

# Pediatric Brain Arteriovenous Malformations

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TO MY FAMILY

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# Abstract

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Brain arteriovenous malformations (BAVMs or AVMs) are high-flow cerebrovascular lesions consisting of a tangle of abnormal blood vessels, the nidus, which acts as an arteriovenous (AV) shunt. The incidence of newly diagnosed AVMs is around 1 case per 100 000 person-years. The incidence peaks between 20 and 40 years of age. The average risk of arteriovenous malformation hemorrhage is estimated to be 2-3% per year. Around 10-20% of AVM patients are under 18 years of age at the time of diagnosis. Despite their relative rarity, AVMs are the most common cause of non-traumatic intracranial hemorrhage (ICH) in the pediatric population. The goal of treatment is to eliminate subsequent rupture risk with minimal neurological morbidity. Treatment options comprise microneurosurgery, radiosurgery, endovascular embolization, or any combination of these.

This thesis aimed to clarify the special characteristics, long-term outcomes, and health-related quality of life (HRQOL) in patients treated for AVM in childhood or adolescence. We also analyzed the risk of AVM recurrence in patients treated under 21 years of age, evaluated by late digital subtraction angiography (DSA) follow-up.

The data on patients were drawn from the Helsinki AVM database. Consisting of 805 AVM patients treated at the Helsinki University Hospital Department of Neurosurgery between 1942 and 2014, the database has been retrospectively collected from medical records and images. In 2016, questionnaires were sent to all living patients over 18 years of age ( $n = 432$ ). The database was updated with the information obtained from the questionnaires and by reviewing all the relevant medical records, images, and death certificates. The questionnaires contained the 15D HRQOL instrument as well as separate questions on symptoms, comorbid conditions, lifestyle, educational level, and self-sufficiency/independence. Of the 432 patients sent questionnaires, 325 (75%) replied.

In Study I, pediatric AVM patients presented with intracranial hemorrhage more often than adults. At the same time, children presented with

epileptic seizures (not associated with hemorrhage) less frequently than adults. Further, children's AVMs were more often deep-located and less often cortical-located than those of adults. We theorized that gradual microhemorrhages from AVMs and the consequent build-up of hemosiderin in the adjacent brain parenchyma might lead to the development of epilepsy over time. Cortical epileptogenic AVMs would therefore come to clinical attention later in life, and their proportion would be lower in children than in adults whereas the proportion of hemorrhagically presenting deep AVMs would be higher.

In Study II, we measured how the Spetzler-Ponce Classification (SPC), admission age, symptomatic epilepsy, and repeated ruptures affect the long-term quality of life, as measured with the 15D HRQOL instrument in patients with ruptured AVMs treated in childhood (<20 years of age at the time of admission). The SPC did not predict the long-term HRQOL score. Repeated ruptures affected the HRQOL in several domains. Symptomatic epilepsy significantly reduced the long-term HRQOL. Admission age had a significant effect on one dimension, namely, the patients youngest at admission were not able to carry out their usual daily activities as well as the other patients.

Study III analyzed the risk of AVM recurrence in patients treated when under 21 years of age. We found three de-novo AVMs, but one of the patients had been diagnosed with hereditary hemorrhagic telangiectasia (HHT) years after the primary treatment. There were thus two actual recurrent sporadic AVMs giving a recurrence rate of 4.9%.

Pediatric patients seem to recover better in the long term, favoring a more aggressive treatment approach. The more frequent hemorrhage presentation does not imply increased hemorrhage risk in the pediatric population; rather it is related to a lower proportion of AVMs coming to clinical attention because of epilepsy. Patients treated for AVMs in childhood or early adulthood should have an imaging follow-up to detect possible later recurrences.

# Tiivistelmä

Aivojen valtimo-laskimoepämuodostumat (arteriovenoosi malformaatiot, AV-malformaatiot, AVM:t) ovat aivoverisuoniperäisiä oikovirtausmuutoksia. Kolme makroskooppista piirrettä ovat AVM:lle ominaisia: syöttövaltimot, ulosvirtauslas- kimot sekä näiden välissä poikkeavista mutkittele- vista verisuonista muodostunut suonirykelmä eli ”nidus”. Korkeapaineinen valtimoveri oikovirtaa niduksen läpi suoraan laskimopuolelle ohittaen hiusverisuonet. AV-malformaatioiden ilmaantu- vuus on n. 1 / 100 000 henkilövuotta, ilmaantu- vuushuippu on 20–40-vuotiailla. Merkittävin AVM:n aiheuttama riski on sen repeytyminen ja aivoverenvuoto, mikä on myös edelleen yleisin AVM:n löytymiseen johtava syy (40–60 % tapauk- sista). Noin 10–20 % AVM-potilaista on lapsia (<18-vuotiaita) diagnoosihetkellä. Suhteellisesta harvinaisuudestaan huolimatta AVM:t ovat yleisin syy lasten ja nuorten ei-traumaattiseen kallonsi- säiseen vuotoon.

Tutkimuksen tavoitteena oli selvittää lapsuu- dessa / nuoruudessa hoidettujen AVM-potilaiden erityispiirteitä, pitkäajan ennustetta ja terve- teen liittyvää elämänlaatua sekä arvioida AVM:n uusiutumisriskiä.

Tutkimuksessa käytettiin Helsingin neuroki- rurgian klinikan AVM-tietopankkia, johon on kerätty tiedot kaikista klinikassa 1942–2014 hoide- tuista AVM-potilaista (805 potilasta). Tiedot on kerätty jälkikäteen potilaskertomusmerkinnöistä ja kuvista. Vuonna 2016 kaikille elossa oleville > 18-vuotiaille potilaille (n=432) lähetettiin kyselykir- jeet. Näistä potilaista 325 (75 %) palautti kyselykir- jeen täytettynä. Kirjeet sisälsivät 15D-elämänlaa- tukyselyn sekä erillisiä kysymyksiä muista oireista, sairauksista, elintavoista, koulutusasteesta ja toi- mintakyvystä. Kyselykirjeiden vastauksista saatu informaatio yhdistettiin sairaskertomusmerkin- nöistä ja kuvantamistutkimuksista saataviin muut- tuihin. Lisäksi kuolleiden kuolinsyyt selvitettiin kuolintodistuksista.

Ensimmäisessä osatyössä osoitettiin lasten AV-malformaatioiden tulevan useammin aivoveren- vuodon ja harvemmin epilepsian vuoksi esille. Lisäksi lapsuudessa esille tulleet AVM:t sijaitsivat useammin aivojen syvissä osissa ja harvemmin aivo-

kuoren seudussa. AV-malformaatioiden ympärillä olevaan aivokudokseen kerääntyy hiljalleen hemosi- deriiniä mikrovuodoista, mikä lisää epilepsian kehity- misen riskiä aikariippuvaisesti. Tämän vuoksi epi- lepsiaherkät aivokuoren seudun AVM:t tulevat usein vasta myöhemmällä iällä esille, jolloin syvissä aivojen osissa sijaitsevan AV-malformaatioiden osuus on lapsuudessa suurempi.

