2015) and hypertension (Greving et al., 2014; Tada et al., 2014). Aneurysm characteristics are also important risk factor for rIAs. Non-modifiable risk factors are same as in the UIAs (**chapter 2.1.3**). Half of the SAH cases occurs during the night or rest, but vigorous exercise, constipation and high coffee consumption might increase SAH risk. (Vlak et al., 2011) However, regular physical exercise reduces the risk for SAH. (Lindbohm et al., 2019)

Larger aneurysm size, aneurysm location, aneurysm growth, irregular shape, multiple aneurysms and previous aneurysmal SAH predicts IA rupture in the future. Larger aneurysms have been shown to have higher annual rupture risk, (Greving et al., 2014) but paradoxically around 20-50% of rIAs are small (≤5 mm) aneurysms. (Molyneux et al., 2002; Ikawa et al., 2018) Irregular shape of IA predicts rupture (odds ratio 7.1; 95% CI, 6.0-8.3) also in small IAs (<7 mm). (Lindgren et al., 2016)

Although controversial, (Wiebers et al., 2003; Morita et al., 2012) hypertension possibly increases aneurysmal SAH risk (hazard ratio, 1.4; 95% CI, 1.1-1.8). (Greving et al., 2014) Smoking can increase the risk of aneurysmal SAH by 2-fold to 7-fold and excessive alcohol consumption can increase the risk 2-fold to 6-fold. (Juvela et al., 1993)

Patients who have two or more first degree relatives with UIA or rIA have 17 times higher risk for aneurysmal SAH compared to other populations and risk of rupture for smaller IAs is also high (Broderick et al., 2009). IA association with

family history suggests that there is genetic contribution involved. Although number of different genes has been identified to be associated with IAs they have been failed to be repeatable in different populations. Following genes has been identified to be related with IAs in more than one studies, CDKN2BAS1 (loci 9p21.3), SOX17 (loci 8q11.23-12.1), EDNRA (loci 4q31.22-31.23) and HDAC9/TMEM195 (loci 7p21) (Zhou et al., 2018). However, these genes explained in one study only around 2% of all heritability IAs (Kurki et al., 2014) while other study found genetic heritability of 22% (Bakker et al., 2020). One study found that strong genetic correlation between UIAs and rIAs, suggesting similar genetic background (Bakker et al., 2020).

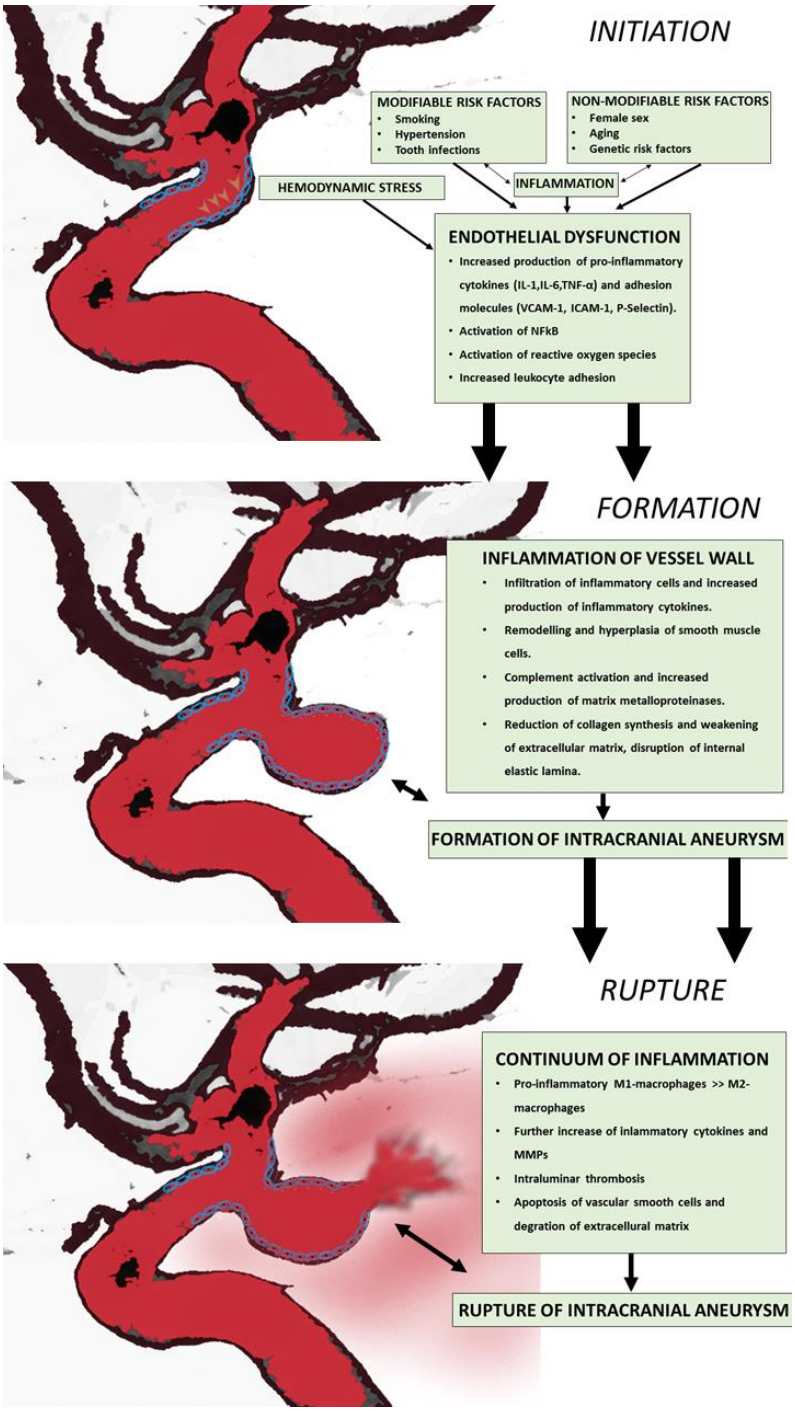


Figure 3. Illustration of intracranial aneurysm pathophysiology (Copyright Dan Laukka)

2.1.5 Screening of unruptured intracranial aneurysms

Because most of the UIAs do not rupture during the lifetime and there are significant risks for treatment complications, UIA screening is warranted only in a population with a high risk of SAH. In these high-risk populations expected prevalence of UIAs is around 10%. One study suggests that screening is cost-effective if expected prevalence of UIA is >10%. Another study showed that UIA screening of general population could even cause loss of quality-adjusted life years. (Thompson et al., 2015)

UIA screening is recommended in patients who have ≥2 affected first degree family members (UIA or rIA), in patients with autosomal dominant polycystic kidney disease, type IV Ehlers-Danlos syndrome, or microcephalic osteodysplastic dwarfism (Thompson et al., 2015).

2.2 Vasculitis and aneurysms

Association between vasculitis and IAs has not been studied extensively and limited to case reports.

Vasculitis is systemic disease which is characterized by inflammation and injury of blood vessels. Vasculitis can affect large vessels, medium vessels and/or small vessels. (Sunderkötter et al., 2018)

The most common large vessel vasculitis are giant cell arteritis and Takayasu arteritis. Giant cell arteritis affects usually carotid, vertebral and temporal arteries. Aneurysms and dissections are related with giant cell arteritis. (Sunderkötter et al., 2018) Takayasu arteritis affects usually aorta and may cause aneurysms and cardiac complications. (Farrah et al., 2019)

Polyarteritis nodosa and Kawasaki disease affects medium sized arteries and are the most common medium vessel vasculitis. (Sunderkötter et al., 2018) In polyarteritis nodosa, microaneurysms and arterial stenosis can develop in visceral arteries, usually in mesenteric and renal arteries. Polyarteritis nodosa can manifest to cerebral arteries, but intracranial aneurysms are rare in patients with polyarteritis nodosa. (Gupta et al., 2013) Kawasaki disease is reviewed in chapter 2.1.5.

The most common small vessel vasculitis is Anti-Neutrophilic Cytoplasmic Autoantibody (ANCA) associated vasculitis. ANCA-associated vasculitis causes necrotizing inflammation of small arteries, arterioles and capillaries. There are three different types of ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. (Sunderkötter et al., 2018) IAs are rare in ANCA-associated vasculitis although central-nervous system involvement is common. (Zhang et al., 2019)

Bechet's disease is vasculitis affecting small- to large vessels (Houman et al., 2007). Central nervous system involvement is rare (5-10%) in Bechet syndrome

(Yazici et al., 2018). It is unclear if Bechet's is associated with increased risk for IAs and limited to case reports (Ha et al., 2016).

2.3 Kawasaki disease and related aneurysms

Kawasaki disease is a vasculitis that affects small and medium-sized vessels (Cohen and Sundel, 2016). Kawasaki disease was first discovered in 1967, meaning that since the first confirmed cases are currently 50 to 60 years old (Cohen and Sundel, 2016) all long-term consequences of Kawasaki disease are unknown. Kawasaki disease occurs usually in childhood and predominantly affects children <5 years of age (Cohen and Sundel, 2016. Incidence of Kawasaki disease varies depending on ethnicity. Reported incidence of Kawasaki disease is highest in Japan (265 per 100 000 children) (Singh et al., 2015) and in Finland the incidence is around 10 per 100 000 children (Salo et al., 2012).

The cause of Kawasaki disease is unknown. Several different bacteria's and viruses has been proposed to trigger Kawasaki disease, but specific causative agent has not been found yet. (Rowley et al., 2018)

Kawasaki disease is treated with intravenous immunoglobulin and acetylsalicylic acid. Without treatment, nearly 25% of patients develop coronary artery aneurysm, which is one of the Kawasaki disease complications. (Kato et al., 1996) Around 2% of Kawasaki disease patients develop also peripheral artery aneurysms. Around 10% of patients have aortic root dilation during the acute phase of Kawasaki disease. (Printz et al., 2011).

Histopathological findings of coronary artery aneurysms (Newburger et al., 2016) and intracranial aneurysms resembles each other (Chalouhi et al., 2013. As in sIAs, (Chalouhi et al., 2013) arterial wall inflammation have a crucial role in the coronary artery aneurysm development (Newburger et al., 2016. Like in intracranial aneurysms, (Chalouhi et al., 2013) macrophages and lymphocytes are seen in the coronary artery aneurysm wall (Newburger et al., 2016).

2.3.1 Kawasaki disease and cerebrovascular complications

During the acute onset of Kawasaki disease 1% to 30% of patients with may develop central nervous system symptoms (facial nerve paresis, meningeal irritation, bulging fontanelle, convulsions, somnolence, headache, irritability) (Tizard E, 2005) and 40-60% may have elevated inflammatory cytokines and pleocytosis in cerebrospinal fluid (Korematsu et al., 2007). Cerebral hypoperfusion is reported in 29% to 72% of KD patients even in those without neurological symptoms.

Hypoperfusion can be seen during the acute phase of KD and in some patients (Ichiyama et al., 1998; Hikita et al., 2011).

Ischemic brain infarction is a rare complication in Kawasaki disease and limited to small number of case reports (Wang et al., 2021).

2.4 White Matter Hyperintensities

White matter hyperintensities (WMH) are considered ischemic lesions and a sign of cerebral small vessel disease (Wardlaw et al., 2016). WMHs appear as brain hyperintensities in T2- and FLAIR (Fluid-attenuated inversion recovery) sequences on brain MRI and are common finding in brain MRI in elderly (Wardlaw et al., 2013) (**Figure 4.)**. WMHs are classified according to their location as deep/subcortical and periventricular WMHs (Wardlaw et al., 2013). Prevalence of WMHs is 3% in those under 40 years' of age and the prevalence rises to 60% from the age of 60 (Zhuang et al., 2018). Another risk factors for WMHs are smoking and hypertension (Mok et al., 2015). Association between hypercholesterolemia and WMHs is uncertain (Mok et al., 2015). WMHs are reported in various vasculitis diseases, especially in systemic lupus erythematosus and primary angiitis of the central nervous system (Soun et al., 2019).

Proposed pathophysiological mechanisms for WMHs are hypoperfusion, blood-brain barrier, inflammation and abnormal cerebrovascular reactivity (Alber et al., 2019). Based on pathological studies, WMHs are characterized by demyelination and axonal destruction (Wardlaw et al., 2015). Periventricular WMHs and deep WMHs has differences in histopathological findings and clinical outcomes (Alber et al., 2019), but imaging studies suggest that both are the result of the same continuous pathology (Wardlaw et al., 2015).

Increased WMH burden is associated with higher risk for stroke, dementia, psychiatric disorders and mortality (Au et al., 2006, Debette at al. 2019). WMHs predicts worse prognosis (Uniken et al., 2021) and earlier permanent institutionalization after ischemic stroke (Sibolt et al., 2015).

WMHs are reported in various vasculitis diseases, especially in systemic lupus erythematosus and primary angiitis of the central nervous system (Abdel et al., 2014). Central nervous system involvement in Kawasaki disease is understudied and limited to single case reports of white matter changes during the acute phase of Kawasaki disease (Masiello et al., 2021).

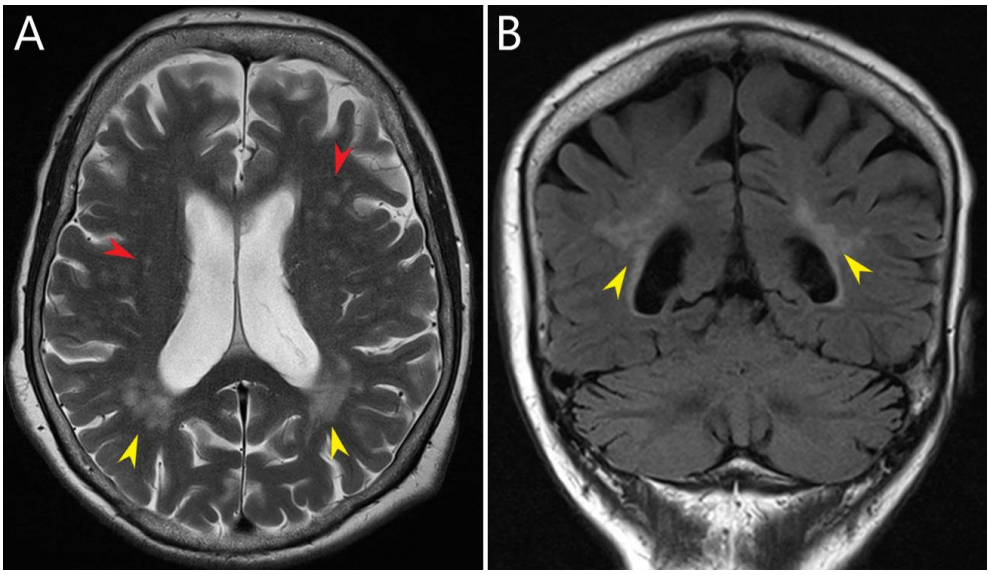


Figure 4. A) Periventricular white matter hyperintensities (yellow arrows) and deep white matter hyperintensities in T2-sequenses. B) Periventricular white matter hyperintensities (yellow arrows) in Fluid-attuenuated inversion recovery (FLAIR) sequenses. (Copyright Dan Laukka)

2.5 Concomitant aortic aneurysms and intracranial aneurysms

Thoracic aortic aneurysms are local dilatation of the ascending aorta, aortic arch or descending thoracic aorta. Thoracic aortic aneurysm is defined as a segmental dilatation of ≥50% compared to non-affected aortic segment (Johnston et al., 1991) or any dilatation over 40 mm (Davies et al., 2002). Prevalence of asymptomatic thoracic aortic aneurysms >5 cm is less than 0.34% in the general population (Itani et al., 2002; Kälsch et al., 2013) and incidental thoracic aortic dilatations (4-5 cm) in 2.7% of general population (Benedetti et al., 2015). Risk of dissection or rupture increases with the aortic diameter (Davies et al., 2002). However, one study suggested that nearly 40% of patients with aortic dissection have aortic diameter <5.0 cm, which is under the recommended diameter for elective surgery (Pape et al., 2007).

Ascending aortic aorta and aortic arch have a different embryological origin than descending thoracic aorta and abdominal aorta. Smooth muscle cells of the ascending aorta and aortic arch develop from neural crest while in descending and abdominal aorta smooth muscle cells develops from the mesoderm. (Kuivaniemi et al., 2015) Genetic risk factors are more predominant in the ascending aorta and aortic

arch aneurysms and traditional cardiovascular risk factors for descending aortic aneurysms. Ascending and aortic arch aortic aneurysms usually do not contain arterial wall atherosclerosis in contrast to descending thoracic aortic and abdominal aortic aneurysms (Elefteriades and Farkas, 2010). Roughly 20% of thoracic aneurysms or dissections shows autosomal dominant pattern of inheritance and several genes has shown to predispose thoracic aortic aneurysms (Pinard et al., 2019). Around 20% of patients with abdominal aortic aneurysms have affected first-degree relative, but like in intracranial aneurysms, causative genes are uncertain (Pinard et al., 2019). Nevertheless, approximately 20% of patients with abdominal aortic aneurysms have concomitant thoracic aortic aneurysm (Gouveia et al., 2020).

Aortic aneurysms and sIAs have overlapping genetic risk factors and comorbidities. Prevalence of sIAs is around 10% in patients with aortic aneurysms (Kuzmik et al., 2010; Rouchaud et al., 2016). Aortic aneurysms could be especially related to fusiform type of IAs (Kurtelius et al., 2019). Connective tissue disorders like Marfan syndrome, Loeys-Dietz and Ehler-Danlos syndrome are risk factors for both, thoracic aortic aneurysms (Erbel et al., 2014) and IAs (Kim et al., 2016). In addition, smoking and hypertension are known risk factors thoracic aortic aneurysms (Hiratzka et al., 2010) and IAs (Vlak et al., 2013).

Bicuspid aortic valve is found in 1-2% of the general population and is the most common congenital valvular disease. Bicuspid aortic valve is associated with ascending aortic dilatation/aneurysms and coarctation of the aorta. From 50% to 70% of patients with bicuspid aortic will develop thoracic aortic dilatation and around 40% thoracic aortic aneurysm and there is a 9-fold risk for thoracic aortic dissections compared to general population. (van De Pol et al., 2017)

In one retrospective study the prevalence of UIAs was 12.9% in patients with bicuspid valve and concomitant coarctation of the aorta and 5.7% in those who had bicuspid valve only (Egbe et al., 2017). Another study showed that patients with aortic coarctation have 5-fold increased risk of intracranial aneurysms (Connolly et al., 2003). Pathophysiological relationship between aortic coarcation and IAs is unclear, but hypertension and inheritance could have important role, whereas in one screening study, no IAs were found in children with the history of aortic coarctation (Donti et al., 2015).

2.6 Fusiform intracranial aneurysms

2.6.1 Epidemiology

Fusiform intracranial aneurysms represent only ~4% of all aneurysms (Saliou et al., 2015) and differ from sIAs by their morphology, pathogenesis, location, and

treatment (Gutierrez et al., 2011). Autopsy studies suggest a population prevalence of < 0.1% for fusiform IAs (Housepian et al., 1958; Hayes et al., 1967).

Fusiform IAs are usually found at older age (mean age 66 years) and are more commonly found in males (64% of patients) (Pico et al., 2015), while patients with sIAs are younger (40-60 years old) and are found more often in females (Vlak et al. 2011).

Symptomatic fusiform IAs are usually presenting with ischemic symptoms (28% of patients) or local mass lesion (22% of patients), while only 3% are caused by SAH. (Flemming et al., 2005) Nearly 50% of fusiform IAs locate in the posterior circulation (Sacho et al. 2014)

2.6.2 Risk factors

Risk factors for fusiform IAs are not well established, but fusiform IAs are often perceived to be related to dissection or atherosclerosis, (Anson et al., 1996) and common associated comorbidities are accordingly hypertension, smoking, hyperlipidemia, diabetes mellitus, coronary artery disease and peripheral artery disease. (Nasr et al., 2018) Genetic risk factors are not well established for fusiform IAs, but about 4% present with a connective tissue disease including autosomal-dominant polycystic kidney disease or Fabry's disease. (Serrone et al., 2014) Unlike sIAs, fusiform IAs are more common in male (2 to 1) (Echiverri et al., 1989).

Estimated annual rupture risk for fusiform IAs is 0.9% and aneurysms ≥10 mm are more prone to rupture in the future (Flemming et al., 2004). Symptomatic fusiform IA or fusiform aneurysms >7 mm in diameter have increased risk of enlargement and especially atherosclerotic fusiform IAs are related with higher risk of progression and worse prognosis (Sacho et al., 2014).

2.6.3 Outcome of symptomatic fusiform aneurysms

Ruptured fusiform IAs are rare and account only 4.5% of all SAH (Sasaki et al., 1991). If a ruptured fusiform IA is left untreated, there is an almost 50% risk of mortality and about a 70% risk of rebleeding (Mizutani et al., 1995).

Patients who presents with mass effect from fusiform IA are at a high risk of poor outcome, the risk of mortality is 40% during the first 4 years after the first symptoms. (Shapiro et al., 2014) Rupture risk of vertrebrobasilar fusiform IAs is 3%/year and risk of ischemic stroke is 8%/year (Nasr et al. 2018).

2.7 Treatment of intracranial aneurysms

IAs can be treated with surgical or endovascular operations. The main goal of these treatments is to block out IA from the blood circulation and prevent IA sac from filling with blood.

This chapter reviews basic surgical and endovascular treatment options for IAs. Specific treatments for UIAs and rIAs are reviewed in the chapter 2.4. Treatment of fusiform IAs is reviewed separately in the chapter 2.4.3

2.7.1 Surgery

2.7.1.1 Clipping

First aneurysm clipping was performed by Walter Dandy in 1938. (Dandy WE, 1938) Microneurosurgical era began when the operating microscope was introduced in the 1960s, resulting in dramatic improvement in surgical outcomes.

In the aneurysm clipping a metal clip is inserted into the aneurysm neck, which stops blood flow into the aneurysm sac (**Figure 5)**. Usually proximal parent artery is prepared before the aneurysm sac exposure. Visualization of the proximal parent artery is crucial for two major reasons. First, in most of the cases proximal parent artery is occluded with the temporary clip before the aneurysm ligation. Temporary parent artery clip decreases intra-aneurysmal pressure and makes aneurysm ligation easier. Second, intraoperative aneurysm rupture may occur in up to 19% patients and occlusion of the parent artery is necessary to control the bleeding. (Elijovich et al 2008).

After the clipping, intraoperative angiography or Indocyanine Green Video angiography is recommended to confirm the patency of the parent artery, branching and distal arteries. While around 10% needs immediate adjustment of the clip because of miss-clipping (Riva et al., 2018).

There are various surgical approaches depending on aneurysm location.

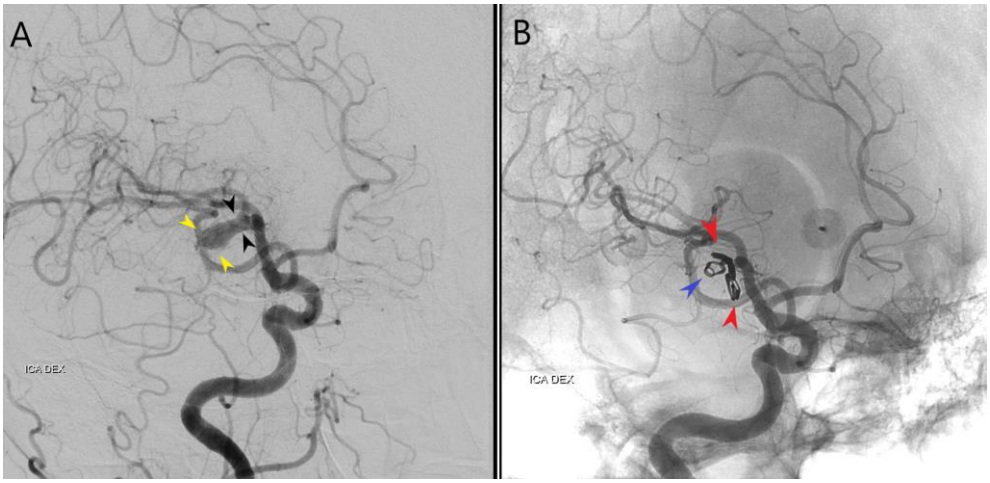


Figure 5. Digital subtraction angiography images showing intracranial saccular aneurysm before clipping (A) and after clipping (B). (A) Saccular intracranial aneurysms with neck (black arrows) and filling sac (yellow arrows). Optimal insertion of the clip is usually base of the neck (black arrows). (B) Two clips (Clip no.1=red arrows, Clip no.2= blue arrow) has been successfully inserted at the base of the neck, preventing aneurysm sac from filling. (Copyright Dan Laukka)

2.7.1.2 Bypass

Bypass surgery can be used in the treatment of complex IAs (giant IAs, non-sIAs, thrombosed aneurysms, calcified aneurysms etc.) in the situations where aneurysm is difficult or impossible to treat with conventional surgical/endovascular treatment and without preserving the parent artery (Wessels et al., 2018)

In the bypass surgery parent artery is trapped proximally and/or distally in relation to IA and bypass craft is inserted distal to aneurysms to ensure distal blood flow. Parent artery can be trapped with endovascular coiling or with surgical clipping (Wessels et al., 2018).

Two main types of bypasses are extracranial – intracranial (EC-IC) and intracranial – intracranial bypass (IC-IC) (Wessels et al., 2018).

In the EC-IC bypass surgery, extracranial artery works as a donor. The most common donor arteries are superior temporal artery and external carotid artery. Depending on the donor and recipient arteries bypass type can be divided to standard flow, intermediate flow and high flow (Wessels et al., 2018).

In situ bypass surgery, reimplantation, reanastomosis and intracranial bypass with grafts can be used in IC-IC bypass surgery (Sanai et al., 2009).

2.7.2 Endovascular

2.7.2.1 Flow diverter stent

Flow diverter stents (FD) are relatively new innovation in the treatment of IAs. Currently there are five different FDs available, Pipeline embolization device (ev3/Covidien/Medtronic), Surpass stent (Stryker Neurovascular), Flow-Redirection Endoluminal Device (FRED, MicroVention, Inc.), SILK stent (Balt Extrusion), and p64 Flow Modulation Device (Phenox). FDA have approved Pipeline Embolization Device (in year 2011) and Surpass Streamline flowdiverter stent (in year 2018) for the wide neck large or giant sIAs or fusiform intracranial aneurysms, located in the internal carotid artery with a diameter between 2.5 mm and 5.3 mm. However, "off label" use of FD to treat different aneurysms in various different locations has widely been used (Limbucci et al., 2020).

Each FD differs slightly from each other in terms of their structure (mesh porosity, size and material) and properties. Unlike other FDs, FRED flow diverter stent consists of two layers, low-porosity inner layer and high-porosity outer layer. This two-layer feature could provide better aneurysm occlusion and deliverability, but there is no evidence of better occlusion rates or clinical outcomes compared to PED stents. (Karsy et al., 2017; Griessenauer et al., 2018)

FD is placed into the parent artery in the site of the aneurysm. Initially after the FD placement, intra-aneurysmal blood flow decreases which causes an intra-aneurysmal thrombosis (Gester et al., 2016). After around a week to eight weeks endothelial cells grows along the stent and aneurysm neck, which is further leading to aneurysm occlusion (Kadirvel et al., 2014).

Patients who are treated with FD requires dual antiplatelet therapy to prevent thromboembolic complications. Symptomatic thromboembolic complications occur in 2-8% of patients and ischemic complication rates of 22.5% have been reported in posterior circulation aneurysms (Adeeb et al., 2018).

Intraprocedural stent thrombosis occurs in 5% of patients who are treated with FD or stent assisted coiling. Recanalization of stent thrombosis is achieved in 82% of cases. Despite successful treatment of stent thrombosis about 21% of patients will have ischemic stroke. Younger age, smoking and incomplete recanalization increases the risk for ischemic stroke after the stent thrombosis (Adeeb et al., 2017).

In post-operative MRI imaging, ischemic lesions are found in 54% of patients who are treated with FD, which is comparable with those who are treated with coiling (ischemic lesions in 64% of patients), balloon-assisted coiling (ischemic lesions in 54% of patients) or stent assisted coiling (ischemic lesions in 61% of patients). Despite quite high rate of ischemic lesions, they do not significantly correlate with clinical outcome or procedure related complications (Iosif et al., 2018).

Hemorrhagic complications are related to FD treatment. Delayed intraparenchymal hemorrhage occurs in 2-3% of patients after the FD treatment (Brinjikji et al., 2013) and 66% of these hemorrhages occurs within a week and 14% after a one month from the treatment (Rouchaud et al., 2016).

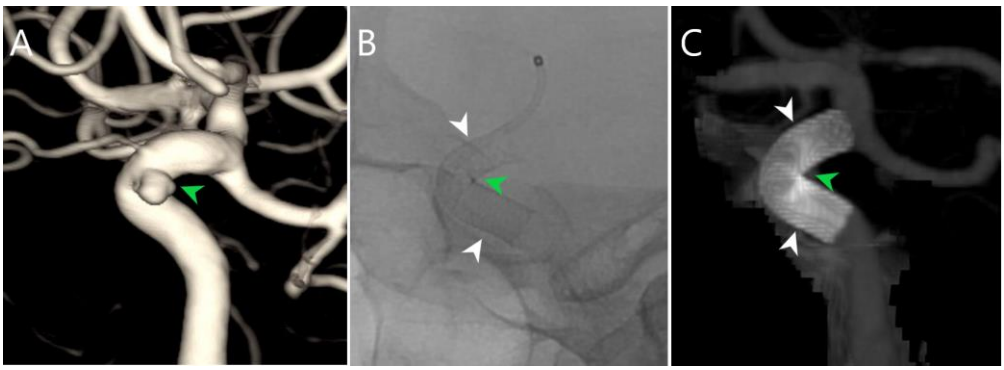


Figure 6. Digital subtraction angiography images presenting flow diverter stent treatment (B, C) of righ internal carotid artery aneurysm (A). (A) Unruptured intracranial aneurysm in the righ internal carotid artery at the level of right ophthalmic artery (green arrow). (B) and (C): Flow diverter stent inserted in the right internal carotid artery (white arrows), covering the intracranial aneurysm (green arrow) and reducing the aneurysm filling after the flow diverter insertion. (Copyright Dan Laukka)

2.7.2.2 Coiling

Coil embolization was introduced in 1991 for the treatment of intracranial aneurysms (Guglielmi et al., 1991) and was approved by FDA in 1995. In this treatment, platinum coils are inserted in the intracranial aneurysm sac. Coils decrease aneurysmal filling and cause intra-aneurysmal thrombosis, which eventually leads to aneurysm occlusion (Dovey et al., 2001).

Traditionally, coiling alone is suitable for sIAs with narrow neck (neck diameter <4 mm, dome-to-neck ratio <2), because in the wide neck aneurysms coils can easily protrude into the parent artery. However, three dimensional coils, balloon assisted coiling and stent assisted coiling has enabled the coil embolization treatment of wide necked aneurysms. (Seibert et al., 2011)

In the balloon assisted coiling, balloon is placed in the parent artery across the aneurysm neck and then temporary inflated. After the balloon inflation coils are placed in the aneurysm. Advantages of balloon assisted coiling are dense coil packing and prevention of coil protrusion.

In the stent assisted coiling stent is inserted in the parent artery across the aneurysm. Coils can be inserted through the stent ("coil-through"), with "jailing" technique in which microcatheter is inserted in the aneurysm before stent deployment, or with "coil stent" technique in which aneurysm is coiled before the stent deployment. Another option is also balloon-stenting in which aneurysm is coiled with balloon assistance before the stent deployment. (Spiotta et al., 2012) In analogue with FDs stent assisted coiling requires dual antiplatelet therapy for the prevention of stent-thrombosis.

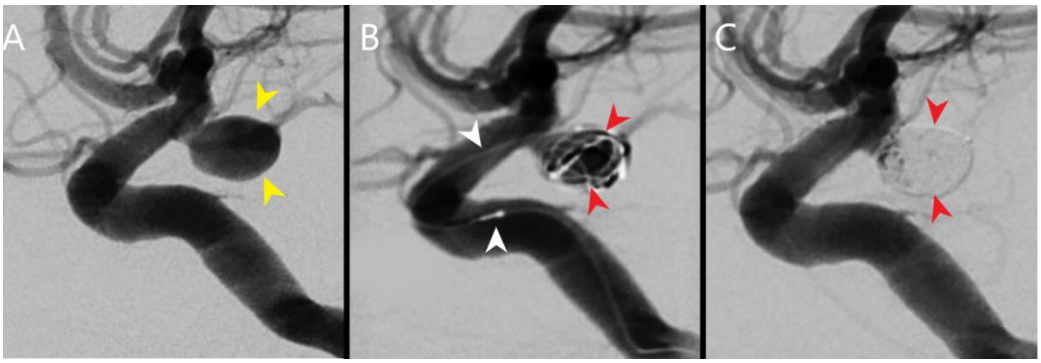


Figure 7. Digital subtraction images presenting endovascular coiling of the right internal carotid artery aneurysm. (Copyright Dan Laukka) (A) Saccular intracranial aneurysm in the right internal carotid artery (yellow arrows). (B) Coils are inserted in to the intracranial aneurysm (red arrows) through the guiding wire (white arrows). (Copyright Dan Laukka)

2.7.2.3 Woven EndoBridge (WEB) Aneurysm Embolization System

Woven EndoBridge (WEB) Aneurysm Embolization System is self-expanding mesh ball which is made of nitinol (nickel titanium). WEB embolization device is developed for the treatment of wide neck saccular aneurysms locating at the branching arteries. WEB embolization device received FDA approval in 2018 for sIAs located in middle cerebral artery, anterior communicating artery, internal carotid artery or basilar artery bifurcations and with a dome diameter 3 mm to 10 mm and either neck size 4 mm or greater or the dome-to-neck ratio from 1 to 2.

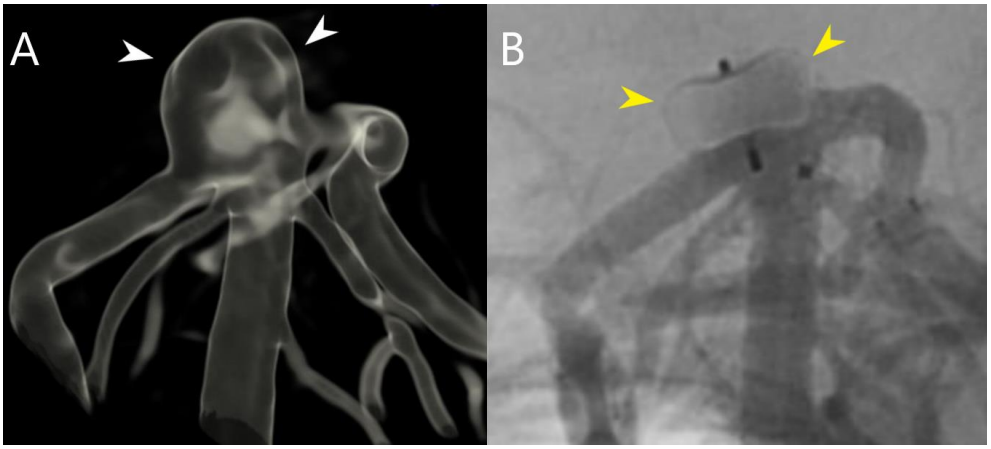


Figure 8. Digital subtraction angiography images presenting WEB-embolization of the saccular basilar artery tip aneurysm. (A) Wide-necked saccular intracranial aneurysm (white arrows) on the tip of the basilar artery. (B): WEB-embolization device inserted inside the intracranial aneurysms (yellow arrows). (Copyright Dan Laukka)

2.8 Management

2.8.1 Unruptured IAs

Unruptured sIAs can be treated with surgical or endovascular treatment or with follow-up. Treatment is evaluated in multidisciplinary neurovascular team and tailored for each patient individually. Patient and aneurysm characteristics determines the treatment modality. Small aneurysms (<3 mm) are considered to have small rupture risk and follow-up with imaging is preferred option over the surgical or endovascular treatment. Aneurysms that grow on the follow-up have a higher rupture risk and thus recommended for treatment. (Etminan et al. 2022)

In selected cases endovascular coiling is better option for UIAs over the clipping. For example, in elderly patients with a posterior circulation saccular UIA endovascular coiling could be better option. (Thompson et al. 2015) There are only a few small randomized studies which have compared surgical clipping and endovascular coiling of the unruptured IAs. Koivisto et al., 2000 study was one of the first randomized studies that compared results of coiling and clipping. They found comparable results between coiling and clipping at one year after treatment of ruptured IA. (Koivisto et al., 2000). In the small trial of Darsaut et al., 2016 there were no difference in patient outcomes between clipping and coiling at 1 year after the treatment, although surgical clipping was associated with longer hospitalization and mild neurological deficits (Darsaut et al., 2016). Posterior circulation aneurysms

were clearly underrepresented in this study. In the ISUA study, from the year 2003, mortality and morbidity rates were 1.8% and 4.7% relating to surgical treatment of UIAs and 2.0% and 9.3% relating to endovascular coiling of UIAs. (Wiebers et al., 2003) One of the disadvantages of coiling is a risk of incomplete occlusion and residual aneurysm flow which could demand retreatment. Retreatment rates are lower in surgical clipping compared to endovascular coiling (Lad et al., 2013). In the endovascular coiling, retreatments could increase long term overall morbidity compared to surgical clipping. After coiling, recurrence rate of 14% have been reported even after the initial complete occlusion of aneurysm (Darlginfer et al., 2016). Overall re-treatment rate after coiling is around 5% and annual rupture risk of coiled aneurysm is around 0.1% in the long-term follow-up. It is not surprising that larger aneurysms are at higher risk of retreatment after coiling. (Koyanagi et al., 2018)

Flow diverter stent treatment could be considered for IAs which are evaluated to carry high risk with other treatment methods, usually these kind of aneurysms are complex by its morphology and/or location. For example giant aneurysms, fusiform aneurysms and aneurysms with a wide neck could be suitable for flow diverter stent treatment. (Chua et al., 2019) In one meta-analysis, the complication rate was 14.6% related to flow diverter stent treatment of UIAs. In one meta-analysis, the complication rate related to flow diver stent treatment of UIAs was 14.6% (Zhou et al., 2017).

2.8.2 Ruptured IAs

2.8.2.1 Management of aneurysmal subarachnoid hemorrhage

Treatment of ruptured IAs are based on the treatment of IA and prevention of the SAH complications.

Ruptured IAs should be treated at least <72 hours after the rupture (Steiner et al. 2013) and and possibly optimal treatment is within 12-24 hours of the rupture (Buscot et al., 2022). Ruptured IAs can be treated with the surgical or endovascular treatment. Main goal of the rIA treatment is to prevent it from rebleeding, because rebleeding is associated with high mortality and poor outcome. Without IA treatment, around 30% will experience rebleeding within a month (Locksley et al., 1966) and 60% of these patients will die and 30% of survivors will stay dependent for daily living (Naidech et al., 2005).

2.8.2.1.1 Hydrocephalus

Patients with hydrocephalus requires external ventricular drainage to lower intracranial pressure. Especially patients with poor neurological status at admission and dilated ventricles should be treated with EVD. About 15-58% of patients with acute SAH have hydrocephalus at first days (Xie et al., 2017) and around 20% of patients requires ventriculoperitoneal shunt (O'Kelly et al., 2009). In patients with good neurological status, but enlarged ventricles, can be observed closely without EVD.

2.8.2.1.2 Vasospasm

One of the recognized complications of SAH is vasospasm (= narrowing of the cerebral artery/arteries), which can lead to brain infarction. Risk of vasospasm usually begin on the third day of bleeding and lasts up to 21 days. The highest risk for vasospasm is between 5-14 days. Roughly 70% of aneurysmal SAH patients develops vasospasm, but only 30% develops neurological symptoms from vasospasm. Delayed cerebral ischemic lesions are found in up to 40% in patients with aneurysmal SAH. (Budohoski et al., 2014) To prevent vasospasm, calcium channel blocker (nimodipine) is administered routinely in SAH patients. Nimodipine decreases delayed cerebral ischemia and improves clinical outcomes (Velat et al., 2011).

In patients with symptomatic vasospasm blood pressure level should be elevated and in cases where symptoms do not resolve with blood pressure management, intra-arterial nimodipine or angioplasty can be used. (Bauer et al., 2014)

2.8.2.1.3 Tranexamic acid

At admission tranexamic acid are administered for three days or until aneurysm has been treated to prevent rebleeding (Connolly et al., 2012). Although antifibrinolytic therapy reduces rebleeding rates approximately 35%, it is related with higher risk for cerebral ischemia and do not improve clinical outcome (Baharoglu et al., 2013).

2.8.2.2 Aneurysm treatment

In the recent Cochrane analysis which compared outcomes between the surgical clipping and endovascular coiling of rIAs, endovascular coiling was considered better treatment option in both anterior and posterior circulation rIAs if both treatment modalities was feasible. In the surgery group, 32% had poor outcome and 11% died after one year of treatment, while in the endovascular group, 24% had poor

outcome and 9% died at the same time point. In this analysis, endovascular coiling was related with reduced risk for poor outcome risk ratio 0.77 (95% CI, 0.67-0.87) and reduced mortality at 12 months risk ratio 0.8 (95% CI, 0.63-1.02). Despite better outcomes of endovascular coiling, there are higher risk of rebleeding in the endovascular coiling compared to surgical clipping at one year (relative risk 1.83; 95% CI, 1.04-3.23) and at 10 years (relative risk 2.69; 95% CI, 1.5-4.81). (Lindgren et al. 2018)

Guidelines recommend surgical clipping in ruptured middle cerebral arteries and in patients with a large hematoma (>50ml) associating with rIA. (Connoly et al., 2012)

Studies about flow diverter treatment of ruptured sIAs are scarce and based on small series. The main problem of flow diverter stents in the setting of acute SAH is requirement of dual antiplatelet therapy. Dual antiplatelet therapy increases the risk for hemorrhagic surgical complications, while SAH patients may need neurosurgical procedures such as EVD, ventriculoperitoneal shunt and craniotomy or craniectomy. Dual antiplatelet therapy is associated with increased risk hemorrhagic complications related to EVD insertion. In SAH patients with dual antiplatelet therapy, radiographic hemorrhage is seen in 26.7% and symptomatic hemorrhages in 8.3% (Hudson et al., 2019). If endovascular stent treatment is anticipated and patient most likely requires EVD (hydrocephalus, intraventricular hemorrhage, altered consciousness), EVD placement should be considered to be done before the aneurysm treatment to minimize hemorrhagic complication risk (Cohen et al., 2018).

In the meta-analysis of Dossani et al., 2019, the overall mortality rate of 15.5% and complication rate of 27.5% were related to flow diverter stent treatment of rIAs. Re-rupture rate was 3.5% and mortality rate relating to re-rupture was 100%. In the stent assisted coiling of rIAs, mortality rate of 19%, ischemic and hemorrhagic complications of 13% and re-rupture rate of 5% has been reported (Bodily et al., 2011).

WEB embolization device could be a viable option for wide neck rIAs with a favorable outcome of 55%, which is comparable with endovascular clipping or coiling. (Sauvigny et al., 2019) With WEB embolization device, sufficient occlusion rate can be achieved in 85% of treated rIAs or UIAs. (Arthur et al., 2019)

Stent assisted coiling requires dual antiplatelet therapy in the same way as flow diverter stents and could complicate the treatment of acutely ruptured IA. Stent assisted coiling carries significantly higher complication risk compared to conventional coiling in the setting of acute SAH. Complication rate can reach 20.2% in stent assisted coiling which is nearly two times higher than in conventional coiling. However, in stent assisted coiling mortality rate is 6% and favorable outcome is achieved in 73% of patients, which are comparable with outcomes in conventional coiling. In contrast, aneurysm occlusion rates are higher in stents

assisted coiling compared to conventional coiling (73% vs 61%) and carries lower aneurysm recurrence rates (5% vs 17%). (Zhang et al., 2018)

2.8.3 Fusiform IAs

Fusiform intracranial aneurysms are considered complex because of its morphology and because they usually locate in the posterior circulation (Coert et al., 2007). Fusiform intracranial aneurysms can be treated with deconstructive techniques (surgical or endovascular trapping of parent artery) or with reconstructive techniques (trapping with bypass, endovascular stenting) (Awad et al., 2017).