Toisessa osatyössä analysoitiin 15D-elämänlaa- tumittarin avulla <20-vuotiaana hoidettujen vuota- neiden AVM-potilaiden pitkäajan terveyteen liit- tyvä elämänlaatu. Tutkimuksessa arvioitiin Spetzler-Ponce luokituksen (SPC:n), oireisen epi- lepsian, diagnoosihetken iän ja toistuvien AVM:n vuotojen vaikutusta pitkäajan terveyteen liitty- vään elämänlaatuun. SPC ei vaikuttanut merkitse- västi pitkäajan terveyteen liittyvään elämänlaa- tuun. Toistuvat AVM:n aiheuttamat vuodot laski- vat elämänlaatua usealla osa-alueella. Oireinen epilepsia laski elämänlaatua merkittävästi. Diag- noosihetken iällä oli merkittävä vaikutus yhdellä 15D-mittarin osa-alueella. Nuorimmat (<10-vuoti- aat) potilaat eivät selviytyneet yhtä hyvin päivittäi- sistä toimista myöhemmin elämässä kuin vanhem- malla iällä (>10 vuotiaana) diagnosoidut potilaat.

Kolmannessa osatyössä tutkittiin alle 21-vuoti- aana hoidettujen AV-malformaatioiden uusiutumis- riskiä DSA-kuvantamisella. Tutkimuksessa löydet- tiin kolme uusiutunutta AV-malformaatioita. Yhdellä näistä potilaista oli diagnosoitu alkuperäisen AVM-leikkauksen jälkeen hereditaarinen hemorra- ginen telangiektasia (HHT). Täten varsinaisia spora- disia AV-malformaatioita todettiin kahdella poti- laalla ja näin ollen uusiutumisriski oli 4,9 %.

Lapsipotilaat näyttävät toipuvan paremmin kuin aikuiset, minkä vuoksi aktiivisempi hoitolinja on perusteltua. Lasten AVM:t tulevat aikuisia useammin vuodon vuoksi esille, mutta vuotoriski ei ole aikuisia suurempi. AVM:n aiheuttama epi- lepsia puhkeaa myöhemmällä iällä, minkä vuoksi vuotoa esille tulneiden AV-malformaatioiden osuus on suurempi lapsilla kuin aikuisilla. Lapsuu- dessa tai varhaisaikaisuudessa hoidetuille AVM-potilaille tulisi järjestää kuvantamisseuranta mahdollisten uusiutuneiden AV-malformaatioiden todentamiseksi.



# Abbreviations

|               |                                                             |               |                                              |
|---------------|-------------------------------------------------------------|---------------|----------------------------------------------|
| <b>AED</b>    | Antiepileptic drug                                          | <b>KRAS</b>   | Kirsten rat sarcoma viral oncogene homologue |
| <b>AV</b>     | Arteriovenous                                               | <b>MAPK</b>   | Mitogen-activated protein kinase             |
| <b>AVICH</b>  | Arteriovenous malformation-related intracerebral hemorrhage | <b>MEG</b>    | Magnetoencephalography                       |
| <b>AVM</b>    | Arteriovenous malformation                                  | <b>MEK</b>    | MAPK/ERK kinase                              |
| <b>BMP</b>    | Bone morphogenic protein                                    | <b>MProsV</b> | Median prosencephalic of Markowski           |
| <b>CCF</b>    | Carotidocavernous fistula                                   | <b>MRA</b>    | Magnetic resonance angiography               |
| <b>CI</b>     | Confidence interval                                         | <b>MRI</b>    | Magnetic resonance imaging                   |
| <b>CM-AVM</b> | Capillary malformation-arteriovenous malformation           | <b>mRS</b>    | Modified ranking scale                       |
| <b>CSF</b>    | Cerebrospinal fluid                                         | <b>mTOR</b>   | Mechanistic target of rapamycin              |
| <b>CT</b>     | Computed tomography                                         | <b>NICU</b>   | Neurointensive care unit                     |
| <b>CTA</b>    | Computed tomographic angiography                            | <b>NIS</b>    | Nationwide inpatient sample                  |
| <b>DAVF</b>   | Dural arteriovenous fistula                                 | <b>OR</b>     | Odds ratio                                   |
| <b>DSA</b>    | Digital subtraction angiography                             | <b>PI3K</b>   | Phosphoinositide 3 kinase                    |
| <b>DTI</b>    | Diffusion-tensor imaging                                    | <b>QALY</b>   | Quality-adjusted life years                  |
| <b>ERK</b>    | Extracellular signal-regulated kinase                       | <b>QOL</b>    | Quality of life                              |
| <b>Fe</b>     | Ferumoxytol                                                 | <b>RAF</b>    | MAPK                                         |
| <b>FMAP</b>   | Feeding mean artery pressure                                | <b>SAH</b>    | Subarachnoid hemorrhage                      |
| <b>Gd</b>     | Gadolinium                                                  | <b>SD</b>     | Standard deviation                           |
| <b>GOS</b>    | Glasgow outcome scale                                       | <b>SMG</b>    | Spetzler-Martin grading                      |
| <b>HH</b>     | Hunt & Hess                                                 | <b>SPC</b>    | Spetzler-Ponce classification                |
| <b>HHT</b>    | Hereditary hemorrhagic telangiectasia                       | <b>SSS</b>    | Superior sagittal sinus                      |
| <b>HRQOL</b>  | Health-related quality of life                              | <b>TMS</b>    | Transcranial magnetic stimulation            |
| <b>ICGA</b>   | Indocyanine green angiography                               | <b>TOF</b>    | Time-of-flight                               |
| <b>ICH</b>    | Intracerebral hemorrhage                                    | <b>VEGF</b>   | Vascular endothelial growth factor           |
| <b>IQR</b>    | Interquartile range                                         | <b>WFNS</b>   | World federation of neurological surgeons    |
| <b>IV</b>     | Intravenous                                                 | <b>WHO</b>    | World health organization                    |
| <b>IVH</b>    | Intraventricular hemorrhage                                 |               |                                              |

# List of original publications

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This thesis was based on the following three original research articles.

**I: Oulasvirta E, Koroknay-Pál P, Hafez A, Elseoud AA, Lehto H, Laakso A.** Characteristics and Long-Term Outcome of 127 Children with Cerebral Arteriovenous Malformations. *Neurosurgery*. 2019 Jan 1;84(1):151-159. doi: 10.1093/neuros/nyy008. PMID: 29518249.

**II: Oulasvirta E, Pohjola A, Koroknay-Pál P, Hafez A, Roine R, Sintonen H, Laakso A.** Long-term health-related quality of life in patients with ruptured arteriovenous malformations treated in childhood. *J Neurosurg Pediatr*. 2022 Jun 24:1-9. doi: 10.3171/2022.5.PEDS2284. Epub ahead of print. PMID: 35901751.