Deconstructive techniques carry high risk of ischemic complications and could be more suitable for aneurysms located in distal non-dominant arteries (posterior inferior cerebellar artery aneurysms, anterior inferior cerebellar artery and superior cerebellar artery) (Awad et al., 2017). Deconstructive treatment of ruptured non-saccular vertebrobasilar IAs carry a risk of 14% morbidity and 13% mortality, and neurological complications may occur in up to 31% of patients (Awad et al., 2017).

In one series 21.9% and 24% of poor outcomes were associated with surgical treatment of unruptured giant fusiform IAs located in posterior circulation and anterior circulation respectively (Drake et al., 1997).

Treatment of ruptured fusiform IAs with flow diverters are limited to small studies or case reports. In the report of Maus et al., 2018, fifteen patients with a ruptured posterior circulation non-saccular aneurysm were treated with flow diverter stent with a technical success rate of 93% and with no aneurysm re-rupture. In their series, mortality rate was 47%, though all of the patients who died were poor grade subarachnoid hemorrhage (World Federation of Neurosurgical Societies grading 4 or 5). (Maus et al., 2018)

Good clinical outcomes of 95% have been achieved for unruptured non-saccular posterior circulation aneurysms, with a complication rate of 7.1%, and complete occlusion rate of 90.2% (Wang et al., 2019).

3 Aims of the study

Study I Is childhood Kawasaki disease associated with increased risk for intracranial aneurysms in adulthood?

Study II Is childhood Kawasaki disease associated with increased risk for white matter hyperintensities in adulthood?

Study III Are saccular IAs related to increased risk for thoracic aortic aneurysms or dilatations?

Study IV What are the outcomes of the flow diverter stent treatment for acutely ruptured posterior circulation fusiform IAs?

4 Study I: Unlikely association between Kawasaki disease and intracranial aneurysms: a prospective cohort study.

Abstract. Kawasaki disease (KD) is a vasculitis that can cause aneurysm formation in coronary arteries and, more rarely, in peripheral arteries. A possible connection between KD and intracranial aneurysms is unclear. The purpose of this study was to determine if KD is associated with intracranial aneurysms. In this prospective cohort study, all patients hospitalized and diagnosed with KD in the authors' hospital district area in the period from 1978 to 1995 were identified. Patients with a current age ≥ 25 years and a history of KD in childhood were included in the study, which was conducted between 2016 and 2017. Magnetic resonance angiography (MRA) of the brain was performed in all patients. Forty patients (25 males), whose mean age was 33.5 ± 3.9 years (mean ± standard deviation), were eligible for study inclusion. The mean age at KD diagnosis was 3.9 ± 3.1 years, and the mean follow-up was 29.5 ± 4.3 years. Six patients (15%) had coronary arterial lesions during the acute illness of KD. None of the patients (0%) had intracranial aneurysms on brain MRA, which is significantly under the prevalence of 10% (95% CI, 0%-8.8%, p = 0.03) that is the recommended limit for intracranial aneurysm screening. The study results suggest that KD is not associated with an increased prevalence of intracranial aneurysms and that screening for intracranial aneurysms is not warranted in patients with a history of KD.

4.1 Introduction

Kawasaki disease (KD) is a vasculitis that affects small and medium-sized vessels and usually occurs in childhood. (Cohen and Sundel, 2016) Its incidence varies among different countries from 3.4 cases/100,000 persons in Thailand to 265 cases/100,000 persons in Japan. (Singh et al., 2015) In Finland the incidence is 11 cases/100,000 persons. (Salo et al., 2012) Coronary artery aneurysms are the most recognized complication of KD and develop in approximately 25% of patients without immunoglobulin treatment. (Kato et al., 1996) Systemic artery aneurysms have been reported in up to approximately 2% of KD patients. (Kato et al., 2016)

The mechanism of intracranial aneurysm formation is poorly understood and multifactorial, however, as in KD, inflammation plays an important role in the pathogenesis of aneurysm formation. In addition, vascular histopathological findings are similar between KD and intracranial aneurysms. (Chalouhi et al., 2013; Newburger et al., 2016) A possible connection between KD and intracranial aneurysms is unknown, and very few long-term follow-up studies have focused on this area. (Muneuchi et al., 2006)

Therefore, the aim of our study was to determine if the prevalence of unruptured intracranial aneurysms is higher in adult patients who had KD in childhood than in the general population.

4.2 Materials and Methods

4.2.1 Study Patients

This study was approved by the local Ethics Committee Hospital District of Southwest Finland. Written informed consent was obtained for all participants.

This prospective cohort study was conducted at our hospital between 2016 and 2017. Our neurosurgical department is responsible for the treatment and evaluation of all diagnosed intracranial aneurysms in our hospital district area (approximately 870,000 persons). All possible deaths are updated automatically in the electronic patient record system that our hospital uses.

Patients with KD who had been treated and diagnosed in our hospital district area between the years 1978 and 1995 were retrospectively identified using a diagnostic code (ICD-9 code 446.1 and ICD-10 code M30.3). Patients with a current age ≥ 25 years and a history of KD in childhood were included in our study, and hospital records were reviewed to confirm the diagnosis. The diagnosis of KD was based on the American Heart Association (AHA) 2004 diagnostic criteria for complete KD. (Newburger et al., 2004)

Eighty-seven patients were diagnosed with KD in the period between 1978 and 1995. According to a retrospective review of the medical records, all 87 patients were alive, and none had been diagnosed with intracranial bleedings or intracranial aneurysms. We sent a study invitation letter to 60 patients who fulfilled our study criterion of a current age ≥ 25 years, the remaining 27 patients had ages < 25 years and were excluded from the study. Of these 60 patients, 40 consented to participate in our study. Despite repeated invitation letters, the other 20 patients did not respond to the study invitation.

All participants underwent brain MR angiography (MRA) at our hospital. Prior to the MRA, patients were interviewed to gather all medical history and any history of intracranial aneurysms in patient relatives. Information about the medical treatment of KD and coronary artery lesions was collected from old patient records.

The time of flight (TOF) angiography technique was used to evaluate cerebral arteries. MRA scans were obtained on a Philips Ingenia 3-T scanner (Philips Medical Systems). MRA using a TOF sequence with a TR of 23 msec, TE of 3.5 msec, matrix of 640 × 640, and slice thickness of 1.2 mm was performed to evaluate arteries of the brain. The TOF images were interpreted, and 3D reconstructions in two different planes were created and interpreted.

Brain imaging studies were evaluated by a neuroradiologist (R.P.) with over 24 years' experience in neuroradiology. We did not use blinded radiological evaluation in this nonrandomized study setting.

4.2.2 Statistical Analysis

The 95% confidence intervals for the prevalence of aneurysms were computed based on the exact binomial distribution using the Clopper-Pearson estimation method and compared to an expected prevalence of 10%.7 Statistical analyses were done with the SAS system for Windows (version 9.4, SAS Institute Inc.). A p value < 0.05 was considered as statistically significant. Assuming that the prevalence of unruptured intracranial aneurysms is 0% in patients with KD, a sample size of 36 patients would provide a statistically significant difference from the prevalence of 10%, with 80% power and a 2-sided p value < 0.05. Values are expressed as the mean ± standard deviation.

4.3 Results

Forty patients participated our study and underwent brain MRA examination. Patient characteristics are listed in Table 1. The mean age at follow-up was 33.5 ± 3.9 years (range 25.2–40.4 years), and 25 of the 40 patients were males. The mean follow-up time was 29.5 ± 4.3 years (range 20.7–38.9 years), and mean age at

diagnosis of KD was 3.9 years (range 0.25–11 years). According to the medical charts, 2 patients had a coronary artery aneurysm and 4 had coronary artery dilation at the onset of KD, and no coronary artery lesions were found on routine follow-up with ultrasound. None of the patients had a history of intracranial bleedings, connective tissue disorders, or polycystic kidney disease. One patient reported a ruptured intracranial aneurysm in one first-degree relative. Fourteen (35.0%) patients were active smokers, 7 (17.5%) were ex-smokers, and 19 (47.5%) were never smokers. One (2.5%) patient had hypertension. None of the patients experienced neurological symptoms after the onset of KD.

Table 1. Demographic and clinical characteristics of 40 KD patients with brain MRA

Characteristic	**Value**
Mean age at FU in yrs (SD)	33.5 (3.9)
Male sex, no. (%)	25 (62.5%)
Mean age at diagnosis of KD in yrs (SD)	3.9 (3.1)
Management of KD, no. (%)	
IVIG	3 (7.5%)
IVIG + ASA	18 (45%)
ASA	12 (30%)
Antibiotics	3 (7.5%)
No treatment	1 (2.5)
Data not available	3 (7.5%)
Mean FU in years (SD)	29.5 (4.3)
Coronary artery aneurysm, no. (%)	2 (5%)
Coronary artery dilation, no. (%)	4 (10%)
Active smokers, no. (%)	14 (35%)
Ex-smokers, no. (%)	7 (17.5%)
Hypertension, no. (%)	1 (2.5%)

ASA = acetylsalicylic acid, FU = follow-up, IVIG = intravenous immunoglobulin, SD = standard deviation. (Table 1, from Laukka et al. 2019 study)

4.4 Discussion

Although KD was first described in the 1960s in Japan14 and about 10 years later in the United States16 and Europe, (Uehara et al., 2012) all the possible long-term consequences of this disease are still unknown. Aneurysm formation in the coronary arteries and, more rarely, in the peripheral arteries is characteristic of KD. Although vasculitis also affects the cerebral arteries in KD, the possible risk of intracranial aneurysms has not been well evaluated.

Our unique study showed that childhood KD is unlikely to be associated with intracranial aneurysm formation over a long-term follow-up of 30 years (21–39 years). We did not find any intracranial aneurysms in the 40 patients with a history of KD. To our knowledge, there have been no other long-term follow-up studies with brain MRA in KD patients.

There were several reasons to conduct this study. First, there are 15 case reports of intracranial aneurysms (73% ruptured aneurysms) related to polyarteritis nodosa, (Gupta et al., 2013) which is considered equivalent to KD in the infantile form, (Landing et al., 1977) and 3 case reports of aneurysmal subarachnoid hemorrhage in KD patients. Ahn et al; Tanaka et al; and Ishida et al., have reported aneurysmal subarachnoid hemorrhage after KD in a 13-month-old, a 12-year-old, and a 20-year-old patient, respectively. (Ahn et al., 2010; Ishida et al., 2014; Tanaka et al., 2007) In the reports of Tanaka et al. 2014 and Ishida et al. 2007, histopathological examinations of ruptured intracranial aneurysms revealed inflammatory changes similar to those in the coronary arteries in KD. (Ishida et al., 2014; Tanaka et al., 2007) Second, the mechanism of coronary artery aneurysm formation resembles intracranial aneurysm formation. In coronary artery aneurysms and intracranial aneurysms, T cells, monocytes, and macrophages are seen in the vessel wall, leading to destruction of the media and eventually aneurysm formation. (Burns and Glode 2004; Turjman et al., 2014) We theorized that patients with KD might have an increased risk of intracranial aneurysm formation with the same mechanism as coronary artery aneurysm formation because mild cerebral vasculitis has been found in 35.7% of KD patients in an autopsy study. (Amano and Hazama 1980) In addition, localized cerebral hypoperfusion has been reported in 29%–72% of KD patients without neurological symptoms during the acute illness (Hikita et al., 2011; Ichiyama et al., 1998) and lasting even several months after the acute illness, (Hikita et al., 2011) possibly indicating cerebral vasculitis. Also, neurological complications occur in 1%–30% of KD patients, including irritability, aseptic meningitis, lethargy, transient hemiplegia, cerebral infarction, ataxia, seizures, and focal encephalopathy. (Tizard 2005)

Finally, only one previous study has investigated cerebral arteries in the follow-up after KD. (Crawley et al., 1999) Muneuchi et al.,'s 2006 study (Muneuchi et al., 2006) included 24 patients with a median age of 8.9 years and a median follow-up

of 6.8 years, whereas our study included 40 patients with a median age of 34 years and median follow-up of 30 years. Only 6 patients had coronary artery involvement in our study, but in accordance with our findings, Muneuchi et al., did not find any intracranial aneurysms in the KD patients despite the fact that these authors included only patients with coronary artery aneurysms. Most of the coronary aneurysms regress within 2 years after the onset of KD, (Friedman et al., 2016) but it is very unlikely that intracranial aneurysms would regress in the same way in KD patients during long-term follow-up because once an intracranial aneurysm is diagnosed, it usually grows or remains stable. (Morita et al., 2012)

The estimated overall prevalence of unruptured intracranial aneurysms is 3.2% in the general population with no significant difference among different countries. The prevalence of unruptured aneurysms increases with age, especially after the third decade of life. (Vlak et al., 2011) Because most of the aneurysms do not rupture and there are significant risks of treatment-related complications, screening is not recommended for the general population and is only warranted in patients with a high risk of intracranial aneurysm formation and rupture. The prevalence of unruptured intracranial aneurysms is approximately 10% in high-risk populations, such as patients with ≥ 2 affected first degree relatives, autosomal-dominant polycystic kidney disease, or Ehlers-Danlos syndrome, thus, intracranial aneurysm screening is recommended in these patients. (Thompson et al., 2015) We chose to include patients with ages ≥ 25 years because very few studies have evaluated the prevalence of unruptured intracranial aneurysms in young patients (age < 30 years) (Vlak et al., 2011) and unruptured intracranial aneurysms are extremely rare in patients younger than 25 years old even in those with a family history of intracranial aneurysms. (Bor et al., 2014) Other reasons were that we wanted to maximize the follow-up time and there is a national consensus in Finland that the intracranial aneurysm screening age starts at 25 years. Previous studies have concluded that intracranial aneurysm screening is not effective unless the expected prevalence of intracranial aneurysms is > 10%. (Gupta et al., 2013) We found that the prevalence of intracranial aneurysms was 0% in KD patients with a confidence interval of 0%–8.8%, which is comparable to that in the general population30 and significantly lower than the recommended screening limit7 of 10% ($p = 0.030$).

4.5 Limitations

Although only 40 patients took part in our study, it is the largest and longest follow-up study with brain MRA in KD patients to this day and is sufficient to show that the prevalence of intracranial aneurysms is comparable with that in the general population.

The cause of KD is unknown. The incidence of KD varies among different ethnicities, which may suggest that there are genetic risk factors for KD. Identified susceptibility genes for KD have not been shown to explain differences in incidence rates. (Onouchi 2018) Several different bacteria and viruses have also been proposed to trigger KD. (Rowley 2018) Although there seems to be an ethnic contribution to KD, the diagnostic criteria for complete KD are the same globally, (Newburger et al., 2004) and our results probably have good generalizability with other countries.

Because of the inclusion criterion for age (≥ 25 years), most patients in this study were diagnosed with KD before the 1990s. Treatment of KD could have been more variable in the late 1970s to mid-1980s. According to the retrospective review of patient records in our study, the clinical characteristics of KD were the same from 1978 to 1995 and fulfilled the diagnostic criteria for complete KD, not leading to significant selection bias. However, KD diagnosis is based on clinical criteria, and it is possible that some of the patients may have originally suffered from another condition mimicking KD, but as no intracranial aneurysms were found, this does not contradict our findings.

4.6 Conclusions

Our results suggest that KD is unlikely to be related to an increased risk for intracranial aneurysms and that screening for intracranial aneurysms is unnecessary in patients with a history of KD.

5 Study II: Brain White Matter Hyperintensities in Kawasaki Disease: a prospective case-control study

Abstract. Cerebrovascular involvement of Kawasaki disease (KD) is poorly studied. White matter hyperintensities (WMH) indicate cerebral small vessel disease and increase the risk for stroke. We investigated whether childhood KD is associated with WMHs and other cerebrovascular findings later in adulthood. In this case-control study, patients diagnosed with KD (cases) at our tertiary hospital between 1978 and 1995 were invited to brain magnetic resonance (MRI) between 2016 and 2017. Migraine patients (controls) with available brain MRI were matched with cases (ratio 4:1) by age (±2 years) and sex. Two blinded neuroradiologists evaluated independently cerebrovascular findings from the brain MRI scans. Modified Scheltens' visual rating scale was used to evaluate WMH burden and the total WMH volume was measured using manual segmentation. Mean age [years, (SD)] at the time of brain MRI was 33.3 (3.8) and 32.8 (4.0) for cases (n = 40) and controls (n = 160), respectively (P = 0.53). Mean follow-up time for cases was 29.5 years (4.3). Total volume of WMHs (median) was 0.26 cm^3 (IQR 0.34) for cases and 0.065 cm^3 (IQR 0.075) for controls, P = 0.039. Cases had higher total WMH burden (P = 0.003), deep WMH burden (P = 0.003), and more periventricular WMHs (prevalence 7.5 vs. 0%, P = 0.008) than controls. Cases had greater risk of having total Scheltens' score ≥2 vs. < 2 (odds ratio, 6.88; 95% CI, 1.84-25.72, P = 0.0041) and ≥3 vs. < 3 (odds ratio, 22.71; 95% CI, 2.57-200.53, P = 0.0049). Diabetes type 1/type 2, hypertension, smoking status or hypercholesterolemia were not risk factors for WMH burden, p > 0.1. Myocarditis at the acute phase of KD increased the risk for periventricular WMHs (P < 0.05). Three cases (7.5%) and three controls (1.9%) had lacune of presumed vascular origin (P = 0.096). History of KD could be associated with an increased WMH burden. More studies are needed to confirm our results.

5.1 Introduction

Kawasaki disease (KD) is a childhood vasculitis affecting small and medium-sized arteries of the entire body (Cohen and Sundel, 2016) and 30% may present central nervous system symptoms (Tizard, 2005) and signs of intracranial vasculitis (Amano and Hazama, 1980). Symptomatic brain infarct is rare in KD patients and is limited to case reports (Wang et al., 2021).

White matter hyperintensities (WMH) usually indicate cerebral small vessel disease (Wardlaw et al., 2015). High WMH burden is associated with an increased risk of death, stroke, psychiatric disorders, and dementia (Au et al., 2006; Debette et al., 2019). Prevalence of WMH increases with age from 5% in healthy young adults (Hopkins et al., 2006) to over 60% in elderly (Lam et al., 2021). Compared to the general population, migraine patients have a higher risk for WMHs (Kruit et al., 2004; Palm-Meinders et al., 2012; Hamedani et al., 2013) with a prevalence of 11% in children (Eidlitz-Markus et al., 2013) and 39–44% in young adults without a significant differences between migraine subtypes (Dobrynina et al., 2021).

Although previous studies suggest that KD affects also cerebral vessels (Amano and Hazama, 1980; Ichiyama et al., 1998; Tizard, 2005; Hikita et al., 2011) this area is poorly studied and it is unknown if KD is associated with WMHs later in adulthood (Muneuchi et al., 2006). However, a recent study found that KD might increase the risk for hemorrhagic and ischemic stroke (Lin et al., 2022).

The objective of this study was to investigate if KD is associated with WMHs and other cerebrovascular findings in the long-term follow-up.

5.2 Methods

5.2.1 Standard Protocol Approvals, Registrations, and Patient consents

This study was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all cases in the study. Informed consent was not required for controls, because controls were included from a retrospective register. All methods were performed in accordance with STROBE guidelines and the Declaration of Helsinki.

5.2.2 Study population

5.2.2.1 Cases

KD patients who were diagnosed and treated in the catchment area of the Turku University Hospital (population of 887,000 citizens) from 1978 to 1995 were identified retrospectively by using diagnostic codes (International Classification Code-9, 446.1, International Classification Code-10, M30.3). Diagnosis was confirmed from the patient records for each patient according to American Heart Association (AHA) 2004 diagnostic criteria for complete KD (Newburger et al., 2004). Patients with a current age of ≥25 years and a history of KD occurring in childhood were included in this study. Age criteria were based on the protocol for this cohort described in the earlier study (Laukka et al., 2019). Patients with current age < 25 years, Marfans syndrome, Ehler-Danlos syndrome type IV, polycystic kidney disease, or history of intracranial aneurysms or bleeding were excluded. Patients with a positive family history of intracranial aneurysms were also excluded.

There were 87 KD patients diagnosed between 1978 and 1995. Of 87 KD patients, 27 were excluded because of age < 25 years. Based on a review of patient records, none of the 87 KD patients had been diagnosed with ischemic or hemorrhagic stroke before beginning the study enrollment year 2016. An invitation letter was sent to 60 patients who met the inclusion criteria and 40 of them were willing to participate in the study, and 20 refused. Prior to brain magnetic resonance imaging (MRI), patients were interviewed for past medical history (hypertension, diabetes mellitus, hypertension, migraine, hyperlipidemia, depression, history of stroke, neurological symptoms), medication, smoking, alcohol consumption, and possible signs of heart or lung problems.

Of 40 cases, 37 had accurate information on which drug KD had been treated with and 37 patients had accurate information about echocardiographic data during the acute phase of KD. Of 37 patients 22 were treated with intravenous immunoglobulin and 15 patients with aspirin only.

This was a population-based study since all the patients were collected from our catchment area.

5.2.2.2 Controls

All patients who had undergone brain MRI for any reason (n = 39,993) between 2003 and 2020 in our tertiary hospital were reviewed to include migraine patients (controls). Of these patients, 1,062 had migraine diagnoses (International Classification Code-10, G43.0-G43.3) in patient records. Of 1,062 migraine patients, 68 were excluded because of intracranial tumor, history of acute brain infarction,

sinus thrombosis, or subarachnoid- /intracerebral hemorrhage. None of the controls had a history of KD, other vasculitis, or brain diseases. From 994 migraine patients, controls were matched (four controls to one case) randomly by age (±2 years at the time of the brain MRI) and sex with cases. Patient records were reviewed for hypertension, hypercholesterolemia, type 1 and type 2 diabetes, smoking, and migraine subtype. Smoking was categorized as never smoker vs. current- or ex-smoker.

5.2.3 Brain Imaging and Analysis

5.2.3.1 Brain MRI Data Acquisition

For cases, MRI scans were conducted on a Philips Ingenia 3T scanner (Philips Medical Systems, Best, the Netherlands). Axial 3D T2-weighted sequence with TR (Repetition Time) of 2,500 ms (milliseconds), TE (Time Echo) of 250 ms, matrix of 352 × 352, and slice thickness of 1 mm (millimeters) was obtained. We also obtained a coronal 2D FLAIR (Fluid Attenuation Inversion Recovery) sequence with TR of 4,800, TI (Time Inversion) of 1,650 ms, TE of 285 ms, matrix of 352 × 352, and slice thickness of 3 mm, sagittal 3DT1 sequence with TR of 81 ms, TE of 3.7 ms, matrix of 320 × 320 and slice thickness of 1 mm was obtained as well as susceptibility-weighted sequence with TR of 20 ms, TE of 27 ms, matrix of 512 × 512 and slice thickness of 2 mm. These sequences were obtained to find and exclude any brain pathology. MR angiography using an axial Time-Of-Flight (TOF) sequence with TR of 23 ms, TE of 3.5 ms, matrix of 640 × 640, and slice thickness of 1.2 mm was performed to evaluate the arteries of the brains. TOF images were interpreted as such and also 3D reconstructions in two different planes were built and interpreted.

For controls, MRI scans were conducted with any available 1.5-3T scanners at our catchment area with a routine MRI protocol that includes the following sequences, T1- and T2-weighted sequences, susceptibility-weighted sequences, and FLAIR sequences. MRI scanner type and field strength for each control is presented in Supplementary Table 1.

Supplementary table 1. MRI scanner types for each control and number of controls with white matter hyperintensities (WMH) for each MRI scanner. (Laukka et al. 2022)

MRI scanner	Field strenght (Tesla)	n=160	(Scheltens' score >0) (n=)
Ingenia (Philips Healthcare)	3	26 (16%)	5
Achieva (Philips)	3	22 (14%)	4
Signa HDxt (GE healthcare)	3	5 (3%)	2
MAGNETOM Skyra (Siemens Medical Systems, Erlangen, Germany)	3	1 (1%)	0
Intera (Philips)	1.5	28 (18%)	2
MAGNETOM Avanto (Siemens Medical Systems, Erlangen, Germany)	1.5	24 (15%)	0
MAGNETOM Symphony (Siemens Medical Systems, Erlangen, Germany)	1.5	13 (8%)	1
MAGNETOM Avanto fit (Siemens Medical Systems, Erlangen, Germany)	1.5	11 (7%)	1
Genesis Signa (GE healthcare)	1.5	8 (5%)	0
MAGNETOM Aera (Siemens Medical Systems, Erlangen, Germany)	1.5	8 (5%)	3
Optima MR360 (GE healthcare)	1.5	7 (4%)	0
MAGNETOM Essenza (Siemens Medical Systems, Erlangen, Germany)	1.5	3 (2%)	0
Ingenia (Philips)	1.5	3 (2%)	0
Gyroscan intera (Philips)	1.5	1 (1%)	0

5.2.3.2 Measurement of WMH

For controls and cases, two neuroradiologists (each with more than 10 years of experience in neuroradiology), blinded to case–control status and clinical data, evaluated independently the number, the location, and the size of WMHs from the fluid-attenuated inversion recovery (FLAIR)-sequences and T2-weighted images. In addition, microbleeds and lacunes of presumed vascular origin were evaluated in the same blinded fashion. Conflicting interpretations between the two radiologists were resolved by the consensus of the two interpreters.

Lesions ≥2 mm were categorized as WMH. Modified Scheltens' visual rating scale was used to evaluate WMH burden (Scheltens et al., 1993; Young et al., 2008; Lou et al., 2010), because WMHs located in the basal ganglia or brainstem were excluded according to neuroimaging standards for WMHs (Wardlaw et al., 2013). Modified Scheltens' visual rating scale provides a scoring system for

periventricular WMH (0–9 points) and deep white matter hyperintensities (0–24 points) (Supplementary Table 2) (Young et al., 2008; Lou et al., 2010). WMH located < 10 mm from the ventricles was categorized as periventricular WMH (DeCarli et al., 2005). Subcortical WMHs was categorized as deep WMHs.

In addition, SmartBrush® (Smartbrush 2.0, Brainlab AG, Feldkirchen, Germany) segmentation tool was used for manual segmentation for WMH volume from FLAIR-sequences. SmartBrush® is a semi-automatic program that is FDA-approved for tumor-outlining and allows also manual segmentation. SmartBrush® has good usability, the accuracy is less dependent on clinical experience and accuracy is comparable with other segmentation tools (Rana et al., 2015; Porz et al., 2016).

Lacune of presumed vascular origin was categorized as a round or ovoid, subcortical, fluid-filled cavity of between 3 and 15 mm in diameter from T1-weighted, T2-weighted, and FLAIR sequences (Wardlaw et al., 2013). Location of lacune was defined by vascular territory (Wardlaw et al., 2013). Microbleeds were evaluated from susceptibility sequences and differentiated from spontaneous intracerebral hemorrhages with T1-weighted and T2-weighted or FLAIR sequences (Wardlaw et al., 2013).

Supplementary Table 2. Scheltens' visual rating scale (Laukka et al. 2022)

Periventricular hyperintensities	**Score (0-6)**	
Occipital caps	0-2	0= absent
Frontal caps	0-2	1= ≤5 mm
Bands along lateral ventricles	0-2	2= > 5mm and < 10 mm
White matter hyperintensities	**Score (0-24)**	
Frontal	0-6	0= absent
Parietal	0-6	1= <3 mm, n ≤5
Occipital	0-6	2= <3 mm, n > 6
Temporal	0-6	3= 4-10 mm, n ≤ 5
		4= 4 mm, n > 6
		5= > 11 mm, n > 1
		6= confluent

5.2.4 Statistical Analysis

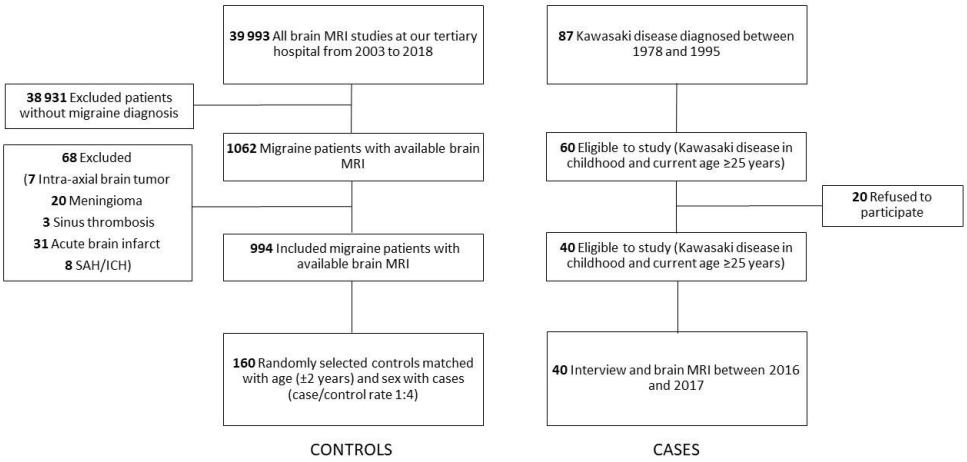
All analyses were performed using SPSS Statistics 27 (IBM Corp., Armonk, NY, USA).

Mean ages within cases and between cases and controls were compared with a two-sample *t*-test. Percentage distribution of total, deep, and periventricular Scheltens' score were compared between cases and controls by using Chi-square test and Fisher's exact test to evaluate total, deep and periventricular WMH burden. Chi-square and Fisher's exact test were also used to test the association of categorical variables with Scheltens' score. Scheltens' score was dichotomized to 0 vs. ≥1 to compare prevalence and risk factors for total WMHs, deep WMHs, and periventricular WMHs within cases and controls, and between cases and controls with chi-square and Fisher's exact test. In those with positive WMH findings (Scheltens' score ≥ 1), Scheltens' score values were compared between cases and controls by using Mann-Whitney *U*-test. To further evaluate WMH burden, Scheltens' score was dichotomized to ≥2 vs. < 2 and ≥3 vs. < 3 and binary logistic regression was used to evaluate risk factors (Kawasaki disease, hypertension, diabetes type 1 or type 2, current smoker/ex-smoker and hypercholesterolemia) for Scheltens' score. *P*-values < 0.05 were considered as statistically significant. Missing data for each variable were excluded from the analyses. WMH volumes between cases and controls were compared by using Mann–Whitney *U*-test.

Cohen's kappa (k) analysis was used to evaluate inter-observer agreement for the WMH prevalence at the first evaluation round. Kappa value between 0.00 and 0.20 was defined as a slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement (Landis and Koch, 1977).

5.3 Results

Demographics and mean Scheltens' scores for cases and controls are presented in Table 1 and the study population in the flow chart Supplementary Figure 1. Mean age for cases (n = 40) and controls (n = 160) was 33.3 (SD, 3.8) years and 32.8 (SD, 4.0) years, $P > 0.5$. Of the cases and controls, 62.5% were men. KD was diagnosed at an average age of 3.9 years and the mean follow-up time (from KD diagnosis to brain MRI) was 29.5 years (SD, 4.3). Of the 160 controls, 147 had undergone brain MRI because of migraine-related symptoms (Supplementary Table 3).



Supplementary Figure 1. Flow chart (Laukka et al. 2022)

5.3.1 Cases vs. controls

Total WMH volume (median) in cases and controls was, 0.26 cm^3 (IQR 0.34 cm^3) and 0.065 cm^3 (IQR 0.075 cm^3), respectively, P = 0.039 (Table 1). According to Scheltens' score, cases had higher total WMH burden (P = 0.003), deep WMH burden (P = 0.003) and more periventricular WMHs (prevalence 7.5 vs. 0%, P = 0.008) compared to controls. There were no microbleeds in cases or in controls. Lacune of presumed vascular origin was found in three cases (7.5%) and in three controls (1.9%), P = 0.096. (Table 1) The distribution of Scheltens' score is presented separately in Figure 1. Brain MRI findings in cases with a highest Scheltens' scores are presented in Figure 2. Cases had greater risk of having total Scheltens' score ≥2 vs. < 2 (odds ratio, 6.88; 95% CI, 1.84–25.72, P = 0.0041) and ≥3 vs. < 3 (odds ratio, 22.71; 95% CI, 2.57–200.53, P = 0.0049) (Table 2).

Table 1. Demographics for 40 cases and 160 controls. (Laukka et al. 2022)

Variable	Cases (n=40)	Controls (n=160)	p-value
Mean age at time of brain MRI, years (SD)	33.3 (3.8)	32.8 (4.0)	0.53
Female sex, *n* (%)	15 (37.5)	60 (37.5)	1.0
Hypertension, *n* (%)	2 (5)	15 (9.4)	0.53
Hypercholesterolemia, *n* (%)	0 (0)	11 (6.9)	0.13
Type 1 diabetes, *n* (%)	1 (2.5)	3 (1.9)	1.0
Type 2 diabetes, *n* (%)	1 (2.5)	16 (10)	0.20
Migraine with aura, *n* (%)	2 (5.0)	69 (43.1)	<0.001
Migraine without aura, *n* (%)	2 (5.0)	91(56.9)	<0.001
Never smoker, *n* (%)	19 (47.5)	66 (54.1)	0.58
Smoker/ex-smoker, *n* (%)	21 (52.5)	56 (45.9)	0.58
Missing data for smoking, *n*	0	38	
Brain MRI findings			
Prevalence of WMHs, *n (*%)	8 (20)	18 (11.3)	0.14
Prevalence of deep WMHs, *n* (%)	8 (20)	18 (11.3)	0.14
Prevalence of periventricular WMHs, *n* (%)	3 (7.5)	0 (0)	0.008
Total WMH volume (cm^3), median (IQR)	0.26 (0.34)	0.065 (0.075)	0.039
Total Scheltens' Score, median (IQR)	4.0 (4.5)	1.0 (0)	0.003
Scheltens' score for deep WMH, median (IQR)	3.0 (3.0)	1.0 (0)	0.003
Scheltens' score for periventricular WMH, median (IQR)	0 (1.5)	0 (0)	0.007
Lacune of presumed vascular origin, *n (%)*	3 (7.5)	3 (1.9)	0.096
Vascular territory for lacune			
Posterior cerebral artery, *n*	2 (5.0)	3 (1.9)	0.26
Middle cerebral artery, n	1 (2.5)	0 (0)	0.20
Hemorrhage/microbleeds, *n (%)*	0 (0)	0 (0)	1.0
Cerebral artery stenosis	0 (0)	N/A	

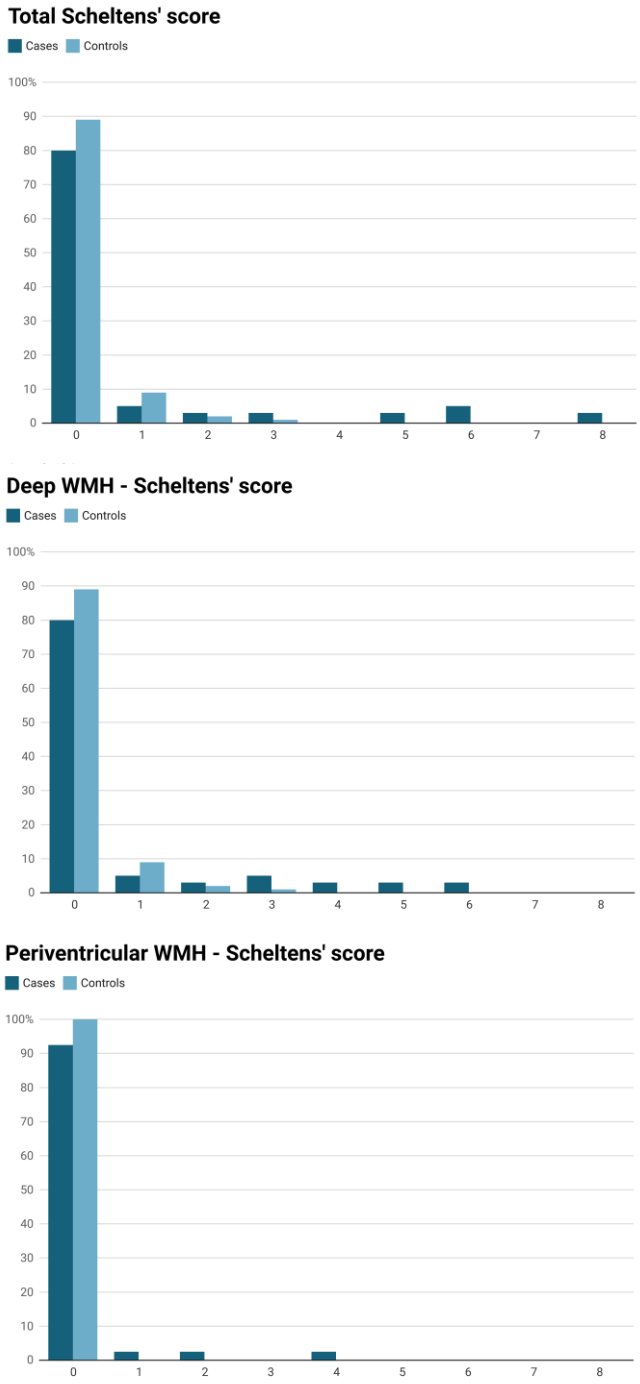


Figure 1. White matter hyperintensity scores (WMH) assesed by Scheltens' visual rating scale in 40 cases (Kawasaki disease) and 160 controls (migraine patients). (Laukka et al. 2022)

Table 2. Risk factors Total Scheltens' score ≥2 vs. <2 and ≥3 vs. <2 with binary logistic regression. (Laukka et al. 2022)

Characteristic	**Total Scheltens' score ≥2 vs. <2 OR (95% CI), p-value**	**Total Scheltens' score ≥3 vs. <2 OR (95% CI), p-value**
Kawasaki disease	6.88 (1.84-25.72), p= .0041	22.71 (2.57-200.53), p= .0049
Diabetes mellitus (type 1 or 2)	0.94 (0.11-7.84), p= .96	-
Hypertension	1.29 (0.15-10.93), p= .81	2.39 (0.26-21.77), p= .44
Current smoker/ex-smoker	0.45 (0.11-1.81), p= .26	0.54 (0.10-3.03), p= .0.48
Hypercholesterolemia	-	-

5.3.1 Cases

None of the cases had been diagnosed with ischemic stroke during the time-period between KD diagnosis and follow-up MRI. Of the 37 cases with available information on complications during the acute onset of KD, seven had myocarditis during the acute phase of KD and two of them (28%) had periventricular WMHs, while those without myocarditis (n = 30) did not have any periventricular WMHs (0%), P = 0.03. Females had more deep (P = 0.002 and periventricular WMHs compared to males. Prevalence of deep WMHs was higher in patients with myocarditis (prevalence 42.9%) than in those without myocarditis (prevalence 13.3%), but the difference was not statistically significant (P = 0.1). Prevalence of deep and periventricular WMHs were similar in those who were treated with intravenous immunoglobulin and those who were not (P > 0.3). Five patients had coronary artery aneurysm or dilatation during the acute phase of KD and one of them had deep WMH. Two patients had coronary artery aneurysms and none of them had WMH findings. (Supplementary table 4)

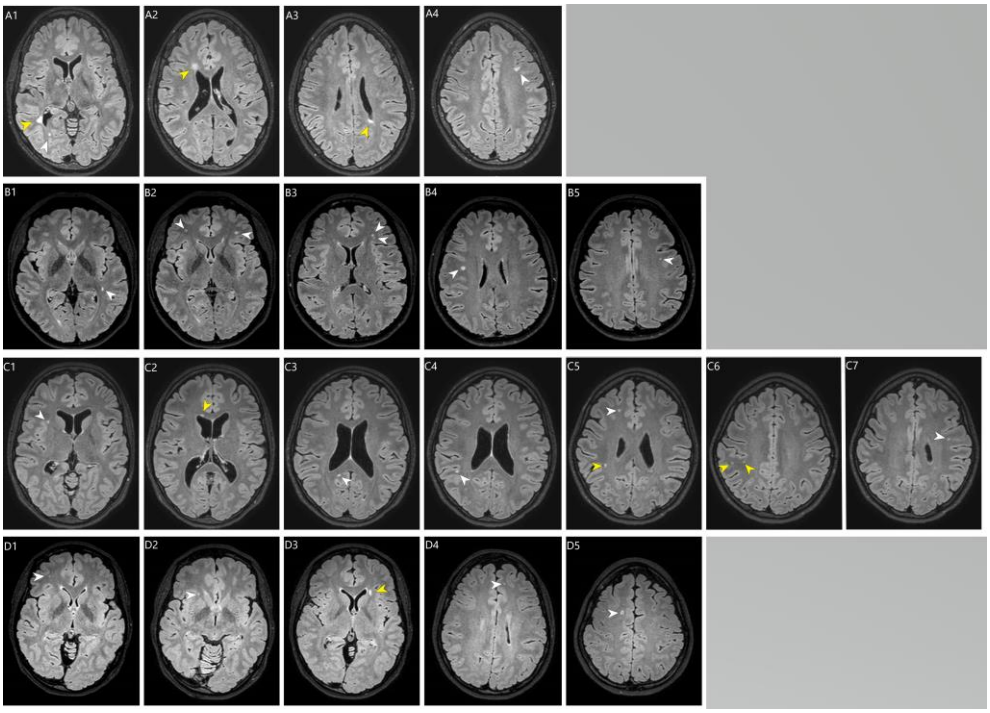


Figure 2. Brain MRI (T2-flair) of the white matter hyperintensities in four cases (Kawasaki disease). **(A1–A4)** a case (Kawasaki disease) with a total Scheltens' score of 8. **(A1)** Periventricular WMH > 5 mm in the right occipital horn (yellow arrow; Scheltens' score = 2) and in the deep occipital lobe WMH < 3 mm (white arrow; Scheltens' score = 1). **(A2)** Periventricular WMH > 5 mm in the right frontal horn (yellow arrow; Scheltens' score 2). **(A3)** Periventricular WMH > 5 mm in the left ventricle (yellow arrow; no score, because already score has been given from this area). **(A4)** deep WMH 4–10 mm in the left frontal lobe (white arrow; Scheltens' = score 3). **(B1–B4)** a case (Kawasaki disease) with a total Schelten score of 6. **(B1)** deep WMH 4–10 mm in the left temporal lobe (white arrow; Scheltens' score = 3). **(B2–B5)** multiple deep WMH in the both frontal lobes (white arrows), in the **(B2)** (left white arrow) and **(B4)** (white arrow) the size of the largest WMHs are 4–10 mm (Scheltens' score = 3). **(C1–C7)** a case (Kawasaki disease) with a total Schelten score of 6. **(C1, C5, C7)** multiple deep WMH < 3 mm in the frontal lobes (white arrows; Scheltens' score = 1). **(C2)** periventricular WMH ≤ 5 mm in the right frontal horn (yellow arrow; Scheltens' score = 1). **(C3)** deep WMH < 3mm in the right occipital lobe (white arrow; Scheltens' score = 1). **(C4)** (white arrow); **(C5)** (yellow arrow); and **(C6)** (yellow arrows): deep WMHs in the right parietal lobe, in the **(C4)** (white arrow) size of WMH is 4–10 mm (Scheltens' score = 1). **(D1–D5)** a case (Kawasaki disease) with a total Schelten score of 5. **(D1, D2, D4, D5)** Deep WMHs in the frontal lobes (white arrows). In the **(D5)** (white arrow) the size of the WMH is 4–10 mm (Scheltens' score = 3). **(D3)** periventricular WMH size > 5 mm next to left frontal horn (yellow arrow; Scheltens' score = 2). (Laukka et al. 2022)

5.3.2 Inter-observer agreement

Inter-observer agreement for WMHs was fair (k = 0.42; CI 95%, 0.25–0.60) for the first evaluation. Of 200 study subjects, there were disagreements in 26 interpret of WMHs, which was resolved by consensus in the second evaluation. WMH volume and Scheltens' score had a good correlation $\rho = 0.77$, $p < 0.0001$.