**III: Oulasvirta E, Koroknay-Pál P, Numminen J, Hafez A, Raj R, Jahromi BR, Niemelä M, Laakso A.** Recurrence of brain arteriovenous malformations in pediatric patients: a long-term follow-up study. *Acta Neurochirurgica (Wien)*. 2023 May 4. doi: 10.1007/s00701-023-05612-8. Epub ahead of print. PMID: 37140647.

The publications are referred to in the text by their Roman numerals.

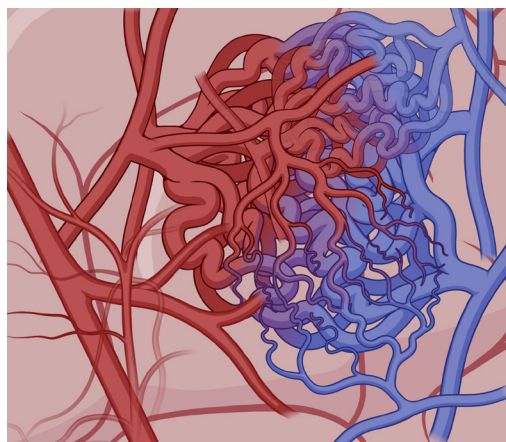
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# 1 Review of the literature

## 1.1 Definition

Brain arteriovenous malformations (BAVM or AVM) are high-flow cerebrovascular lesions consisting of a tangle of abnormal blood vessels. Three macroscopic features are pathognomonic for these lesions: feeding arteries, draining veins, and, between them, a mesh of abnormal vessels - the nidus - which acts as an arteriovenous (AV) shunt through several fistulas (Fig. 1). Owing to recent advances in the pathobiology of these lesions, their characterization will most likely become even more specific in the future. For example, hereditary hemorrhagic telangiectasia (HHT) genotype AVMs may well be distinguished from sporadic AVMs, as the underlying mutations are in different genes, and sporadic AVMs tend to be larger and more complex in their angioarchitecture.<sup>1</sup>

**Fig. 1. Schematic illustration of cortical brain AVM.**



There are other types of intracranial vascular malformation besides brain AVMs: vein of Galen AVMs, cavernous malformations, dural arteriovenous fistulas (DAVF), carotidocavernous fistulas (CCF), venous malformations, venous varices, and other rarer types of cerebrovascular anomaly.

Pure vein of Galen AVMs are embryological vascular malformations that develop in the first trimester of gestation as a result of shunts forming between arteries and the median prosencephalic

vein of Markowski (MProsV). The process leading to the formation of these arteriovenous shunts during vascular development is unknown. Owing to high-flow arterial shunting, the anterior segment of the MProsV, rather than regressing as in normal vascular development, gradually enlarges, forming the “aneurysmal” dilatation known as the vein of Galen malformation (the name is actually a misnomer as the dilated vein is MProsV).<sup>2</sup>

Cavernous malformations are clusters of hyalinized, dilated, thin-walled capillaries and are therefore not shunt lesions by definition. Abnormal capillaries leak and cause typical surroundings of hemosiderin.<sup>3</sup>

Dural arteriovenous fistulas and CCFs are acquired shunt lesions without the intervening nidus present in AVMs.

Further, brain AVMs do not include venous malformations, venous varices, or other rarer types of cerebrovascular anomaly.

Brain AVM is the most accurate term and, therefore, preferable to cerebral AVM, which eliminates more caudal formations.<sup>4</sup> Earlier and imprecise nomenclatures such as “real” AVM or “pial” AVM (some brain AVMs do not reach any pial surface) should also be avoided.

## 1.2 Flow dynamics and histopathology

Arteriovenous malformations are characterized by high-pressure arterial blood shunting through the nidus, leading to chronic hemodynamic changes in the feeding arteries and draining veins. Due to the arteriovenous shunt, the feeding mean artery pressure (FMAP) is significantly lower than the mean arterial pressure (MAP), whereas the draining vein pressure is higher than the mean venous pressure, leading to increased flow through the nidus.<sup>5</sup> Chronic hemodynamic stress and abnormal angiogenesis lead to histopathological changes such as dilatation of vascular lumens accompanied by thin and irregular muscular and elastic layers, intimal hyperplasia, islands of sclerotic tissue, and arterialization of the draining veins accompanied by incompetent

elastic lamina. The nidus is composed of abnormal vessels with properties of arteries and veins. The increased pressure load on the venous side is a consequence of a missing capillary bed, and, together with pathological vessels, creates an environment where an AVM rupture and intracranial hemorrhage may occur. In a prospective study by Duong and associates, FMAPs were measured with super-selective angiography in 340 brain AVM patients.<sup>6</sup> After multivariate analysis, only increased FMAP and exclusively deep venous drainage were associated with hemorrhagic presentation. Deep venous drainage was proposed to lead to an increased pressure gradient across the vasculature of the nidus.

The chronic hemodynamic stress caused by shunting blood can also lead to the formation of flow-related aneurysms, which occurred in 18% of AVM patients according to a meta-analysis conducted in 2012.<sup>7</sup> As these flow-related changes develop in a time-dependent manner, they are reported to be more frequent in adult AVM patients than in children.<sup>8-10</sup> Flow-related aneurysms occur along vessels that supply the AVM and are classified as either proximal (to a primary feeding artery) or distal (if located along a feeding artery). Intranidal aneurysms occur within the nidus of the AVM. Venous varices may develop distal to the nidus as a consequence of high-pressure arterial flow.<sup>11</sup>

Observations have recently been made on an abnormal perinidal capillary network.<sup>12,13</sup> It has been found that dilated capillaries (10 to 25 times larger than normal capillaries) form a ring (1 to 7 mm) around the nidus, and are connected to the nidus, feeding arteries, draining veins, and surrounding normal brain vessels. These capillaries do not have basement membranes and astrocytic foot processes, and the endothelial cells have fenestrated luminal surfaces and significant gaps between the endothelial intercellular junctions.<sup>12</sup> The authors hypothesized that the incompetent blood-brain barrier of perinidal capillaries and increased fluid permeability might explain the hemorrhages and edema sometimes experienced after surgical AVM resection.<sup>12</sup>

In contrast to cavernous malformations, the AVM nidus may include intervening neuronal parenchyma. Parenchymal components are typically gliotic and hemosiderin stained.<sup>12</sup>

## 1.3 Anatomic characterization

Brain AVMs are extremely heterogeneous, ranging from small superficial relatively easily treatable lesions to vastly complex eloquently located massive lesions.<sup>14,15</sup> Because of the wide variation between the lesions and consequent risk involved in treatment, different classifications based on distinct anatomical features have been developed.<sup>16-18</sup> The distinction between different types of AVM is important because the rupture risk seems to vary depending on the anatomical features.<sup>7,19,20</sup>

Arteriovenous malformations are commonly classified by location as deep or superficial. Venous drainage could be similarly classified as deep or superficial. The size of the AVM nidus is categorized as small (<3 cm), medium (3-6 cm), or large (>6 cm). All these factors are combined in the most commonly used surgical risk assessment scale, the Spetzler-Martin Grading (SMG) scale.<sup>16</sup> Table 1.