5.4 Discussion

In this long-term follow-up study of KD patients, WMH burden and prevalence of periventricular WMHs were significantly higher in patients with a history of KD compared to controls.

KD was first discovered in 1967, yet all long-term effects are still unknown (Cohen and Sundel, 2016). KD patients might have a higher risk for cardiovascular diseases and long-term effects on systemic arteries (McCrindle et al., 2017), but whether KD is linked to cerebrovascular diseases in the long-term is unclear (Muneuchi et al., 2006; Lin et al., 2022). To our knowledge, this study was the first to describe that history of KD is related to increased WMH burden in the long-term follow-up.

There are several possible mechanisms for why KD may be associated with an increased risk of WMHs. Hypoperfusion, the blood-brain barrier dysfunction, and inflammation are the potential underlying pathophysiological mechanisms for WMHs (Alber et al., 2019). Although KD is affecting predominantly medium-sized extracranial arteries, 1–30% might develop central nervous system symptoms (facial nerve paresis, meningeal irritation, bulging fontanelles, convulsions, somnolence, extreme irritability, and headache) in acute KD (Tizard, 2005). Localized cerebral hypoperfusion has been reported in 29–72% of KD patients without neurological symptoms during the acute illness and lasting even several months afterward, possibly indicating cerebral vasculitis (Ichiyama et al., 1998; Hikita et al., 2011). Elevated inflammatory cytokines and pleocytosis in cerebrospinal fluid during the acute phase of KD has been found in 40–60% of patients, suggesting central nervous system inflammation in KD (Korematsu et al., 2007).

Interestingly, KD was particularly associated with periventricular WMHs (prevalence 7.5% in cases and 0% in controls). We also found that myocarditis during the acute phase of KD increased the risk for periventricular WMHs, one explanation for this finding could be hypoperfusion as well. Myocarditis is common in KD and can cause hemodynamic instability in severe cases (Dionne and Dahdah, 2018). Periventricular WMHs are often related to advanced age and cerebral small vessel disease and could be more susceptible to hypoperfusion (ten Dam et al., 2007). Periventricular WMHs and deep WMHs have different histopathological findings and clinical consequences, but studies suggest that periventricular and deep WMHs

are probably a continuum of the same pathological process (Wardlaw et al., 2015). In KD patients, females had more periventricular and deep WMHs compared to males. One explanation could be that females may be more susceptible to WMHs due to genetic risk factors (Sachdev et al., 2016).

In our study, WMH burden was significantly higher in KD patients compared to controls with migraine, despite the fact that in previous studies migraine has been shown to be associated with an increased WMH burden compared to healthy controls (Kruit et al., 2004; Palm-Meinders et al., 2012; Hamedani et al., 2013). Prevalence of WMHs was 20% in KD patients, which is four times higher than reported in healthy young adults with a similar age (Hopkins et al., 2006). In contrast, the prevalence of WMH in cases (migraine patients) was comparable to pediatric migraine patients (11 vs. 11%) (Eidlitz-Markus et al., 2013), but lower than reported in young adults with migraine (Dobrynina et al., 2021).

KD is treated with intravenous immunoglobulin and aspirin to prevent coronary artery aneurysms (McCrindle et al., 2017). Intravenous immunoglobulin treatment may increase the risk for thromboembolic complications (Daniel et al., 2012; Ammann et al., 2016). In the present study, a relatively large proportion of KD patients were diagnosed before intravenous immunoglobulin treatment was established (Furusho et al., 1984), which allowed comparison of groups in terms of treatment. We did not find a significant difference in WMH prevalence or total WMH burden between KD patients treated with or without intravenous immunoglobulin. In KD, coronary artery aneurysms may predispose to more severe systemic inflammation (Lech et al., 2019). In our study, five patients had coronary artery dilatations or aneurysms and only one had periventricular and deep WMHs. Two KD patients had coronary artery aneurysms, but no WMHs. However, because of a small number of patients with coronary artery aneurysms, no conclusions can be drawn from this finding.

Increased WMH burden is associated with a higher risk for stroke, dementia, depression, and all-cause mortality (Au et al., 2006; Debette et al., 2019). Furthermore, increased WMH burden could be associated with different psychiatric disorders in children (Lyoo et al., 2002). Acute ischemic stroke after KD is uncommon and limited to single case reports (Wang et al., 2021). KD could be also associated with an increased risk of epilepsy and neurodevelopmental disorders, but the pathophysiology of these phenomena is unclear (Lin et al., 2019). We did not perform neuropsychological evaluation on study subjects, so no conclusions can be drawn on this issue from our study.

One of the limitations was the modest number of cases in this study. However, this was a population-based study as we reviewed all KD treated and diagnosed in our hospital district area and were able to recruit 40 of 60 patients who met the inclusion criteria for our study.

Migraine patients were selected as a control group because WMHs have been extensively studied in this population and migraine patients are a more homogenous population compared to headache patients in general which increases the repeatability of this study design. We acknowledge that migraine patients have an increased risk for WMHs (Dobrynina et al., 2021), but because we were able to show that WMHs burden is higher in KD compared to migraine patients this does not affect our conclusions and should strengthen our results. Another limitation of the control group was that they were selected retrospectively, which may have caused selection bias. However, one could assume that selection bias would rather have led to a higher number of WMH findings in control patients because migraine patients are not routinely undergoing brain MRI.

Another limitation is that we had no brain MRI imaging during the acute phase KD, so it is uncertain at which point WMHs occurred in Kawasaki disease patients.

There are limitations in the interpretation of WMHs. One major limitation was that brain imaging was performed on control patients with several different MRI scanners, which may have affected WMH interpretation. However, proposed image acquisition standards for WMH imaging (Wardlaw et al., 2013) were achieved also with controls. We evaluated WMH changes on a widely used quantitative visual rating scale (Wardlaw et al., 2013), one reason for this was that applying automatic segmentation tools to different scanners could have caused serious inter-scanner variability (Kuijf et al., 2019). Compared to automatic segmentation tools, visual rating scales are more prone to inter-rater variability, but on the other hand are more achievable methods (Wardlaw et al., 2013). Nevertheless, we used blinded review by two fellowship-trained neuroradiologists, and discrepancies were resolved using consensus. In addition, visual rating scales are comparable to automatic segmentation tools when assessing WMH burden (Valdés Hernández Mdel et al., 2013), but are inferior in grouping small differences and WMH progression (van den Heuvel et al., 2006).

5.5 Limitations

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5.6 Conclusions

Our study suggest that patients with a history of Kawasaki disease might have increased risk for WMHs, but it remains unclear whether WMHs occur during or after the acute phase of KD. More studies are needed to confirm our results.

5.7 Acknowledgements

We thank our scientific nursing staff, Kari Jarkko, Mira Hallenberg, and Fanny Nyroos, for their great help and effort in conducting the imaging studies. We also thank Auria Clinical Informatics for assisting in data collection.

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Authors report no conflict of interest.

5.8 Supplemental tables

Supplementary Table 3. Reason for brain MRI in 160 controls with migraine. (Laukka et al., 2022)

Symptom	**Associated with migraine (n=147)**	**Not associated with migraine (n=13)**
Frequent headache, n (%)	70 (48)	0 (0)
Sensory and/or motor symptoms, n (%)	58 (39)	2 (15)
Visual defects, n (%)	16 (11)	0 (0)
Cognitive symptoms, n (%)	0 (0)	3 (23)
Vertigo, n (%)	3 (2)	2 (15)
Aneurysm screening, n (%)	0 (0)	2 (15)
Seizure, n (%)	0 (0)	2 (15)
Abnormal tendon reflex, n (%)	0 (0)	1 (8)
Sleep walking, n (%)	0 (0)	1 (8)

Supplementary Table 4. Clinical characteristics and their risk factors for deep and periventricular white matter hyperintensities (WMH) in 40 cases during the acute onset of Kawasaki disease (KD) and at the brain MRI. (Laukka et al. 2022)

Variables	**Total n=40**	**Deep WMH n=8**	**p-value**	**Periventricular WMH n=3**	**p-value**
Acute onset of KD, demographics					
Age at KD diagnosis, mean years, (SD)	3.9 (3.1)	Yes: 5.0 (3.9) No: 3.7 (2.9)	0.3	Yes: 1.8 (1.2) No: 4.1 (3.2)	0.2
Sex, *n (%)*					
Female	15 (37.5)	7/15 (46.7)	0.002	3/15 (20)	0.046
Men	25 (62.5)	1/25 (4.0)		0/25 (0)	
IVIG treatment, n (%)					
Yes	22 (52.5)	5/22 (22.7)	1.0	3/22 (13.6)	0.3
No	15 (37.5)	3/15 (20.0)		0/15 (0)	
Missing data	3 (7.5)	0/3 (0)		0 (0/3)	
Coronary artery dilatation/aneurysm, n (%)					
Yes	6 (15)	1/6 (16.7)	1.0	1/6 (16.7)	0.3
No	31 (80)	6/31 (19.4)		1/31 (3.2)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Coronary artery aneurysm, n (%)					
Yes	2 (5.0)	0/2 (0)	1.0	0/2 (0)	1.0
No	35 (87.5)	7/35 (20)		2/35 (5.7)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Myocarditis, n (%)					
Yes	7 (17.5)	3/7 (42.9)	0.1	2/7 (28.6)	0.03
No	30 (75.0)	4/30 (13.3)		0/30 (0)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Hepatitis, n (%)					
Yes	5 (12.5)	1/5 (20.0)	1.00	0/5 (0)	1.00

No	32 (80.0)	6/32 (18.8)		2/32 (6.3)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Gallbladder hydrops, n (%)					
Yes	2 (5.0)	0/2 (0)	1.00	0/2 (0)	1.00
No	35 (87.5)	7/35 (20)		2/35 (5.7)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Meningitis, n (%)					
Yes	3 (7.5)	1/3 (33.3)	0.48	0/3 (0)	1.00
No	34 (85.0)	6/34 (17.7)		2/34 (5.9)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Anterior uveitis, n (%)					
Yes	6 (15.0)	0/6 (0)	0.6	0/6 (0)	1.0
No	31 (77.5)	7/31 (22.6)		2/31 (6.5)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Relapse requiring re-treatment, n (%)					
Yes	4 (10)	1/4 (25)	1.0	0/4 (0)	1.0
No	36 (90)	7/36 (19.4)		3/36 (8.3)	
Kawasaki Disease Shock Syndrome	0 (0)	-		-	
Follow-up demographics					
Mean age at brain MRI, years (SD)	33.3 (3.8)	Yes: 33.1 (2.9) No: 33.3 (4.1)	0.9	Yes: 30.3 (2.9) No: 33.5 (3.8)	0.1
Migraine with aura, *n (%)*					
Yes	2 (5)	0/2 (0)	1.0	0/2 (0)	1.0
No	38 (95)	8/38 (21.1)		3/38 (7.9)	
Migraine without aura, *n (%)*					
Yes	2 (5)	0/2 (0)	1.0	0/2 (0)	1.0
No	38 (95)	8/38 (21.1)		3/38 (7.9)	
Hypertension, *n (%)*					
Yes	1 (2.5)	0/1 (0)	1.0	0/1 (0)	1.0
No	39 (97.5)	8/39 (20.5)		3/39 (7.7)	
Type 1 diabetes, *n (%)*					
Yes	1 (2.5)	0/1 (0)	1.0	0/1 (0)	1.0
No	0 (0)	8/39 (20.5)		3/39 (7.7)	

Type 2 diabetes, *n (%)*	0 (0)	-		-	
Hypercholesterolemia, *n (%)*	0 (0)	-		-	
Smoking, *n (%)*					
Smoker or ex-smoker	21 (52.5)	3/21 (14.3)	0.4	1/21 (4.8)	0.6
Never smoker	19 (47.5)	5/19 (26.3)		2/19 (10.5)	
Symptomatic ischemic stroke, *n (%)*	0 (0)	-		-	-
Neurological symptoms, *n (%)*	0 (0)	-		-	-
Depression, *n (%)*					
Yes	3 (7.5)	1/3 (33.3)	0.5	1/3 (33.3)	0.2
No	37 (92.5)	7/37 (18.9)		2/37 (5.4)	

Supplementary Table 5. Clinical characteristics and their risk factors for deep white matter hyperintensities (WMH) in 160 controls. There were no periventricular WMHs in controls. (Laukka et al. 2022)

Variables	**Total n=160**	**Deep WMH n=18**	**p-value**
Mean age at brain MRI, years (SD)	33.3 (3.8)	Yes: 34.4 (3.5) No: 32.6 (4.1)	0.3
Sex			
Female	60 (37.5)	5/60 (8.3)	0.5
Men	100 (62.5)	13/100 (13.0)	
Migraine, n (%)			
With aura	69 (43.1)	10/69 (14.5)	0.3
Without aura	91 (56.9)	8/91 (8.8)	
Hypertension, n (%)			
Yes	15 (9.4)	2/15 (13.3)	0.68
No	145 (90.6)	16/145 (11.0)	
Type 1 diabetes, n (%)			
Yes	3 (1.9)	0/3 (0)	1.0
No	157 (98.2)	18/157 (11.5)	
Type 2 diabetes, n (%)		-	
Yes	16 (10)	4/16 (25.0)	0.086
No	144 (90)	14/144 (9.7)	
Hypercholesterolemia, n (%)		-	
Yes	11 (6.9)	1/11 (9.1)	1.0
No	149 (93.1)	17/149 (11.4)	
Smoking, n (%)			
Smoker or ex-smoker	56 (35.0)	8/56 (14.3)	0.4
Never smoker	66 (41.2)	9/66 (13.6)	
Missing data	38 (23.8)	1/38 (2.6)	
Symptomatic ischemic stroke, n (%)	0 (0)	-	

6 Study III: Prevalence of thoracic aortic aneurysms and dilatations in patients with intracranial aneurysms.

Abtract. The prevalence of intracranial aneurysms (IAs) is higher in patients with aortic aneurysms. However, there are lack of studies investigating prevalence of thoracic aortic aneurysms (TAAs) in patients with IAs. The objective of this study was to evaluate the prevalence and risk factors for thoracic aortic dilatations (TADs) and TAAs in patients with IAs. We retrospectively reviewed data from 1777 patients with diagnosed IAs at our institution between 2006 and 2016. We included 411 patients with saccular IAs and available imaging studies (computed tomography or magnetic resonance imaging) of all thoracic aortic segments. TAD was defined according to age- and sex-matched normograms, and TAA as a diameter of greater than 4.0 cm. A total of 83 patients (20%) had TAD or TAA. The prevalence of TADs and TAAs were 18% (n = 74) and 8% (n = 31) without significant difference between unruptured and ruptured IAs (P = .7). Of the 74 patients with TAD, 22 (30%) had multiple TADs and 66% of the TADs located in the aortic arch. Older age (odds ratio [OR], 1.04, P = .006), rheumatic disease (OR, 4.73, P = .009) and alcohol abuse (OR, 4.77, P = .01) were significant risk factors for TAD/TAA. The prevalence of TADs and TAAs is considerably greater in patients with IAs compared with reports from the general population, suggesting that IAs might be associated with aortopathy and might share a similar pathogenetic background with TADs/TAAs. Especially patients with IAs and a history of rheumatic disease and/or alcohol abuse are at high risk for TADs/TAAs.

6.1 Introduction

Thoracic aortic aneurysms (TAAs) are a potentially fatal disease whose complications (aneurysms/dissections) have high mortality. Nearly 60% of patients with a ruptured TAA die before the hospital admission (Johansson et al., 1995) and fewer than 30% of these patients are alive at 5 years after the treatment of ruptured TAA. (Goodney et al., 2011) In patients treated electively the perioperative mortality rate is 6% to 7% for unruptured TAAs. (Goodney et al., 2011) The short-term mortality rates for acute type A and type B dissection are 14% to 16% in surgically treated patients compared with 6% to 7% after endovascular treatment. (Mussa et al., 2016) TAA is typically defined as a segmental dilatation of 50% or greater compared with normal diameter (Johnston et al., 1991) or any dilatation that is greater than 40 mm. (Davies et al., 2002) The prevalence of asymptomatic TAA has been measured in 0.16% to 0.34%. (Itani et al., 2002; Kälsch et al., 2013) Incidentally noted ascending aortic dilatation (4-5 cm) has been reported in 2.7% of the general population. (Benedetti and Hope 2015) The risk of thoracic aortic dissections or rupture increases with aortic diameter. The annual risk of rupture or dissection is less than 2% for a thoracic aortic diameter of 4.0 to 4.9 cm and approximately 7% for diameter of less than 6 cm. (Davies et al., 2002) Routine imaging follow-up is recommended for dilatations of 3.5 to 5.4 cm. Elective treatment of TAAs is recommended if the growth rate is greater than 0.5 cm per year or diameter exceeds 5.5 cm, or at smaller diameters in the presence of connective tissue disease or a family history of rupture (threshold of 45-50 mm). Although most of the TAAs are asymptomatic before rupture or acute dissection, it is important to find possible high-risk groups for thoracic aortic dilatation (TAD) that would benefit from follow-up and adequate medical and surgical management. (Hiratzka et al., 2010)

Aortic aneurysms and intracranial aneurysms (IAs) share similar comorbidities and genetic risk factors, (van't Hof et al., 2016) and about 10% of patients with TAA also have IAs. (Kuzmik et al., 2010; Rouchaud et al., 2016) One prior study reported prevalence of ascending TAA of 4.7% in patients with IAs. (Goyal et al., 2015) However, larger studies evaluating the entire thoracic aorta in the patients with IA are not available.

The objective of this study was to evaluate the prevalence and risk factors for TADs and TAAs in patients with saccular IAs.

6.2 Materials and Methods

6.2.1 Study Patients

This study was approved by the local institutional review board. Patient consent was not required because of the retrospective study design.

We reviewed retrospectively records for 1777 patients diagnosed with ruptured or unruptured IAs at our institution between 2006 and 2016. Patients with fusiform IAs (n = 62) and patients without imaging of the entire thoracic aorta or imaging with catheter angiography (n = 1304) were excluded. A total of 411 patients with saccular IAs and either available contrast-enhanced computed tomography angiography (CTA), unenhanced CT or magnetic resonance imaging (MRI) with sufficient coverage of the all three thoracic aortic segments (ascending thoracic aorta, aortic arch, and descending thoracic aorta) were identified and included in this study. Imaging was not eletrocardiographically gated. Among the 411 patients, we also identified 133 patients with echocardiogram to evaluate the bicuspid aortic valve (BAV) by report. The aortic valve was evaluated sufficiently in every echocardiogram report. BAV was diagnosed if only two functional cusps were mentioned in the echocardiogram report. Thoracic aortic dimensions were evaluated by two authors. About 40 cases per each reviewer were also examined by a board-certified radiologist from our study group to ensure reliability of measurements.

From CT, CTA, and MRI studies, thoracic aortic dimensions were measured perpendicular to the axis of blood flow from the axial cuts (cut thickness of $\leq$3 mm) at three points: (1) the midascending aorta, (2) the mid-descending aorta at the level of pulmonary artery bifurcation, and (3) the aortic arch at the level of maximum diameter. The thoracic aorta was also evaluated for coarctations from imaging studies and from medical charts. All measurements were done with Carestream Vue Motion workstation, version 12.2.0.0960 (Carestream Health, Inc, Rochester, NY).

Sex- and age-matched as well as site-specific cut-off values for TAD and aneurysms were used from the study by American College of Radiology (McComb et al., 2016) (Table I). Aortic dilatation was defined as +two SD from the normal reference value and an aneurysm as a diameter of greater than 4.0 cm. If a dilatation and/or aneurysm was identified at a location other than the standardized measurement points, this was reported as the diameter for that aortic segment.

The characteristic of the IAs were evaluated from digital subtraction angiography, CTA, and magnetic resonance angiography images. In patients with multiple IAs, characteristics were evaluated for ruptured or for largest unruptured IA. The maximum diameter was measured for dome height and width, as well as the aneurysm neck. The dome-to-neck ratio (maximum dome width/maximum neck width) was calculated for each patient. IAs with daughter sacs or protrusions were

defined irregular. IA location was categorized as follows: internal carotid artery, middle cerebral artery, anterior cerebral artery, and posterior circulation arteries.

Data from patient records were collected at the time IA were first diagnosed, including age, gender, smoking, alcohol consumption, hypertension, history of intracranial and aortic aneurysms in first-degree relatives, diabetes, history of Turner syndrome, connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome type IV, Loyes-Dietz syndrome), rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, Sjögren syndrome, polymyalgia rheumatica, scleroderma, spondyloarthritis, systemic lupus erythematosus), vasculitis (Takayasu arteritis, Kawasaki disease, giant cell arteritis, polyarteritis nodosa, Churg-Strauss syndrome, Henoch-Schönlein purpura, Bechet's disease), and peripheral arterial disease.

Alcohol abuse was defined as 288 g or more of ethanol per week for men and 192 g or more for women, or if the patient was diagnosed with alcoholism (International Statistical Classification of Diseases and Related Health Problems, diagnosis code F10.2). Diabetes was defined as diabetes requiring oral medication or insulin. Dyslipidemia was defined as those with a low-density lipoprotein cholesterol of 3.0 mmol/L or greater or a total cholesterol of 5.0 mmol/L or greater.

Table I. Upper limits of normal thoracic aortic diameter (mean + 2 s.d.) from McComb et al., 2016 study.

Age (y)	**55-59**	**60-64**	**65-69**	**70-74**
Mid-ascending aorta (cm)/sex	4.1/M, 3.97/F	4.22/M, 3.97/F	4.31/M, 3.95/F	4.14/M, 4.12/F
Aortic arch (cm)/sex	3.3/M, 3.14/F	3.5/M, 3.15/F	3.53/M, 3.15/F	3.52/M, 3.2/F
Mid-descending aorta	3.16/M, 2.83/F	3.17/M 2.96/F	3.41/M, 3.08/F	3.35/M 3.01/F

6.2.2 Statistical Analysis

Statistical analysis was performed by using IBM SPSS statistics 23 for Windows (IBM, Armonk, NY). Interclass correlation (ICC), proposed by Shrout and Fleiss,15 was used to assess the inter-rater reliability of imaging measurements. According to Meyer's study, (Meyers 1974) the following scale for ICC were used to determine the inter-rater reliability: poor (<0.7), fair (0.7–0.8), good (0.8–0.9), and high (≥0.9).

Between-group differences were evaluated with $\chi 2$ or Fisher's exact test for proportions and an independent samples t-test for continuous variables and binary logistic regression. Continuous variables are reported either as mean and standard deviation or as median and interquartile range as appropriate. Multivariable binary regression was performed by including variables with a $P < .10$ in a model with backward selection (Wald), P values of less than .05 were considered statistically significant. Multiple imputation was used for missing data.

6.3 Results

From 1777 patients with diagnosed IA, a total of 411 patients with saccular IA and available imaging of the entire thoracic aorta were included (Fig 1). Available imaging modalities of thoracic aorta are represented in the flow chart (Fig 1 and Table II). No patients had a history of connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome), Turner syndrome, or vasculitis. None of the patients had a history of aortic dissections. Baseline characteristics with normal and abnormally dilated aorta (TAD or TAA) are presented in Table II. Of the 23 patients with rheumatic disease, 15 patients had rheumatoid arthritis, 5 patients polymyalgia rheumatica, 2 patients psoriatic arthritis, and 1 patient Sjögren syndrome.

A total of 96 TADs and 32 TAAs were found in 74 patients (18.0%) and 31 patients (7.5%), respectively. Altogether, 83 patients (20.2%) had TAD or TAA. Multiple TADs were noted in 22 of 74 patients (29.7%) and multiple TAAs in 1 of 31 patients (3.2%, Fig 2). Altogether, 20 patients had TAD in two aortic segments and two patients in all three aortic segments. Among 96 TADs, 63 (65.6%) TADs located in the aortic arch. The prevalence of ascending aortic, aortic arch, and descending aortic dilatations was 4.1% (n = 17), 15.3% (n = 63), and 3.9% (n = 16), respectively. The prevalence of ascending aortic, aortic arch, and descending aortic aneurysms was 7.1% (n = 29), 0.5% (n = 2) and 0.2% (n = 1), respectively. From 133 patients with an available echocardiogram, 2 patients (1.5%) had BAV, but no concurrent TAD or TAA. In one patient, thoracic aortic coarctation was operated previously in childhood, in the same patient, a TAD was found in the descending thoracic aorta.

In a multivariable binary regression model (Fig 3), rheumatic disease (odds ratio [OR], 4.73; 95% confidence interval [CI], 1.47-15.2, P = .009), alcohol abuse (OR, 4.77; 95% CI, 1.38-16.5, P = .01), and older age (OR, 1.04; 95% CI, 1.01-1.06, P = .006) emerged as significant independent predictors of abnormally dilated aorta (TAD or TAA).

6.3.1 Inter-rater reliability

Both raters had good to high reliability of aortic measurements as assesses against those by a board-certified radiologist (ICC values of 0.91, 0.82, and 0.87 by T.F., and 0.89, 0.81, and 0.84 by E.P. for ascending aorta, aortic arch, and descending aorta, respectively)

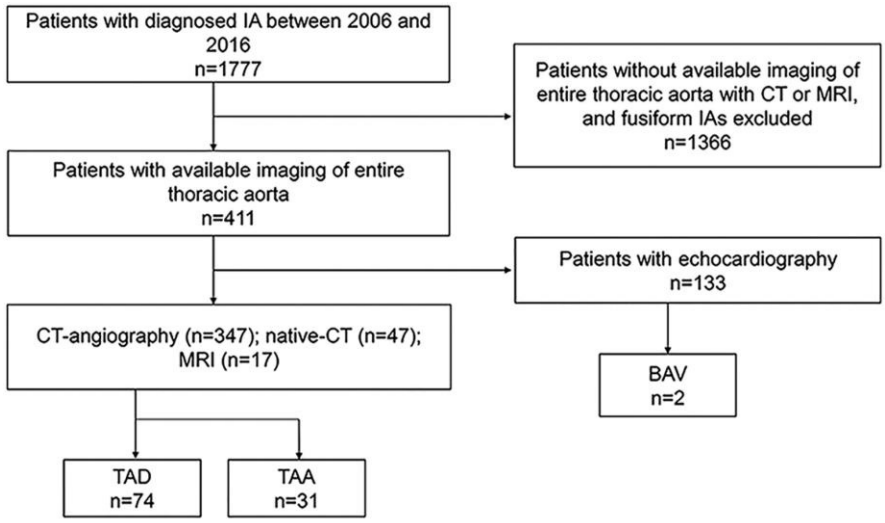

Figure 1. Flow chart. BAV, Bicuspid aortic valve, CT, computed tomography, IA, intracranial aneurysms, MRI, magnetic resonance imaging, TAA, thoracic aortic aneurysm, TAD, thoracic aortic dilatation. (Laukka et al., 2019)

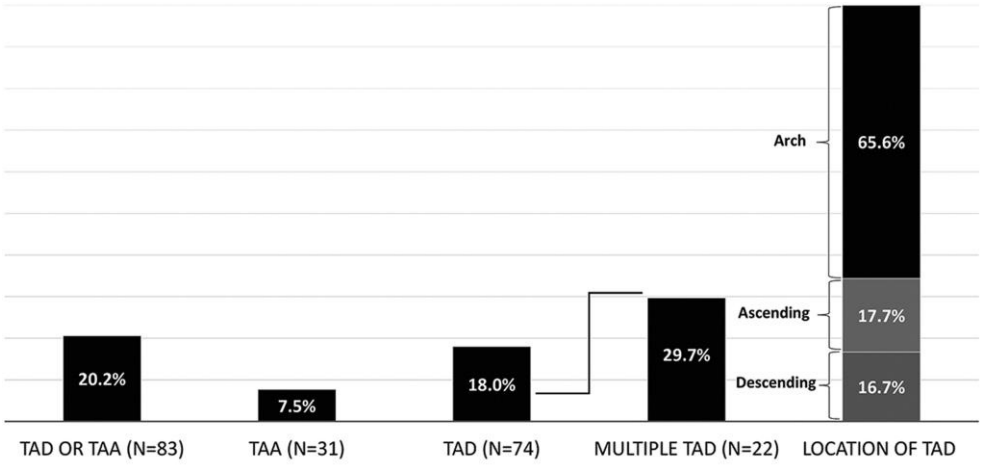

Figure 2. Prevalence of thoracic aortic dilatations (TADs) and aneurysms (TAAs) in patients with intracranial aneurysms (IAs). (Laukka et al., 2019)

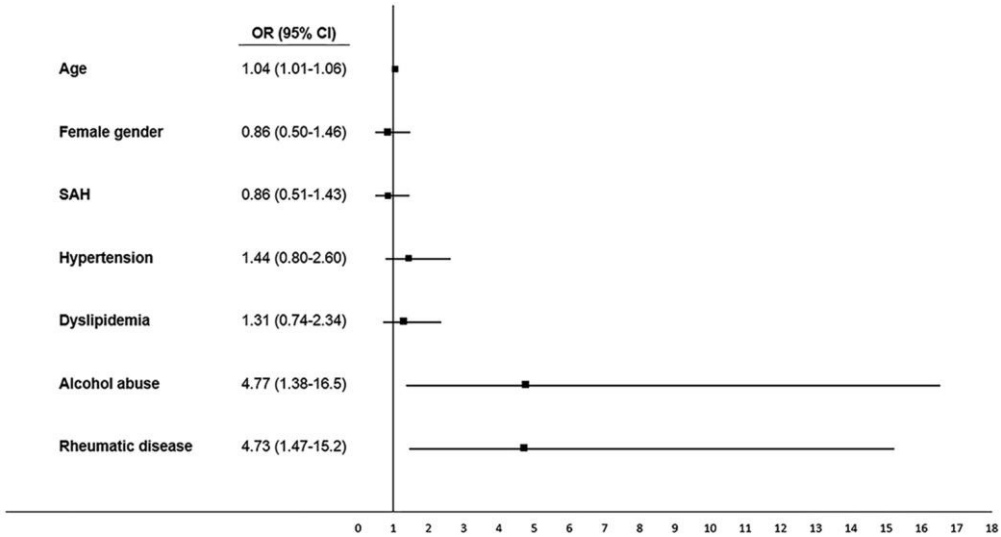

Figure 3. Predictors of thoracic aortic dilatations (TADs) or aneurysms. CI, Confidence interval, OR, odds ratio, SAH, subarachnoid hemorrhage. (Laukka et al., 2019)

Table II. Baseline characteristics for patients with saccular intracranial aneurysms relative to the normal and dilated thoracic aorta (+2 SD from normal reference value or aortic diameter over >4.0 cm). (Laukka et al., 2019)

	Normal aorta (n=328)	**TAD or TAA** (n=85)	***p* value**
Age, mean years (SD)	58.9±12.3	64.2±8.6	**>0.001**
Subarachnoid hemorrhage, n (%)	189 (57.6%)	47 (55.3%)	0.70
Female, n (%)	208 (63.4%)	52 (61.2%)	0.70
Imaging modality, aorta			
Non-enhanced CT	37	10	
CT-angiography	274	73	
MRI	17	0	
Catheter angiography	0	2	
Past medical history, n (%)			
Never smoker	100 (30.6%)	26 (30.6%)	0.80
Ex-smokers	60 (18.3%)	15 (40.0%)	0.80
Active smokers	122 (37.3%)	34 (40.0%)	0.80
Alcohol abuse	6 (1.8%)	6 (7.1%)	**0.02**
Hypertension	167 (51.2%)	56 (65.9%)	**0.016**
Type II diabetes	40 (12.3%)	10 (11.8%)	0.90
Dyslipidemia	78 (23.9%)	30 (35.3%)	**0.034**
COPD/asthma	52 (16.0%)	16 (18.8%)	0.53
Autoimmune disease	13 (4.0%)	10 (11.8%)	**0.005**
Immunosupressive medication	22 (6.7%)	7 (8.2%)	0.63
History of AMI	18 (5.5%)	8 (9.4%)	0.19
CAD	27 (8.3%)	7 (8.2%)	0.99
Extracardiac arteriopathy	22 (6.8%)	6 (7.1%)	0.62
Carotid stenosis	22 (6.8%)	7 (8.2%)	0.63
History of stroke	65 (20.0%)	15 (17.9%)	0.66
Coarctation of the aorta	0	1 (1.2%)	0.21
Family history, n (%)			
Non-ruptured IA	20 (6.1%)	6 (7.1%)	0.61
Ruptured IA	27 (8.3%)	8 (9.4%)	0.51
Aortic aneurysm	1 (0.3%)	0 (0%)	0.23
Abdominal aortic aneurysm	3 (0.9%)	1 (1.2%)	0.22
Intracranial aneurysm			
Irregular shape, n (%)	178 (59.5%)	49 (62.0%)	0.69
Maximum width, mm (SD)	7.4±6.4	6.9±4.7	0.51
Maximum height, mm (SD)	7.2±6.0	7.0±4.5	0.77

Dome-to-neck ratio (max. dome width/neck width)	1.9±2.0	1.6±0.7	0.31
No. of aneurysms	2.5±0.9	2.5±1.2	0.96
Location, n (%)			
ACA	66 (20.1%)	25 (29.4%)	0.066
ICA	81 (24.7%)	17 (20.0%)	0.36
MCA	119 (36.3%)	32 (37.7%)	0.82
Posterior circulation	62 (18.9%)	11 (12.9%)	0.20
Aortic diameter			
Ascending aorta, mm (SD)	31.8±3.6	38.1±3.5	**<0.001**
Aortic arch, mm (SD)	28.0±2.9	34.3±6.3	**<0.001**
Descending aorta, mm (SD)	24.4±2.9	28.3±3.8	**<0.001**

Abbreviations: COPD, chronic obstructive pulmonary disease, AMI, acute myocardial infarction, CAD, coronary artery disease, IA, intracranial aneurysm, ACA, anterior cerebral artery, ICA, internal carotid artery, MCA, middle cerebral artery

6.4 Discussion

We found that the prevalence of TADs and aneurysms is significantly higher in patients with IAs than in the general population based on earlier reports. As the threshold of +two SD essentially represents the 95% CI, the prevalence of dilatations in the current study was almost nine-fold to the expected prevalence. We also found that patients with an IA with rheumatic disease and high alcohol consumption are at a significantly greater risk of having TADs. Interestingly, 65.6% of the dilatations were located in the aortic arch and 30% of patients with TAD had multiple TADs. To our knowledge, our study is the largest to date to assess the association of TADs and saccular IAs and to include all three thoracic aortic segments (aortic arch, and ascending and descending aorta) with contemporary diagnostic imaging modalities. (Hiratzka et al., 2010)

6.4.1 Prevalence of TADs and TAAs

In the current study, the prevalence of abnormally dilated aorta (TAD or TAA) was 20.2%. The prevalence of TADs and TAAs was 18.0% and 7.5%, respectively. Goyal et al (Goyal et al., 2015) in a 2015 study reported a TAA prevalence of 4.7% in patients with IA. This difference may best be explained by the current study measuring all three thoracic aortic segments, whereas Goyal et al (Goyal et al., 2015) were only measuring the ascending aorta. Although the studies used for reference values were different, the thresholds for were very similar, accordingly, the rate of ascending aortic dilatation was virtually identical between the current study and the previous report. We found that the prevalence of ascending aortic dilatations that

were greater than 4.0 cm was 7.1% in the IA population. This prevalence is higher than that reported in the general population (prevalence of 2.7%). (Benedetti and Hope 2015)

In a study by Kuzmik et al (Kuzmik et al., 2010) from 2010, patients with TAA had a 9% prevalence of IAs and prevalence of IAs were higher when the descending aorta was aneurysmatic (33%) compared with the ascending aorta (7.1 %). In their study, only patients with operated TAA were included, possibly neglecting smaller thoracic aneurysms and dilatations. In addition, they did not describe aortic arch aneurysms separately. We found that nearly two-thirds of TADs located in the aortic arch, which is an unusual location for a TAA, typically aortic arch aneurysms account for approximately 10% of all TAAs. (Isselbacher 2005) The natural history of aortic arch aneurysms is poorly understood, but these patients are usually older with a greater burden of comorbidities. (Yiu and Cheng 2016) Nearly one-half of the patients with Turner syndrome have an elongation in the aortic arch, (Ho et al., 2004) but because no patients had Turner syndrome in our study, this finding does not explain the high prevalence of aortic arch TADs. Multiple aortic lesions are usually related to aortic arch aneurysms, (Crawford et al., 1984) which can explain high prevalence of multiple TADs in our study.

Finally, although BAVs are related to concomitant TAAs (Michelena et al., 2011) and an increased prevalence (7.7%-9.8%) of IAs, (Schievink et al., 2010; Egbe et al., 2017) only two patients (prevalence of 1.5%) had BAV in our study without concomitant TADs or TAAs. The 1.5% prevalence of BAV is comparable with the normal population (Larson and Edwards 1984) and in line with previous studies that have evaluated the prevalence of BAVs in patients with IAs. (Goyal et al., 2015)

6.4.2 Risk Factors for TAAs and TADs

TAAs and IAs shares similar risk factors, for instance, connective tissue diseases such as Marfan syndrome, Ehlers-Danlos syndrome type IV, and Loeys-Dietz syndrome, (Hiratzka et al., 2010; Kim et al., 2016) as well as habitual risk factors such as smoking and hypertension (Hiratzka et al., 2010; Vlak et al., 2013). Saccular IAs, TAAs, and abdominal aortic aneurysms share a similar genetic background (van't Hof et al., 2016) and approximately 20% of TAA patients have at least one first-degree relative with an arterial aneurysm (Albornoz et al., 2006). Our results, however, suggest that smoking, hypertension, or a positive family history of IAs is not an additional risk factor for TAAs or TADs. In addition, none of the patients in this study had a diagnosis of connective tissue disease, which is inconsistent with the high prevalence of TAD and TAA in our study. The absence of traditional risk factors for aneurysms, presence of multiple TADs, and abnormally high proportion

of dilatations in the aortic arch in our study suggests that there could be a hitherto unknown risk factor—genetic or acquired—shared between IAs and TAAs.

Instead, we found that rheumatic diseases and excessive alcohol consumption are major risk factors for concomitant TAD/TAA in patients with saccular IA. There is a lack of studies related to major alcohol consumption as a risk factor for TAAs. These studies have exclusively focused on abdominal aortic aneurysms with contradictory results, some studies have found alcohol consumption to decrease (Stackelberg et al., 2014) and others to increase (Wong et al., 2007) the risk for abdominal aortic aneurysms. Shovman et al (Shovman et al., 2016) in 2016 reported rheumatoid arthritis as a risk factor for TAA with an OR of 1.4 in the general population. In the present study, the risk of TAD was threefold for patients with rheumatic disease in a population with an overall prevalence of TAD almost one hundred times greater than reported for the general population. We defined rheumatic disease beyond only rheumatoid arthritis to include other autoimmune entities, which can explain this difference, although 65% of those categorized as having rheumatic disease indeed had rheumatoid arthritis. Autoimmune diseases can present with aortitis, which can consequently lead to aortic aneurysm formation. (Gornik and Creager 2008) The relationship between rheumatic diseases and IA formation has not been described previously, although autoimmune diseases might be associated with an increased risk of subarachnoid hemorrhage. (Ramagopalan et al., 2013) However, in accordance with a previous study, (Goyal et al., 2015) we did not find differences in the presentation of TAA or TAD between ruptured and unruptured IAs.

6.5 Limitations

This was largest study to date to evaluate the entire thoracic aorta in patients with IA. Only patients with widely accepted imaging modalities for TAA diagnosis were included. Because of the retrospective nature of the study, one of the limitations was a potential selection bias, especially in patients with unruptured IA. In our institution, CTA is usually performed to the level of pulmonary artery during the initial diagnosis of subarachnoid hemorrhage. However, in patients with an unruptured IA, chest imaging could have been performed for more various reasons. Different imaging modalities (CTA, CT, MRI, catheter angiography) might give different aortic diameters. In our study, 84% of patients (n = 347) had CTA and 11% of patients (n = 47) had a CT from the thoracic aorta with an equivalent prevalence of TADs (~21%) between these two imaging modalities. Thoracic aortic measurements were made from an MRI in 17 patients. None of the patients with an MRI had a TAD or an aneurysm. Another potential limitation is the lack of a control group of ethnically Finnish patients with measured thoracic aortic diameters and without IA,

which may introduce sampling bias. We did, nonetheless, use normative reference values from a previous large study with patients of Caucasian ethnicity. We defined a TAA as a dilatation of greater than 4.0 cm, which can overestimate the prevalence of TAA in our population. However, the exact threshold diameter for a dilatation to be categorized as an aneurysm is not entirely clear from the existing literature.

Finally, our population-based study might be well generalizable with other populations. In Finland, the incidence of aneurysmal subarachnoid hemorrhage is comparable with other Nordic countries (approximately 10/100,000 persons) (Korja et al., 2016) and the prevalence of unruptured IAs is similar globally. (Vlak et al., 2011) In addition, incidence of TAA/dissections in Finland (approximately 5/100,000 per year) (Pan et al., 2018) is also comparable with other countries. (Hiratzka et al., 2010)

6.6 Conclusions

The prevalence of TAAs and dilatations is higher in patients with intracranial saccular aneurysms and especially in patients with a history of rheumatic disease and/or alcohol abuse. Our results suggest that IAs could be associated with aortopathy. In addition, IAs and TAAs/dilatations might share a similar specific pathogenetic background beyond traditional risk factors such as smoking and hypertension.

7 Study IV: Acute Treatment of Ruptured Fusiform Posterior Circulation Posterior Cerebral, Superior Cerebellar, and Posterior Inferior Cerebellar Artery Aneurysms With FRED Flow Diverter: Report of 5 Cases.

Abstract. Flow diverter (FD) treatment of ruptured fusiform posterior cerebral artery (PCA), posterior inferior cerebellar artery (PICA), and superior cerebellar artery (SCA) aneurysms are limited to single reports. To study the safety and efficacy of FD treatment for ruptured fusiform aneurysms of the PCA, SCA, and PICA. Five patients with ruptured posterior circulation fusiform aneurysms and treated with a Flow-Redirection Endoluminal Device (FRED/FRED Jr, Microvention, Tustin, California) stent in the acute phase of subarachnoid hemorrhage between 2013 and 2016 were included and reviewed retrospectively. Two aneurysms located on the PICA, 2 on PCA, and 1 on the SCA. Mean treatment time with FD was 5.8 d (range, 0-11 d) from ictus. The technical success rate was 100%. On admission 2 patients were Hunt and Hess grade 1, 2 patients grade 3, and 1 patient grade 4. At discharge, 4 patients (80%) were independent (modified Ranking Scale (mRS) $\leq$2) and 1 patient had severe disability (mRS 4). None of the patients had aneurysmal rebleeding. All 5 aneurysms were completely occluded on angiographic follow-up (range, 3-22 mo). One patient had permanent intraprocedural in stent thrombosis and brain infarction. One patient had spontaneous nonaneurysmal intracerebral hemorrhage 1 mo after FD treatment. External ventricular drainage was inserted in 3 patients and ventriculoperitoneal shunt in 2 patients without hemorrhagic complications despite dual antiplatelet therapy. FD could be considered as a treatment option for ruptured fusiform aneurysms located on PCA, PICA, or SCA when other treatment options are challenging.