Deep location and deep venous drainage increase both surgical risk and the risk of AVM rupture.<sup>7,15,19,20</sup> While larger nidus size increases the surgical risk, the effect on rupture risk has been controversial.<sup>7,15,19</sup>

## 1.4 Development and pathobiology

Earlier, AVMs were considered to form as a result of a malfunction in embryogenesis during vascular development, hence the name “malformation”.<sup>21-23</sup> However, AVMs have shown growth,<sup>24,25</sup> spontaneous regression,<sup>26,27</sup> and de-novo formation,<sup>28,29</sup> implying that they are more dynamic in nature than would be expected from mere static structural developmental malformations. In recent years, developments in molecular AVM studies have shown that AVMs harbor endothelial somatic mutations,<sup>30-32</sup> suggesting that AVMs may be acquired rather than congenital lesions. Most of the reported de novo AVMs (excluding the lesions recurring after obliteration) have been associated with previous cerebrovascular pathologies, such as cavernomas,<sup>33</sup> ischemic and hemorrhagic strokes,<sup>34-36</sup> Moya-Moya disease<sup>37</sup> and aneurysms,<sup>38</sup> or with their management. The causality between the previous insults or diseases that led to brain imaging in the first place and de novo AVMs found later is unclear. The incidence of AVMs

peaks between the third and fourth decades of life.<sup>39</sup> They are also frequently found in children,<sup>8</sup> suggesting that, in most cases, AVMs develop at early stages of life. Moreover, neonatal<sup>40–42</sup> and even prenatal<sup>43</sup> presentations have been reported. Reports of prenatal AVMs are, however, very scarce despite the widespread use of prenatal ultrasound. The majority of extracranial AVMs are found at birth, after which they tend to expand.<sup>44</sup>

#### 1.4.1 Angiogenesis of AVMs: KRAS / RAF-MEK-ERK (MAPK) pathway

The KRAS gene contains instructions for making a protein called Ras. This activates downstream signaling cascades such as the RAF-MEK (MAPK [mitogen-activated protein kinase] / ERK [extracellular signal-regulated kinase] Kinase)-ERK pathway and the PI3K (phosphoinositide 3 kinase)/ AKT/mTOR (mechanistic target of rapamycin) pathway.<sup>45</sup> The RAF-MEK-ERK pathway controls cellular growth, survival, differentiation, and angiogenesis.<sup>46</sup> Dysregulation of the MAPK pathway has been linked to various human cancers.<sup>47</sup>

A recent landmark study<sup>30</sup> identified somatic activating KRAS gene mutations in 45 of 72 AVM samples, and none in 21 paired control samples. Using droplet digital PCR, the researchers found that KRAS mutations are explicitly present in the endothelial AVM cells. In further investigation of the downstream signaling pathways, they found that mutant Ras protein specifically activates the RAF-MEK-ERK but not the PI3K-AKT pathway (Fig. 2). They also found increased RAF-MEK-ERK signaling in the endothelial cells of AVM samples without the mutant KRAS. Furthermore, they showed that the mutant KRAS increased the expression of genes related to angiogenesis, vascular development and proliferation, and endothelial migration. Finally, they demonstrated *in vitro* that endothelial cells with the KRAS mutation had increased migratory behavior as well as disassembly of adherens junctions and that these changes could be partly reversed with MEK inhibitors. Further studies have identified other activating mutations downstream in the MAPK pathway from the AVM samples.<sup>32,48</sup> Each of these mutated genes is involved in the MAPK/ERK kinase cascade. These findings indicate that the RAF-MEK-ERK pathway plays a critical role in AVM development.

Fish et al. demonstrated that KRAS mutated endothelial cells led to brain AVM formation in both postnatal and adult mice models.<sup>31</sup> Similar findings were made in developing zebrafish with an activating KRAS mutation, as embryos exhibited hemorrhages accompanied by AV shunts, as well as changes in vascular morphogenesis, such as increased endothelial cell size, ectopic sprouting, and expanded vascular lumens. Eventually, the brain hemorrhage risk was reduced, and the existing AV shunts were partly reversed by the MEK inhibitors.<sup>31</sup> Whether MEK inhibition can reverse human AVMs that may have been present for decades has yet to be determined. Nonetheless, a recent case report showed efficacy in reducing the size and caliber of a cutaneous AVM treated with a MEK inhibitor Trametinib.<sup>49</sup> Finally, in a 14-year-old girl with a recurrent brain AVM, Walcott et al. detected a rare stop-gain mutation in SMAD9, which resulted in downstream abnormalities in the bone morphogenic protein (BMP) signaling pathway.<sup>50</sup> The same mutation led to AVM formation in zebrafish models.<sup>50</sup>

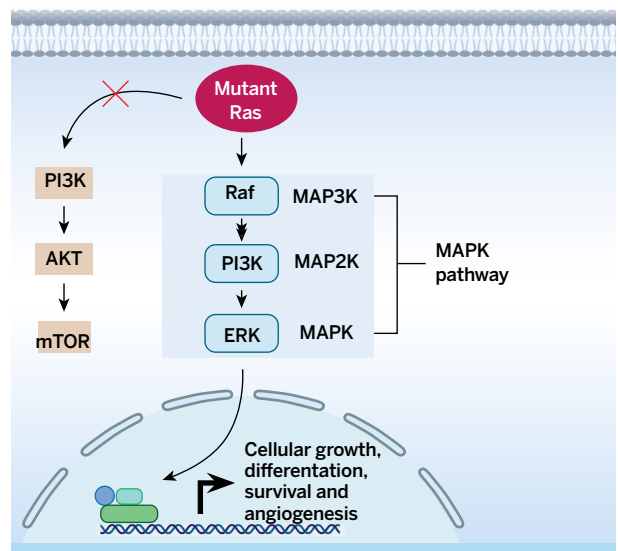


**Fig. 2.**

Illustration of the MAPK signaling pathway, which is overactive in endothelial cells of AVMs. Mutant Ras in AVMs does not activate the PI3K pathway. In addition to the mutated KRAS gene, activating somatic mutations have been found downstream in the MAPK pathway.

## 1.5 Hereditary AVMs

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant vascular disease with a prevalence of approximately 1 in 5000 to 1 in 10 000.<sup>51</sup> Patients with HHT have AVMs and telangiectasias in multiple organs: brain, lungs, liver, GI-tract, and skin.<sup>52</sup> Mutations in three genes (ENG<sup>53</sup>, ALK1 or ACVRL1<sup>54</sup>, and SMAD4<sup>55</sup>) have been identified in HHT patients. On the basis of these mutated genes, HHT is classified as HHT1, HHT2, and JP (juvenile polyposis)-HHT. All of the identified mutations in HHT are involved in the signal transduction of TGF- $\beta$  family members.<sup>56,57</sup> HHT1 (ENG mutations) and HHT2 (ALK1 mutations) account for more than 90% of all HHT cases.<sup>58</sup> BAVMs are seen in 10.4% of HHT patients. HHT1 patients had a considerably greater prevalence of BAVMs than HHT2 patients (13.4% vs. 2.4%).<sup>59</sup> HHT-associated BAVMs are on average smaller (< 3 cm) than sporadic BAVMs.<sup>59</sup>

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is a rare autosomal dominant inherited disorder occurring in 1:100000 individuals.<sup>60</sup> Capillary malformations (CMs), which are characteristic of these patients, are made up of enlarged capillaries that increase blood flow near the surface of the skin. They appear as small (<1-2 cm), round and pink-to-red patches on the skin, some surrounded by a pale halo.<sup>61</sup> About 30% of patients with CM-AVM also have fast-flow AVMs or arteriovenous fistulas (AVFs) in the brain, skin, muscle, bone, or spine.<sup>62</sup> CM-AVM syndrome is caused by mutations in the RASA1 gene, which encodes a protein known as p120-RasGAP.<sup>61</sup> The p120-RasGAP inactivates Ras signaling and the mutated RASA1 gene results in the generation of nonfunctional p120-RasGAP protein.

Bannayan-Riley-Ruvalcaba syndrome, caused by germline mutations in the PTEN gene, has also been associated with aggressively behaving intracranial AVMs.<sup>63</sup>

## 1.6 Epidemiology

The true prevalence of brain AVMs is hard to estimate since they are rare and can be asymptomatic throughout a patient's life. German research involving 2536 healthy young men (applicants for military service in the German Air

Force) with cranial magnetic resonance imaging (MRI) found incidental AVMs in five of them, corresponding to a prevalence of 0.2%.<sup>64</sup> The researchers used a standard protocol with T1, T2, and FLAIR sequences with 2 mm slices. In the event of any suspicious findings, 3D time-of-flight (TOF) – magnetic resonance angiography (MRA) and gadolinium (Gd) enhanced series were performed. However, the sensitivity of Gd-enhanced MRI is not always sufficient to detect small AVMs.<sup>65</sup> Further, since the Gd-enhanced series were applied only to those with suspicious findings on standard MRI, a significant proportion of AVMs could have been missed. The study population was also very selected. Meta-analysis on incidental MRI findings reported 0.05% prevalence for brain AVMs.<sup>66</sup> In Scotland, a community-based retrospective study found a prevalence of 18 cases per 100 000 adults, but the AVMs were almost all symptomatic.<sup>67</sup> In a historical hospital-based autopsy series, prevalence was as high as 500-600 cases per 100 000 persons, but these results are unreliable due to selection bias and the diverse classification of AVMs at the time of the study.<sup>68,69</sup> In one series of 8038 medicolegal autopsies, five brain AVMs were detected, corresponding to a prevalence of 0.06%.<sup>70</sup> To complicate matters further, AVMs can thrombose and disappear.<sup>26</sup> Considering all the above, the actual prevalence may lie at around 0.1-0.5%.

The incidence of newly diagnosed AVMs is around 1 case per 100 000 person-years in industrialized countries with modern medical services.<sup>39,71,72</sup> The incidence peaks at between 20 and 40 years of age,<sup>19,73</sup> suggesting that most AVMs are probably already formed in childhood.

Using the Nationwide Inpatient Sample (NIS) data, a large retrospective population-based study in the USA found 4485 AVMs in 619 167 spontaneous ICH (intracerebral hemorrhage) patients over 18 years of age, indicating that AVMs cause about 0.7% of ICHs in the adult population.<sup>74</sup> However, pediatric patients were excluded from the study even though AVMs are the most common cause of non-traumatic ICH in children.<sup>75</sup> According to the latest meta-analysis, AVMs are responsible for 68.3% of all children's ICHs.<sup>75</sup> If we apply the same percentage to the NIS-based study's 2455 excluded pediatric patients, we get approximately 1680 more AVM-

caused ICHs, and the overall proportion of AVMs in all of the ICHs would then be 1.0%.

Although hemorrhage from AVM is generally considered less dangerous than aneurysmatic subarachnoid hemorrhage (SAH) or spontaneous hypertensive ICH, it is still associated with a 10% to 50% risk of permanent disability and a 5% to 25% risk of mortality.<sup>20,76–80</sup> However, Taylor et al. observed that if the patient's age was included, the differences in mortality and morbidity rates between AVM-related ICH and spontaneous ICH diminished.<sup>81</sup>

### 1.6.1 Excess mortality

Overall annual mortality rates for all AVM patients have ranged from 0.7% to 2.9%.<sup>73,76,82–86</sup> The only study analyzing the annual excess mortality of AVM patients compared with the matched general population is from Laakso et al. in 2008.<sup>87</sup> This study included 155 conservatively managed AVM patients, whose cumulative excess mortality in a 30-year period was two-fold compared to the age-, sex-, and historical period-matched general population of Finland. Conversely, if AVM was completely eradicated, the cumulative excess mortality decreased to 1.15 in the 30-year period. There is inevitably some selection bias in the results of this study. However, the study period was very long, starting in the 1950s when the attitude towards AVMs was much more conservative, thus limiting this bias.<sup>87</sup>

### 1.6.2 Rupture risk

The average risk of AVM rupture and hemorrhage is estimated to be 2–3% per year.<sup>7,19,20,76</sup> However, the risk varies considerably, depending on different factors. The most consistently reported risk for a subsequent hemorrhage is a previous rupture.<sup>7,19,84,85,88–92</sup> Of the many disease- and patient-specific risk factors analyzed regarding rupture risk, the most consistently reported are deep location and exclusively deep venous drainage.<sup>7,19,88,90</sup> A meta-analysis of 3923 patients and 18 423 patient-years of follow-up also recognized flow-related aneurysms as an independent risk factor for subsequent hemorrhage.<sup>7</sup>

One confounding factor in rupture risk analysis is that the risk seems to be highest in the first few years after diagnosis and later decreases. That most of the diagnosed AVMs are sympto-

matic could indicate some kind of hemodynamic instability at the time of presentation, which later stabilizes, thus restoring the rupture risk to the baseline.<sup>19</sup>