7.1 Introduction

Ruptured fusiform intracranial aneurysms (IA) are uncommon and account for only 4.5% of all subarachnoid hemorrhages (Sasaki et al., 1991). Without treatment there is a high risk of rebleeding and mortality up to 71% and 47% respectively (Mizutani et al., 1995). Approximately 78% of posterior circulation fusiform IAs are located on the vertebral or basilar artery, 20% on the posterior cerebral artery (PCA) and 2% on the posterior inferior cerebellar artery (PICA). (Coert et al., 2007) Ruptured fusiform superior cerebellar artery (SCA) aneurysms are an extremely rare entity and limited to about 20 case reports. (Lamis et al., 2014) Because of the rarity, there is a lack of evidence for the best treatment option for the ruptured PCA, PICA, and SCA fusiform aneurysm. Fusiform IAs can be treated with deconstructive (surgical/endovascular parent artery occlusion) or reconstructive techniques (trapping with bypass, endovascular stenting) (Awad et al., 2017).

Deconstructive techniques carry a risk for brain infarction and may be more suitable for nondominant distal PICA, anterior inferior cerebellar artery, and SCA aneurysms while flow diversion could be a better treatment option for basilar, vertebral, and PCA aneurysms, without compromising parent artery patency. (Awad et al., 2017)

Although there are earlier reports of posterior circulation aneurysms treated with flow diversion, most of these aneurysms has been unruptured, located in the basilar or vertebral artery and treated with Pipeline Embolization Device (Medtronic Inc, Dublin, Ireland). (Wang et al., 2016) Treatment of acutely ruptured fusiform IAs with flow diverter stents (FD) is still limited to single reports and none of these have been treated with the Flow-Redirection Endoluminal Device (FRED) FD (Microvention, Tustin, California). (Maus et al., 2018; Kiyofuji et al., 2018)

In this study we present unique case series of ruptured fusiform IAs located in PCA, PICA, and SCA arteries and treated with FRED flow diverter in the acute phase of subarachnoid hemorrhage (SAH) with a good patient outcome.

7.2 Materials and Methods

7.2.1 Study Patients

This retrospective study was approved by a local institutional review committee. Patients diagnosed with acute aneurysmal SAH related to a fusiform posterior circulation aneurysm and treated in the acute phase endovascularly with the Flow-Redirection Endoluminal Device (FRED/FRED Jr, Microvention) in our hospital district area between 2013 and 2016 were included in this study. These aneurysms

were considered to be untreatable with conventional endovascular techniques (coiling or stent/balloon assisted coiling) or surgically and FD treatment-related risks were evaluated to be lower compared to conservative management. Because of off-label use of FD, the decision was carefully discussed within our multidisciplinary neurovascular team as well as with the patient or relatives. Patient consent was not needed, because this was a retrospective study and there were no ongoing study relating to primary treatment with FD in these patients.

7.2.2 Procedure Details

All patients were treated under general anesthesia via transfemoral artery approach. Patients received intraprocedural Heparin 5000 to 7000 U iv and aspirin 250 to 500 mg iv and in addition abciximab 0.25 mg/kg iv bolus and 0.125 mg/kg infusion were administered for 4 patients (patients 1, 2, 4, and 5). Patient 3 was preloaded with 60 mg Prasugrel before intervention. Other patients started with loading dose 60 mg 2 h before the abciximab infusion was finished. Prasugrel 10 mg/d per os was continued for 6 mo and aspirin 100 mg/d was continued for 12 mo postoperatively in 4 patients and in 1 patient Prasugrel was discontinued after 1 mo because of late intracerebral hemorrhage.

7.2.3 Study Outcome Measures

Clinical data, complications, and relevant imaging data on admission, during the hospitalization and on follow-up were evaluated. Clinical outcome was evaluated at the first hospital discharge, at 3-mo and at 1-yr follow-up by modified Ranking Scale (mRS). Aneurysm measurements were evaluated from digital subtraction angiography (DSA) and angiographic follow-up from DSA or magnetic resonance angiography. The O'Kelly Marotta (OKM) grading scale (O'Kelly et al., 2010) for flow diversion was used to categorize aneurysm filling (OKM A = total filling, OKM B = subtotal filling, OKM C = entry remnant, and OKM D = no filling) on the immediate and follow-up angiographic results. (O'Kelly et al., 2010)

7.3 Results

7.3.1 Patient and Aneurysm Characteristics

A total of 5 patients (4 females, 80%) with a mean age of 56.6 yr (range from 44 to 72 yr) were included in this study from 128 patients who were treated with FD from 2013 to 2016. Demographic data are presented in Table 1.

Five ruptured fusiform aneurysms were treated with the FRED/FRED Jr FDs (Microvention Inc) in the acute phase of SAH (range, 0-11 d after ictus). Patients were treated with FD alone. Two aneurysms were located on the PCA, 2 on the PICA, and 1 on the SCA. The average size (width) of all aneurysms was 4.1 mm (range, 4.0-4.4 mm). Diameter of the parent artery averaged 1.8 mm (range, 1.2-2.3 mm). Aneurysm characteristics are presented in Table 2.

Three patients required external ventricular drainage due to acute hydrocephalus and 2 of these patients required permanent ventriculoperitoneal shunt. External ventricular drainages were inserted before the FD treatment.

Table 1. Patient characteristics (Laukka et al., 2019)

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Age/sex	44/F	53/F	72/M	59/F	55/F
Smoking	no	N/A	N/A	no	N/A
HH	3	4	1	1	3
GCS	14	7	15	15	10
Fisher scale	4	4	2	1	4
Vasospasm (n= 2)	no	yes	no	no	yes
EVD (n= 3)	no	yes	yes	no	yes
VPS (n= 2)	no	yes	no	no	yes
mRS1	1	2	2	1	4
mRS2	0	1	1	2	3
mRS3	0	n/a	1	1	3

HH= Hunt and Hess grade, mRS1= modified Ranking Scale at first hospital discharge after the subarachnoid hemorrhage, mRS2= modified Ranking Scale at 3-month follow-up, mRS3= modified Rankin Scale at 1-year follow-up, EVD= external ventricular drainage, VPS= ventriculoperitoneal shunt, n/a= not available

7.3.2 Complications and Outcome After Flow Diversion

The technical success rate was 100%. There were no aneurysmal rebleeding. All neurosurgical procedures were carried out without hemorrhagic complications. Patient outcomes are shown in Table 1. At discharge and at 3-mo follow-up 4 patients had a good outcome (mRS ≤2). One patient had severe disability at discharge and at 3-mo follow-up (mRS ≥3). FD-related complications in this study are shown in Table 2.

Patient 1 had transient intraprocedural stent thrombosis (IPST) which resolved with abciximab bolus (0.25 mg/kg iv) during the procedure. Treatment was continued with an abciximab infusion (0.125 mg/kg), which was administered over 15 h. Patient experienced no neurological symptoms from IPST and there were no brain infarctions on the follow-up imaging studies.

Patient 2 had intragastric bleeding 2 wk after the FD treatment.

Patient 3 had permanent IPST and postoperative brain infarction in the right PCA territory. Patient had a deteorientation and left-hand ataxia after the procedure. Abciximab was not administered in this patient.

Patient 4 had a retroperitoneal hemorrhage on the second day after FD treatment likely due to treatment with abciximab for transient IPST. IPST resolved during the procedure and was treated with abciximab with the same protocol as patient 1. The patient experienced no neurological symptoms due to transient IPST and no ischemic complications were seen in the brain magnetic resonance imaging at 4 mo after the treatment. The same patient had spontaneous intracerebral hemorrhage and right homonymous hemianopia 1 mo after the FD treatment.

Patient 5 had transient neurological deterioration and right upper arm plegia 8 d after FD treatment without signs of ischemic events on immediate head computed tomography scan or at the 1-yr follow-up scan.

Table 2. Characteristics of fusiform aneurysms, treatment and complications (Laukka et al., 2019)

Patient	Location (segment)	Size (mm) Widthxlength	Parent artery diameter (mm)	Time to treatment (Days)	Stent size (mm) Widthx length	FD-related complications
1	PCA (P2) l.dx	4.0x7.5	2.2	10	3.5x13	Transient IPST
2	SCA (S1) l.dx	4.0x7.0	1.2	0	Fred jr x 2	Intragastric bleeding
3	PICA (p1) l.dx	4.4x7.7	1.3	11	3.5x13	Permanent IPST, brain infarction.
4	PICA (p3) l.sin	4.0x7.0	2.0	4	3.5x13	Late ICH, transient IPST, retroperitoneal hemorrhage
5	PCA (P2) l.sin	4.3x7.0	2.3	4	3.5x22	Transient neurological symptom

PCA= posterior cerebral artery, SCA= superior cerebellar artery, PICA= posterior inferior cerebellar artery, FD= flow diverter stent, IPST= intraprocedural stent thrombosis, ICH= intracerebral hemorrhage

7.3.3 Angiographic Follow-up

Angiographic follow-up results for each FD treated aneurysm are shown in Table 3. Partial aneurysm occlusion (OKM B) was seen on all 5 patients on immediate postprocedural angiography (Figures 1–3).

Digital subtraction angiographic follow-up (range, 3-22 mo) showing complete occlusion (OKM D) was available for all 5 patients (Figures 1–3). One patient had symptomatic permanent total stent stenosis on periprocedural angiography as well as on angiographic follow-up.

Table 3. Angiographic follow-up (Laukka et al., 2019)

Patient	Immediate	1.Control (months from treatment/imaging modality)	2.Control (months from treatment/imaging modality)
1	OKM B	OKM D /3 months/DSA	OKM D /22 months/DSA
2	OKM B	OKM D/6 months/DSA	N/A
3	OKM B	OKM D /6 months/DSA	N/A
4	OKM B	OKM D/8 months/DSA	OKM D/18 months/MRI+MRA
5	OKM B	OKM D /11 months/DSA	N/A

OKM= O`Kelly-Marotta grading scale (OKM A= total filling, OKM B= subtotal filling, OKM C= entry remnant, OKM D= no filling), N/A= not available

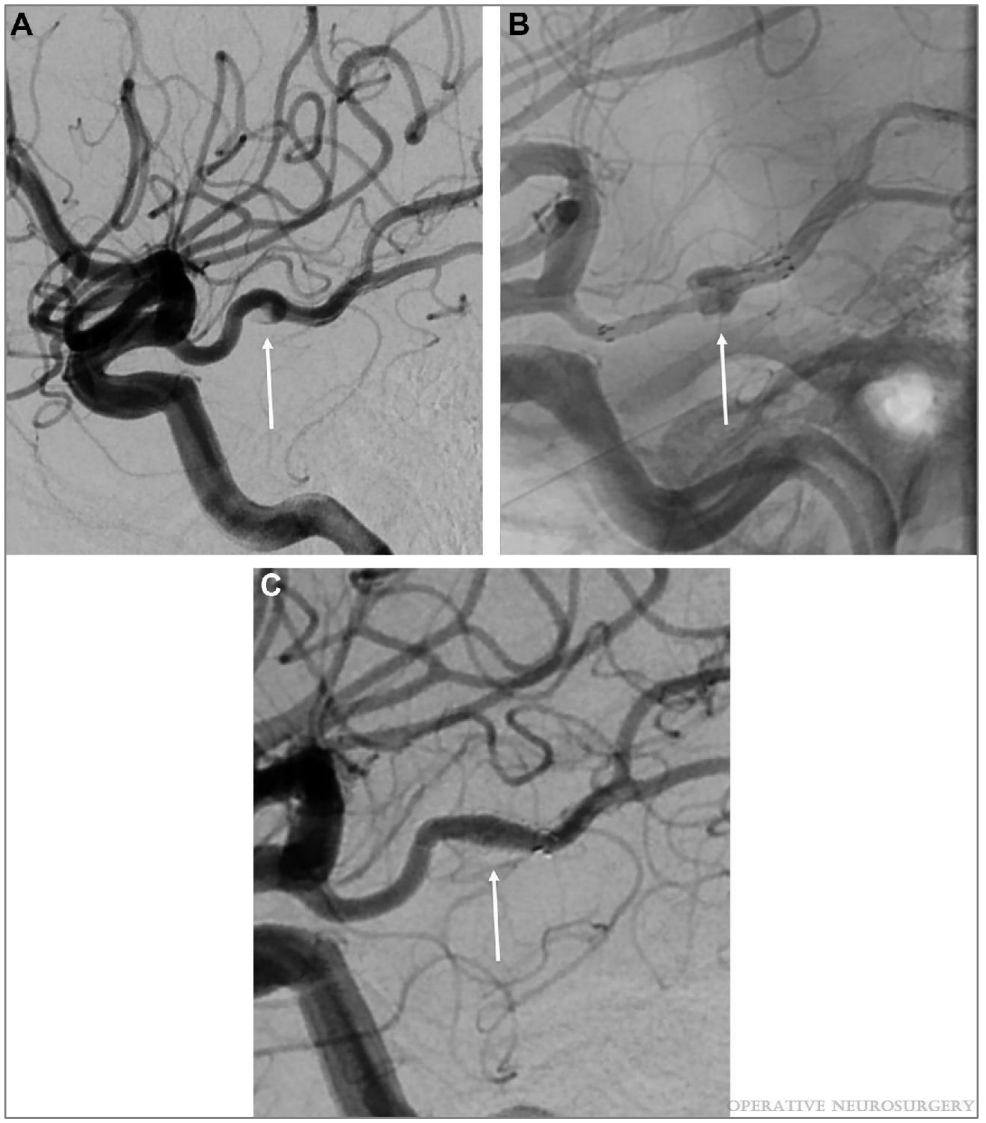

Figure 1. Patient 1 with a ruptured fusiform aneurysm in the P2 segment of the right PCA before the treatment with FRED (DSA). B, Immediate postoperative angiography shows intra-aneurysmal flow reduction (DSA). C, At 22-mo follow-up, total aneurysm occlusion was observed (DSA). (Laukka et al., 2019)

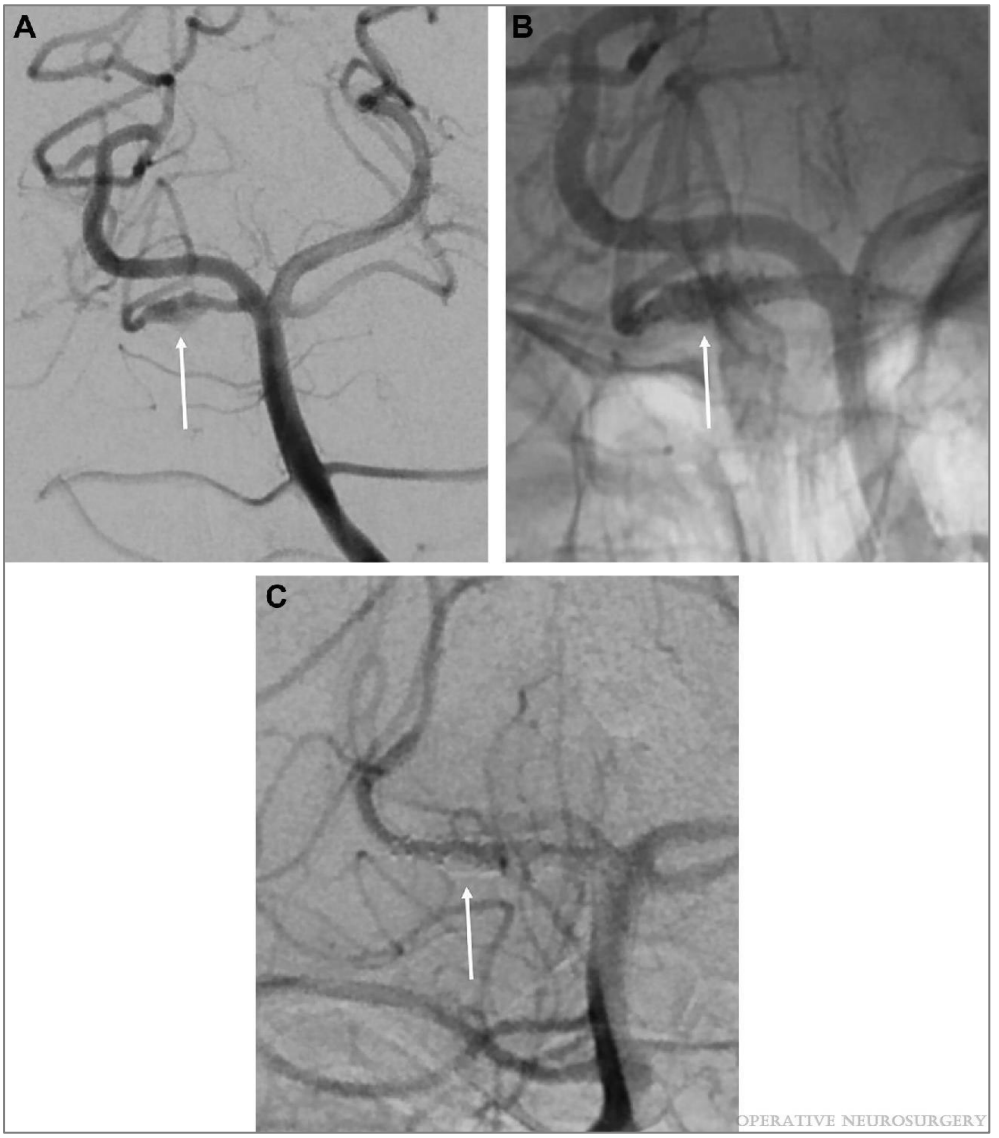

Figure 2. Patient 2 with a ruptured fusiform aneurysm of the right SCA (DSA). B, Patient was treated with 2 FRED Jr stents (Microvention) and immediate postoperative angiography showed intra-aneurysmal flow reduction after the stent implantation (DSA). C, At 6-mo follow-up, total aneurysm occlusion was observed (DSA). (Laukka et al., 2019)

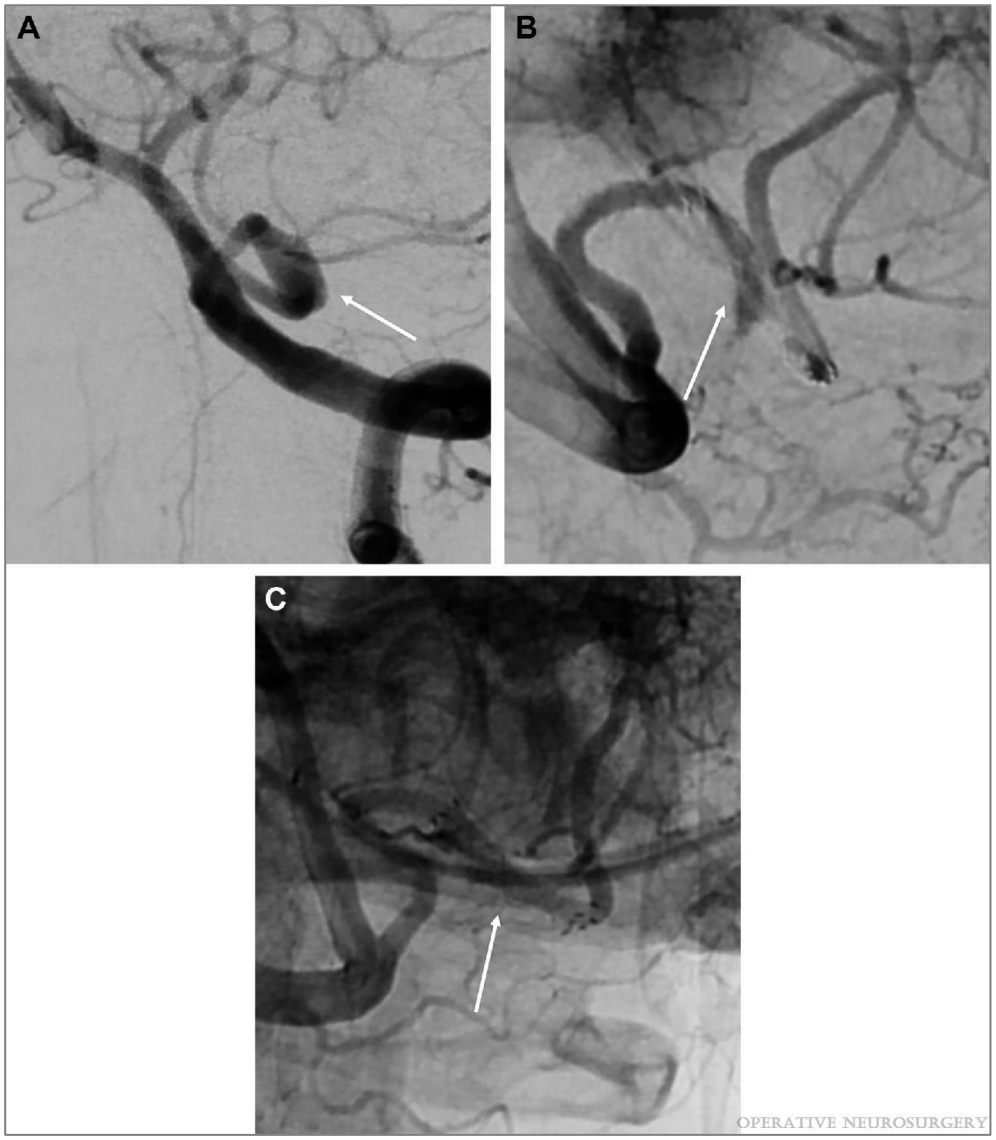

Figure 3. Patient 4 with a ruptured fusiform aneurysm of the left posterior inferior cerebellar artery before the implantation of the FRED (Microvention, DSA). B, Intra-aneurysmal flow-reduction was observed in the immediate postoperative image (DSA). C, At the 8-mo follow-up, complete aneurysm occlusion was observed (DSA). (Laukka et al., 2019)

7.4 Discussion

To our knowledge, this is the first report of patients with ruptured fusiform aneurysms in the SCA, PCA, and PICA arteries, which have been treated with FRED/FRED Jr FDs (Microvention) as a first line treatment in the acute phase of SAH. Previously, FRED/FRED Jr has been used primarily in the treatment of unruptured anterior circulation aneurysms with a similar aneurysm occlusion rates and patient morbidity, mortality, and outcome rates compared to other FDs. (Mohlenbruch et al., 2015; Briganti et al., 2016; Luecking et al., 2017)

In our series, FD was chosen for first line treatment only if other treatment possibilities were not feasible. Due to location of the aneurysms and insufficient collateral circulation we evaluated that parent artery occlusion would have led to serious brain infarction and disability. We chose to use the FRED/FRED Jr flow diverter stent in particularly for these aneurysms with complex angioarchitecture because we are familiar with the smooth delivery properties of the FRED/FRED Jr flow diverter in very tortuous vessels.