### 1.6.3 Presenting symptoms

Intracerebral hemorrhage is still the most common reason why AVMs come to clinical attention (42% to 72% of cases). The hemorrhage rate has, however, been declining concurrently with the increasing availability of cranial MRI, due to which more AVMs are diagnosed as unruptured.<sup>8,19,73,76,85,90,93</sup> Partial seizures without hemorrhage are the second most common symptom and occur in about 30% of patients, more commonly in adults than in children.<sup>8,94</sup> Migraines have also been associated with AVMs, although the causal mechanism is hard to prove.<sup>95</sup> In a randomized trial of unruptured AVMs, there was no difference in the resolution of headaches between treated and non-treated patients.<sup>96</sup> Less common presenting symptoms are focal neurological defects. These can result either from the direct compression effect of the nidus to the brain parenchyma<sup>97</sup> or from the ischemic steal (shunting of blood through the AVM with low resistance, resulting in hypoperfusion of surrounding areas). Nonetheless, many authors have questioned the “steal” effect.<sup>98–101</sup>

## 1.7 Evaluation

As hemorrhage is the most common symptom, many AVMs are diagnosed in emergency departments at the time of rupture. The first line examination in the emergency department is cranial computed tomography (CT), which typically shows parenchymal hemorrhage, sometimes accompanied by intraventricular hemorrhage (IVH) or SAH (Fig. 3). Computed tomographic angiography (CTA), usually performed simultaneously with cranial CT, typically shows a tangle of abnormal vessels suggestive of AVM (Fig. 4). Unruptured AVM is usually found from head MRI, where the AVM is best identified by a combination of TOF-MRA and Gd-enhanced series (Fig. 5). However, a recent report indicated that better sensitivity and specificity could be achieved with Ferumoxytol (Fe)-enhanced MRI.<sup>102</sup>

In the planning of elective surgery, brain MRI

**Fig. 3. Cranial CT of 14-year-old patient with AVM rupture**

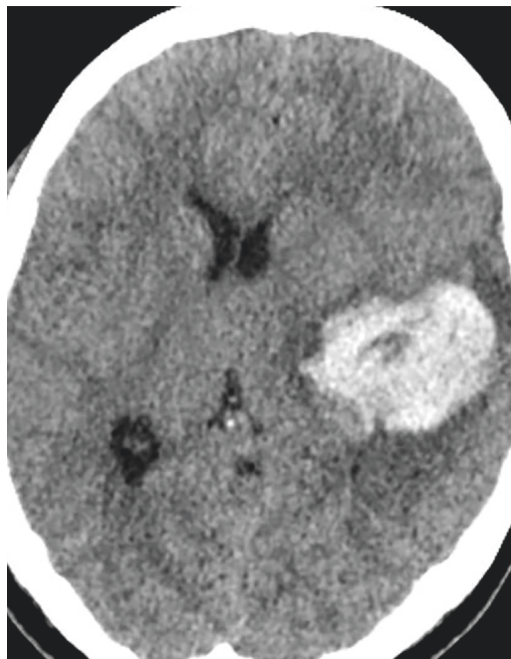
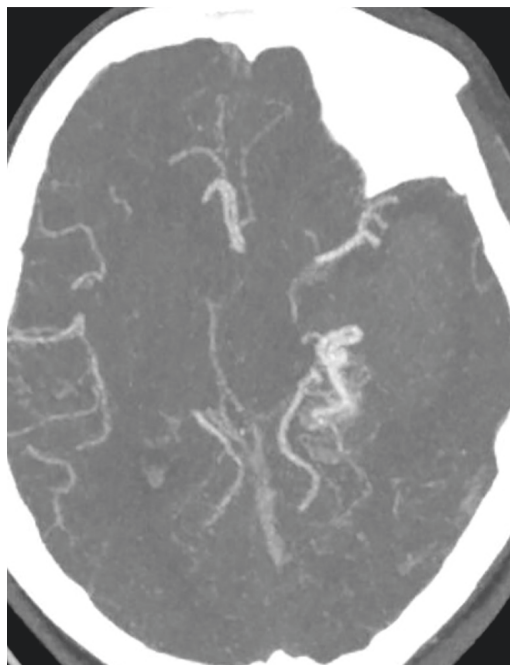


**Fig. 4. Cranial CTA of the same patient demonstrating the ruptured AVM**



is always performed to allow better visualization of the AVM in relation to surrounding parenchymal structures. Additional information may be acquired using functional MRI and transcranial magnetic stimulation (TMS) or magnetoencephalography (MEG) to identify eloquent brain tissue.<sup>103–106</sup> Although not routine practice in most departments, diffusion-tensor imaging (DTI) can be used to distinguish crucial white-matter tracts.<sup>107</sup>

## 1.8 Management

The primary purpose of treatment is prevention of future hemorrhage and possible neurological deterioration. As the treatment itself also carries a risk of neurological morbidity, it is always weighed against the natural history of the AVM (considering the AVM's characteristics, the patient's age and preferences, and the presentation).<sup>15</sup>

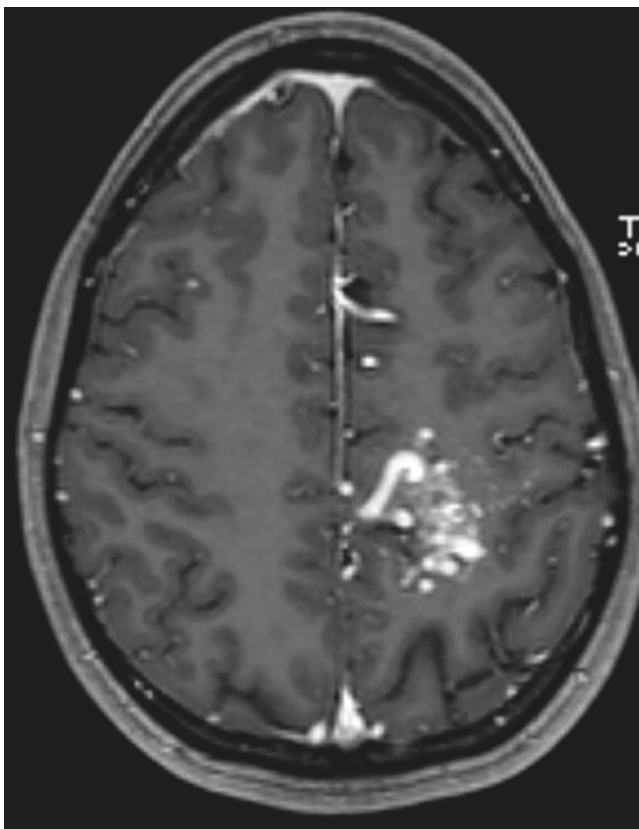
Currently available treatment options include surgical resection, endovascular embolization, radiosurgery, or different combinations of these. The treatment options should be assessed by a

multidisciplinary team comprising a neurosurgeon, endovascular interventionist, and radiation therapist. The goal of the treatment is complete AVM obliteration since partial obliteration does not eliminate the hemorrhage risk and may even temporarily increase it as a result of changed flow dynamics.<sup>20,108,109</sup>

### 1.8.1 Conservative

To date, there have been no randomized trials with a sufficient follow-up time for the comparison of different treatment modalities. The results of the only prospective multicenter randomized trial comparing conservative and interventional treatment in unruptured adult ( $\geq 18$  years) AVM patients were not generalizable because of high selection bias (226 out of 1740 screened patients participated), non-conventional treatments in the interventional arm, excessively short follow-up time (median 33 months), and poor external validity, with only one-third of planned centers participating.<sup>96</sup> Despite the trial's failure to provide guidance on an optimal treatment strategy, there are situations where conservative treat-

**Fig. 5. Brain MRI of a 19-year-old patient with unruptured left-sided rolandic AVM**

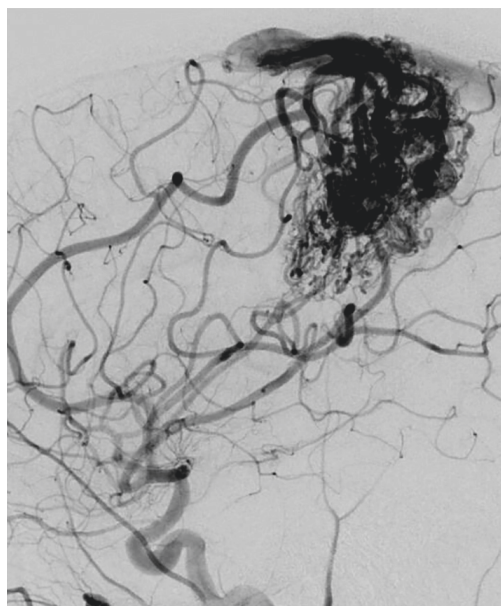


ment is preferred. The simple answer is to refrain from treatments if the risk they involve is higher than the natural risk of the disease. The harder question is how to evaluate those risks. Generally, the older the patient and the higher the AVM grade, the more conservative the approach that should be applied, especially in unruptured AVMs.

### **1.8.2 Microsurgery**

If feasible, complete AVM surgical resection is the gold standard of treatment. Surgical resection is the most reliable treatment modality for achieving complete and immediate eradication of an AVM.<sup>110</sup> It also has the benefit of hematoma evacuation in cases of acute rupture. Obliteration rates after surgical resection vary between case series and depends on patient selection. With the correct patient selection, obliteration rates after surgery have been reported to be approximately

**Fig. 6. DSA of the same 19-year-old patient**



The gold standard in AVM diagnosis is digital subtraction angiography (DSA). As a dynamic investigation, it is the most sensitive and specific in detecting early venous filling due to shunting blood. In the planning of AVM treatment, DSA is essential for proper visualization of the complete angioarchitecture with all the feeding arteries, nidus, draining veins, and possible associated aneurysms.

90-100% in modern series, with a 2-5% rate of treatment-related morbidity.<sup>111-115</sup>

Surgery can be used in combination with other treatment modalities. Endovascular embolization is frequently performed to reduce the blood flow of large AVMs before surgery.<sup>116</sup> However, preoperative embolization itself is not without risk, and the change of flow dynamics due to partial embolization can lead to AVM rupture.<sup>117</sup> Postoperative DSA should be performed promptly after surgery to exclude residual shunting, as the rupture risk will persist until complete obliteration is achieved.<sup>118</sup> Re-operation is often required if residual AVM is observed in the postoperative DSA. Sometimes stereotactic radiosurgery may be applied if re-operation is considered too risky. Volume-staged radiosurgery has also been used to downgrade large high-grade, otherwise inoperable, AVMs into operable AVMs.<sup>119</sup>

During the operation, the feeding arteries

and draining veins can be identified with the aid of intraoperative microscopic-assisted indocyanine green angiography (ICGA). The feeding arteries are coagulated or clipped first since pre-

mature coagulation of the draining veins will lead to bleeding, which can be difficult to control. When, finally, the draining veins are coagulated, the nidus can be removed in one piece.<sup>15</sup>

**Fig. 7. Cortical AVM, intraoperative view**



#### *1.8.2.1 The Helsinki protocol*

Postoperative care according to the Helsinki protocol depends on three factors: AVM size, rupture status, and possible confrontation of surgical complications.<sup>120</sup> Small unruptured SMG I AVMs without surgical complications are extubated in the operating room. At follow-up in the neurointensive care unit (NICU), normotensive systemic blood pressure and strict fluid balance are maintained. Patients with medium-size AVMs or small AVMs with rupture or surgical complications usually go to postoperative imaging under general anesthesia immediately after the operation. Patients stay in the NICU for several days until stabilized; their blood pressure is kept at <120-130, and administration of intravenous (iv) fluids is restricted. Large AVMs or medium-size AVMs with a preoperative

rupture or surgical complications are submitted to strict blood pressure control under general anesthesia whereby systolic blood pressure is kept below 100 mmHg for the first postoperative day and gradually increased thereafter. It is possible that postoperative hemorrhagic complications are caused by swelling of the adjacent brain parenchyma after the shunt lesion has been obliterated and normal blood flow restored, making it prone to hemorrhagic complications. In all AVM patients, DS-angiography is performed straight after the operation or, at the very least, the next day to ensure that AVM obliteration is complete. If residual AVM is seen, further treatment is planned.<sup>121</sup>

#### *1.8.2.2 Management of residual AVMs*

Despite apparently complete surgical resection,

residual AVMs are sometimes encountered. Hoh et al. reported a case series of 324 consecutive patients with a 1.8% incidence of unplanned residuals after surgical AVM resection.<sup>122</sup> Whereas residual AVMs are generally small (<1 cm), due to obstructed venous outflow caused by the operation, the immediate hemorrhage risk may be even higher than the natural risk would have been, and the annual hemorrhage risk thereafter remains the same.<sup>123</sup> Immediate re-operation to ensure complete AVM eradication is therefore generally recommended. However, the residual compartment may sometimes lie deeper in the eloquent structures, and individual risk assessment is necessary. If re-operation is deemed to be too risky, subsequent strict blood pressure control is necessary. Embolization or stereotactic radiosurgery during the immediate postoperative period is not recommended, as obstructed venous drainage may increase the hemorrhage risk involved in these procedures.<sup>15</sup> Residual AVM thrombosis has also been reported, and some authors recommend follow-up imaging for small inoperable residuals with only one draining vein.<sup>124</sup>