7.4.1 Patient Outcomes for Ruptured Posterior Circulation Aneurysms

In our series 80% of patients had a good outcome (mRS ≤2) at discharge and at 3-mo follow-up with 0% mortality.

In one meta-analysis morbidity of 14% and mortality of 13% were related in the deconstructive treatment of the ruptured nonsaccular vertebrobasilar aneurysms without significant difference compared to reconstructive techniques. This meta-analysis however neglected SCA, PICA, and PCA aneurysms. (Sönmez et al., 2015) Oran et al (Oran et al., 2009) reported neurological complications in 31% of patients with SCA, PCA, PICA, and anterior inferior cerebellar artery aneurysms who were treated with deconstructive technique.

Most of the previous FD studies have focused on the Pipeline Embolization Device (Medtronic Inc) in the treatment of ruptured intracranial aneurysms with 68% favorable outcome and 14% mortality in a treatment of ruptured posterior circulation aneurysm, but in these studies 79% of aneurysms have located on the basilar or vertebral arteries. (Wang et al., 2016) In their meta-analysis, Kiyofuji et al., (Kiyofuji et al., 2018) included patients with posterior circulation nonsaccular aneurysms which were treated with FD. They reported mortality and morbidity rates of 21% and 26%, periprocedural stroke of 23%, and long-term occlusion rates of 52%. They also found that vertebral artery aneurysms were related to better neurological outcomes compared to other locations in the posterior circulation. However, only 15 patients had ruptured aneurysm in this meta-analysis.

None of the aneurysms were giant or located on the basilar artery which can explain better outcomes and low mortality rates in our patients compared to previous studies. (Wang et al., 2016) Small average size of aneurysms might also explain 0% rebleeding rates in our series thus aneurysms size >2 cm have higher risk of rebleeding after flow diversion. (Madaelil et al., 2017)

7.4.2 Immediate and Long-Term Occlusion Rates After Flow Diversion

Immediate postoperative angiography showed decreased blood flow in every treated aneurysm and 100% occlusion rate on the follow-up angiography.

It is not well studied how immediate intra-aneurysmal blood flow changes after the flow diversion correlates aneurysm re-rupture rates in the acute setting of SAH. Immediate intra-aneurysmal flow velocity reduction might have only a little effect on lowering intra-aneurysmal pressure right after the flow diversion. (Shobayashi et al., 2013) In a worst case scenario, intra-aneurysmal pressure can even increase and lead to rupture after the flow diversion. (Cebral et al., 2011) Flow diversion might have more efficient immediate flow-reduction effect on fusiform aneurysms compared to saccular aneurysms, (Xiang et al., 2015) though immediate flow-reduction seems not to correlate occlusion rates on the long-term follow-up when treating unruptured aneurysms. (Labeyrie et al., 2016)

FD deployment was successful despite the small size of the parent arteries. Limited data are available on flow diversion in the small parent arteries. The Pipeline Embolization Device FD has deployed successfully in the small parent arteries (<2.5 mm) without complications and with 100% total occlusion rate on follow-up. (Puri et al., 2016) When uni-layer stent is deployed in the small parent artery it might elongate leading to increased porosity and impairment of the flow diversion effect. In contrast to uni-layer stents FRED is a dual-layer stent that consists of a low-porosity inner mesh and a high-porosity outer stent which may provide safer deliverability and more efficient flow diversion.

7.4.3 Acute Stent Thrombosis and Thrombolytic Therapy in the Acute Phase of SAH

Stent thrombosis is one of the complications associating to flow diversion. In one study, 4.6% of patients had intraprocedural in-stent thrombosis after stent deployment. (Adeeb et al., 2017) Some studies suggest, that IPST can be treated safely with abciximab during the acute SAH. (Tahtinen et al., 2009; Golshani et al., 2012; Gentric et al.; 2015) In our study, 4 patients received abciximab bolus and abciximab infusion. Two patients had transient intraprocedural in-stent thrombosis

without signs of brain infarction on the follow-up imaging studies. One patient, who did not receive abciximab during or after the endovascular procedure, had a permanent stent thrombosis and brain infarction but recovered well after the hospitalization (mRS 2). There were no intracranial bleeding complications during the hospitalization period which supports the idea of a safe usage of abciximab during the acute SAH.

In our series, high rate of stent thrombosis might be explained by several factors. First, patients with SAH are at hypercoagulable state (McBride et al., 2017) and disturbed coagulation/fibrinolysis system could increase the risk for stent thrombosis. (Nina et al., 2001; Miao et al., 2018) Second, small parent artery diameter and fusiform morphology might have increased the risk for stent thrombosis. (Srinivasan et al., 2018)

7.4.4 Dual Antiplatelet Therapy and Neurosurgical Procedures

The major concern of FD treatment of acute SAH is the need for dual antiplatelet therapy. Symptomatic hemorrhage risk of 1.4% to 71% relating to external ventricular drainage during anticoagulation therapy has been shown in smaller series. (Bruder et al., 2015) In our series 3 patients required external ventricular drainage and 2 of these patients required ventriculoperitoneal shunt, with none of these patients experiencing hemorrhagic complications. One ventriculoperitoneal shunt was inserted during the acute phase of SAH after FD treatment. Every external ventricular drainage was inserted prior to FD treatment along our normal clinical policy.

7.5 Limitations

There are some limitations in our study. First, this study was retrospective and had limited number of patients. Second, in some patient treatment was delayed because FRED flow diverter stent was not immediately available in our hospital in that time and had to be ordered from the manufacturer separately.

7.6 Conclusions

This small series suggests that the FRED flow diverter stent (Microvention) can be successfully used in the acute treatment of ruptured SCA, PCA, and PICA aneurysms. However, despite the good patient outcomes in our series, FD treatment carries out high risk of complications and should only be considered as a last treatment option in such cases.

8 General discussion and future perspectives

Prevalence of unruptured sIAs is around 3% (Vlak et al., 2011), but approximately only ~0.3% of IAs rupture during the lifetime (Thompson et al., 2015). IA ruptured leads to subarachnoid hemorrhage which affects mostly people at working age. Mortality can reach up to 40% at one year after the subarachnoid hemorrhage (Korja et al., 2013) and only one third of those who survive are able to return back to work (Buunk et al., 2019). Pathophysiology of sIAs is not completely clear, but inflammation has a crucial role (Chalouhi et al., 2013). Risk factors for sIAs are manifold and most likely sum of different genetic and modifiable risk factors (Thompson et al., 2015). Because aneurysmal SAH is such a devastating disease it would be optimal to identify and treat high risk UIAs before the rupture. However, one major issue is that at the moment it is almost impossible to evaluate which UIAs are exactly at the rupture risk (Etminan et al., 2022). It is important to understand pathophysiology of IAs to develop new treatment options for IAs. Endovascular treatment has become the primary treatment for the most of the IAs and it is important to constantly study efficacy and safety of these treatments to optimize safety for the patients (Salem et al., 2021).

Neurosurgical department of Turku University Hospital is responsible for the treatment of intracranial aneurysm disease of around 870 000 people. All aneurysms are evaluated in the multidisciplinary neurovascular team and treatment is tailored individually. Tertiary healthcare in Finland is funded by the government and all patient are eligible to equal treatment no matter of social or economic background. This allows high-quality retrospective registries in Finland with a low bias in patient selection.

In the study I and II we evaluated if childhood Kawasaki disease is associated with increased risk of unruptured sIAs by screening IAs with MRA in 40 adult patients with a history of Kawasaki disease in childhood. In the study III we evaluated if sIAs are associated with thoracic aortic dialations or thoracic aortic aneurysms. In the study IV we analyzed retrospectively outcomes of FRED flow diverter stent in the treatment of ruptured posterior circulation fusiform IAs in five patients who were treated at Turku University Hospital between 2013 and 2016.

8.1 Study I and II

(Study I and II) In this prospective cohort study, we screened IAs and WMHs with brain MRA and MRI for 40 patients with a current age of ≥25 and with a history of Kawasaki disease in a childhood.

In the study (I) we found that none of the patients had intracranial aneurysms. SIA formation and rupture is poorly understood and multifactorial. (Chalouhi et al., 2013) Inflammation plays an important role in the formation of sIAs (Frösen et al., 2019) and also in the formation of coronary artery aneurysms in KD (Newburger et al., 2016). Kawasaki disease is a vasculitis that affects medium sized arteries (Cohen and Sundel, 2016) and the most recognized complication is coronary artery aneurysms (Kato et al., 1996). Cerebral vasculitis has also reported in Kawasaki disease patients. (Amano and Hazama 1980) Our hypothesis was that Kawasaki disease could increase the risk for intracranial aneurysms through the vessel wall inflammation.

We were able to show that prevalence intracranial aneurysms in Kawasaki disease is unlikely over 10% as we did not find any intracranial aneurysms in Kawasaki disease patients. To show smaller differences it would have required unrealistically large number of patients. For example, if we would have expected that the prevalence of intracranial aneurysms is 5% in Kawasaki disease patients we would have to recruit 862 Kawasaki disease patients to show the difference when compared to prevalence of 3.2% (prevalence in general population) with a p-value=0.05 and 80% power. Estimated incidence of Kawasaki disease in under 5 years old (6-12 per 100 000 patients per year) and 5-9 years old patients (2-3 per 100 000 patients per year). (Salo et al., 2012) Number of under 5 years old and 5-9 years old citizens in Southwest Finland is around 25 000 for each age group. Based on incidence and number of citizens for each age groups we estimated that around four children's per year was diagnosed with Kawasaki disease between 1980 and 1988. We were able to find 60 patient with Kawasaki disease and met the inclusion criteria, of which 40 eventually participated in our study. We found patients who fulfilled our inclusion criteria in much larger time period than we expected (from year 1978 to year 1995).

We choose to compare our results with a 10% prevalence figure for the following reasons. Screening of UIAs is recommended in a populations with a high risk of intracranial aneurysms. In these high risk populations, for example, in patients with ≥2 first degree relatives with IAs, the expected prevalence of UIAs is more than 10% (Thompson et al., 2015). While in the general population the prevalence of UIAs is estimated to around 3% (Thompson et al., 2015). In addition, in cost-effective calculations screening could be reasonable in a populations with an expected prevalence of over 10% (Gupta et al., 2013).

In the study (II), we compared WMH prevalence and burden to age- and sex-matched controls with migraine. In the study (II) we found that patients with Kawasaki disease had significantly higher WMH burden compared to controls. These findings suggests that cerebrovascular involvement of Kawasaki disease might be more common than previously thought.

WMHs are considered as a sign of cerebral small vessel disease. WMHs are associated with an increased risk for dementia, stroke, psychiatric disorders and mortality. Up to one third may have neurological symptoms during the acute phase of KD (Au et al., 2006) and cerebral hypoperfusion has been reported in KD patients without or with neurological symptoms (Ichiyama et al., 1998; Hikita et al.; 2011). Symptomatic brain infarcts are rare in KD (Wang et al., 2021), but KD might be associated with an increased risk of cerebrovascular diseases in the long-term (Lin et al., 2021). However, there are lack of prospective studies that have investigated brain findings after the KD (Muneuchi et al., 2006).

Cerebral hypoperfusion due to cerebral vasculitis could explain increased WMH burden in KD patients (Ichiyama et al., 1998; ten Dam et al., 2007; Hikita et al., 2011). In addition, intravenous immunoglobulin could increase risk for thromboembolic complications (Daniel et al., 2012; Ammann et al., 2016). However, we did not find statistically significant difference in KD patients between those who received intravenous immunoglobulin and those who did not.

Because brain MRIs were not performed in the acute phase of KD, it remains unclear at what stage WMHs developed in KD patients. In the future, it would be interesting to study brain MRI findings in a larger KD population and with repeated imaging.

8.2 Study III

In this retrospective study we analyzed thoracic aortic diameters from 411 patients with sIA. We found that 18% of sIA patients had thoracic aortic dilatation and 8% thoracic aortic aneurysm. Interestingly, most of the thoracic aortic dilatations located in the aortic arch (66% of the dilatations).

Previous studies suggest that aortic diseases (bicuspid aortic valve, aortic coarctation, aortic aneurysms) might be associated with increased risk for IAs (Connolly et al., 2003; Schievink et al., 2010; Kuzmik et al., 2010; Rouchaud et al., 2016; Egbe et al., 2017). Fusiform IAs might also be associated with aortic aneurysms (Kurtelius et al., 2019). Some of the aortic diseases are related, for example bicuspid aortic valve is associated with ascending aortic dilatation/aneurysms and aortic coarctation (Michelena et al., 2011; van De Pol et al., 2017), and around 20% of patients with abdominal aortic aneurysms have concomitant thoracic aortic aneurysm (Gouveia et al., 2020). The prevalence of IAs has been reported to be around 10% in patients with aortic aneurysm (Kuzmik et al., 2010; Rouchaud et al., 2016), but the reverse association has been little studied (Goyal et al., 2015).

The increased prevalence of thoracic aortic aneurysms/dilatation in IA patients might be explained by many different factors. IAs and thoracic aortic aneurysms share similar modifiable risk factors such as smoking and hypertension (Hiratzka et al., 2010; Vlak et al., 2013) and non-modifiable risk factors such as Marfan syndrome, Ehlers-Danlos syndrome and Loyes-Dietz syndrome (Erbel et al., 2014; Kim et al., 2016). Thoracic aortic aneurysms and sIAs have also overlapping genetic risk factors (van't Hof et al., 2016). It is possible that, for example, there are so far unknown underlying risk factors (genetic or aquired) between thoracic aortic aneurysms and sIAs.

In conclusion, according to our study the prevalence of thoracic aortic aneurysms and dilatations is higher in sIA patients compared to reports from the general populations. There could be shared risk factors between thoracic aortic aneurysms and sIAs. More prospective screening studies should be carried out to confirm our results.

8.3 Study IV

(Study IV) In this study we found that FRED flow diverter stent is feasible treatment for the ruptured posterior circulation fusiform intarcranial aneurysms located in SCA, PCA or PICA with a good occlusion rate (100% on the follow-up). Fusiform IAs accounts only about 4% of all subarachnoid hemorrhages (Sasaki et al., 1991). In comparison to sIAs, fusiform IAs are more complex to treat with conventional techniques (clipping or endovascular coiling), because fusiform IAs usually lack separate neck and usually locate in the posterior circulation (Awad et al., 2017). Before flow diverter stents, fusiform IAs has been treated with surgical or endovascular trapping of the parent artery with or without bypass (Awad et al., 2017). However, trapping carries a high risk of morbidity, especially for ischemic complications (Oran et al., 2009). Flow diverter stent is a new endovascular treatment which has simplified treatment of the complex intracranial aneurysms without compromising the parent artery. Official indication for flow diverter stent treatment is unruptured wide neck intracranial aneurysms located in the internal carotid artery. However, flow diverter stents have been used as an off-label treatment for the ruptured IAs and IAs beyond the internal carotid artery. (Limbucci et al., 2020) Ruptured posterior circulation fusiform IAs are rare and can be extremely challenging to treat. Without treatment ruptured fusiform IA there are 70% re-rupture risk and mortality can reach up to 50% (Mizutani et al., 1995).

In our series, technical success rate was 100% and there were no re-ruptures. Two patient had major neurological complications (1 brain infarction and 1 late intracerebral hemorrhage) and one patient transient neurological symptom. Two patients had extracranial hemorrhagic complications. Despite complications 80% of the patients had good outcome. Major concern in the treatment of acutely ruptured IAs with flow diverter stent is need for dual antiplatelet therapy. Because patients with SAH may require invasive neurosurgical procedures such as external ventricular drainage, ventriculoperitoneal shunt and craniotomy there are high risk for hemorrhagic complications due to antiplatelet therapy. On the other hand, discontinuation of the antiplatelet therapy increases the risk for stent thrombosis and ischemic complications. In our series, external ventricular drainage was inserted in three patients (60%) before the flow diverter stent treatment and two of these patients required ventriculoperitoneal shunt later. There were no hemorrhagic complications relating to external ventricular drainage or shunt procedures.

Because ruptured SCA, PCA and PICA fusiform aneurysms are rarity the treatment outcomes are limited to case reports and therefore there is no standard treatment for these aneurysms. In our retrospective cohort, FRED flow diverter stent was a technically feasible treatment for ruptured SCA, PCA and PICA fusiform IAs, was efficient to prevent aneurysm re-rupture and 80% of patients had good recovery.

8.4 Future perspectives

With the increase in neuroimaging (ElHabr et al., 2022), it is possible that more incidental UIAs will also be detected. Because treatment related complication risks are 5%-8% it is important to identify those aneurysms which will truly rupture in the future without treatment (Algra et al., 2019). Currently there are no specific imaging or laboratory test to tell which UIAs will certainly rupture in the future. Evaluation of rupture risk is based on the aneurysm related factors (size and shape, location, number of aneurysms) and patient related risk factors (Hackenberg et al., 2018), but these estimations might be inaccurate. For example based on PHASES score patients with >7 mm UIA should be treated (Greving et al., 2014), but in fact almost 50% of rIAs are <5 mm in size (Molyneux et al., 2002).

Another important question is, can UIAs be treated medically to prevent rupture? Randomized double-blinded follow-up studies are hard to implement in this area. This kind of studies would require a very large population and a long follow-up period, which would raise numerous ethical questions. Based on retrospective studies there are some evidence that acetylsalicylic acid could lower the risk for UIA rupture (Can et al., 2018; Hostettler et al., 2018). There is contradictory evidence about statins in preventing UIA rupture (Can et al., 2018; Bekelis et al., 2015). Due to the limited research evidence, initiation of acetylsalicylic acid or statin medication is currently not recommended for UIA patients to prevent rupture (Etminan et al., 2022).

At the time of this dissertation, Germany and Netherlands has initiated prospective randomized trial to study if aspirin and intensive blood pressure treatment reduces IA growth and rupture risk and in University Hospitals in Finland, including Turku University Hospital, is also involving this study (Vergouwen et al., 2018).

Statins reduces vascular inflammation and are widely used in atherosclerotic disease, but there are conflicting results in reducing IA rupture risk. In animals studies statins has decreased inflammation in UIA wall and prevented aneurysm development (Aoki et al 2008), but Tada et al., 2011 found that satins could also induce aneurysmal growth and rupture (Tada et al., 2011). In retrospective human studies statins has reduced risk for rIAs (Yoshimura et al., 2014; Can et al., 2018, Hostettler et al., 2018), but another study found that statins do not reduce risk for rIAs (Bekelis et al., 2015). In addition, Marbacher et al., 2012 did not find association between statin use and UIA risk (Marbacher et al., 2012).

In the future it would be important to develop more accurate methods to evaluate UIA rupture risk. Better imaging methods could help to identify those UIAs which have active aneurysm wall inflammation and thus could be at the risk for rupture.

With developing MRI techniques, MRI could be a potential tool in the assessment of IA rupture risk. Ultra-high field MRI (7 TESLA) can show accurately IA vessel wall irregularities and secondary signs of inflammation which could predict future rupture risk, however availability of ultra-high field MRIs is poor (Leemans et al., 2020). Recent studies has promising results of 3-Tesla MRI imaging with high resolution vessel wall imaging techniques, showing that those aneurysms with a higher rupture risk could have more gadolinium enhancement in the aneurysm wall (Edjlali et al., 2018; Vergouwen et al., 2019). The use of ferumoxytol as a contrast agent can also be a valid method to show the inflammatory state of the aneurysm wall and early enhancement with ferumoxytol might predict UIA rupture risk (Hasan et al., 2012).

Positron emission tomography (PET) could be an option to show UIA inflammation. PET imaging has been used to show inflammation in, for example, aortic aneurysms (Forsythe et al., 2018), carotid plaques (Rudd et al., 2002; Mikail et al., 2022) and coronary artery plaques (Figtree et al., 2022). Despite promising results of MRI imaging, they have not made their way to clinical use yet. Not a single study has yet been conducted that has investigated PET imaging in IAs. However, our research group has started a clinical prospective study to find out whether inflammation of the UIA wall can be demonstrated with PET imaging. In addition to IA rupture risk evaluation, a proper imaging method of IA inflammation could open the way for different pharmaceuticals studies to investigate anti-inflammatory effects with the IA imaging.

In the future it is crucial to achieve more knowledge about aneurysm pathophysiology and risk factors to achieve understanding how to prevent aneurysm rupture. Translational research between different scientific groups is essential to open new dimensions in basic and clinical science

9 Conclusions

Study I — Kawasaki disease is unlikely associated with increased risk for unruptured intracranial aneurysms.

Study II — Kawasaki disease was associated with increased white matter hyperintensities burden, possibly reflecting the long-term cerebrovascular involvement of Kawasaki disease.

Study III — Saccular intracranial aneurysms were associated with increased risk for thoracic aortic aneurysms and dilatations.

Study IV — Flow diverter stent is a feasible treatment option for acutely ruptured posterior circulation fusiform aneurysms when other treatments is not achievable. However, flow diverter stent treatment carries high risk of complications in the acute phase of subarachnoid hemorrhage.

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