### 1.8.3 Stereotactic radiosurgery

Stereotactic radiosurgery is most often used in deep-seated small AVMs (< 3cm) that are not safely accessible with microsurgery. A dose of over 10 Gy can lead to parenchymal damage, whereas 20 Gy is required to induce thrombosis in the AVM, thus generally limiting the use of radiosurgery to small AVMs, ensuring that radiation exposure to the adjacent brain parenchyma is tolerable. It takes approximately one to four years from the time of treatment to potentially complete AVM obliteration (80-90% success rate with selected patients), during which time there continues to be a risk of hemorrhage.<sup>125</sup> The annual rupture risk of AVM is the same as before treatment until complete obliteration has been achieved.<sup>126-129</sup> Moreover, aggressive radiation of the venous drainage has been associated with post-treatment AVM rupture.<sup>130</sup> Post-treatment angiographies showing significant alterations in the venous drainage not accompanied by apparent changes in the nidus should prompt evaluation of possible intervention.<sup>130</sup>

In modern series, symptomatic adverse reac-

tions from radiosurgery developed in 7% to 9% of AVM patients, and approximately 3% suffered an irreversible neurological deficit.<sup>127,129,131,132</sup> The risk of adverse reactions depends on the marginal dose, nidus size, and AVM location.<sup>132,133</sup> Kano et al. reported symptomatic adverse reactions in 22% of AVMs located in the brainstem and in 16% of those located in the thalamus.<sup>132</sup>

#### 1.8.3.1 Endovascular embolization

Luessenhop and Spence pioneered the first case of AVM embolization by injecting silicone microspheres directly into the carotid artery in 1960. Since then, endovascular embolization has undergone substantial development and today plays an important role in AVM management.<sup>134</sup> Innovations such as high-quality digital subtraction angiographies, microcatheters, microguide-wires, and better embolic materials have greatly improved endovascular AVM treatment compared to the early days. During the embolization procedure, blood flow to an arteriovenous malformation is obstructed by depositing occlusive materials into the feeding arteries and the nidus itself through endovascular catheters. The most commonly used embolization materials are currently ethylene-vinyl alcohol copolymer (suspended in DMSO and opacified with tantalum powder; OnyxR) and precipitating hydrophobic injectable liquid (PHIL).<sup>135</sup>

#### 1.8.3.2 Embolization with intent to cure

Curative embolization, aimed at complete AVM obliteration, can be used as the only treatment modality or as an Associate treatment for the residual nidus after microsurgery or radiosurgery. According to a systematic analysis published in 2019, patients who underwent embolization with the intent to cure had cumulative obliteration and complication rates of 58.3% and 24.1%, respectively.<sup>136</sup> The obliteration and complication rates are, however, highly dependent on patient selection. Baharvahdat et al. reported obliteration, morbidity, and mortality rates of 92%, 5%, and 0.4%, respectively, in 224 consecutive SMG 1-2 AVM patients treated with endovascular embolization.<sup>137</sup> In a study of 233 consecutive brain AVM patients treated with embolization, Hartmann et al. found that older patient age, number of embolizations, and absence of a

pretreatment neurological deficit were associated with a new treatment-related neurological deficit.<sup>138</sup> Curative embolization is best suited for small ruptured AVMs, where location makes them challenging for microsurgery.<sup>139,140</sup> Completely embolized AVMs are also at risk of recanalization during follow-up.<sup>141</sup>

#### **1.8.3.3 Partial embolization**

Partial endovascular embolization is most often used preoperatively for large and complex AVMs to shrink the nidus size, reduce the shunting blood flow, and occlude deep arterial feeders that would otherwise be surgically difficult to manage.<sup>142,143</sup> As preoperative embolization is not without risk (Taylor et al. reported 2% and 9% rates of mortality and permanent neurological deficit, respectively)<sup>144</sup>, the risk of combined embolization and surgery should be assessed against the risk of surgery alone. Sometimes embolization can be used before radiosurgery to reduce nidus size or to target high-risk features such as intranidal and flow-related aneurysms.<sup>110,145,146</sup>

Partial embolization prior to radiosurgery as a means of nidus size reduction is an option for large (> 3cm) AVMs that are not amenable to direct radiosurgery.<sup>147</sup> A recent meta-analysis comparing the results of stereotactic radiosurgery alone with those in combination with endovascular embolization reported significantly lower obliteration rates for the embolization + radiosurgery group (48.4% vs 62.7%).<sup>126</sup> It has been hypothesized that the embolic material could lead to inaccurate targeting of radiosurgery or that the embolized part of AVM could recanalize. There is also inevitable selection bias in the results, as the patients with the most complex AVMs are more likely to receive the embolization before radiosurgery, as was also noted by the authors. Embolization can also be used to target specific high-risk structures in otherwise untreatable AVMs, such as flow-related and intranidal aneurysms or ruptured parts of the nidus, with some evidence of subsequent lower hemorrhage risk.<sup>148</sup>

#### **1.8.3.4 Palliative embolization**

Rarely, partial palliative embolization is used in patients with neurological deficits or venous

hypertension signs to decrease nidus size and reduce blood flow through the nidus with the goal of relieving the symptoms.<sup>146,149</sup> Partially obliterated AVMs, however, tend to form new collaterals through neoangiogenesis, rendering the palliative effect short-lived.<sup>150</sup> Sure et al. demonstrated higher expression of vascular endothelial growth factor (VEGF) in partially obliterated AVMs and proposed that it was caused by local embolization-induced ischemia in the nidus.<sup>151</sup>

#### **1.8.4 Flow-related aneurysms**

Aneurysms related to altered flow dynamics occur in around 18% of AVM patients.<sup>7</sup> Treatment depends on their rupture status, location, and diameter. Aneurysms diagnosed with an AVM are classified as non-AVM related, proximal flow-related, distal flow-related, or intranidal.<sup>152</sup>

In the event of hemorrhage, if the AVM-related non-intranidal aneurysm is considered ruptured, it will be treated first in the same way as ruptured saccular aneurysms generally. If the source of bleeding is the AVM itself or the intranidal aneurysm, the AVM together with the intranidal aneurysm should generally be treated first. Nonetheless, in selected patients, preoperative embolization of a feeding artery supplying a ruptured intranidal aneurysm can be performed.<sup>153</sup> In unruptured cases, aneurysms not related to the AVM and proximal flow-related aneurysms are managed with the same protocol as isolated saccular aneurysms. In the event of a distal flow-related aneurysm, the AVM is usually managed first, as up to 80% of distal flow-related aneurysms have been reported to regress after AVM obliteration.<sup>152</sup> However, if the patient is selected for stereotactic radiosurgery, treatment of the feeding artery aneurysm in advance should be considered, as increased hemorrhage risk has been reported in such patients.<sup>154</sup>

### **1.9 Risk assessment scales for AVM surgery**

Arteriovenous malformation patients are an extremely heterogeneous group, which is why surgical outcomes vary enormously, depending on the patient- and disease-specific variables. As a result, different grading scales have been created for predicting outcomes after microsurgical

AVM eradication. Those most often used are the 5-tier Spetzler-Martin grading scale (SMG)<sup>16</sup> and its simplified version the 3-tier Spetzler-Ponce Classification (SPC),<sup>17</sup> which is sometimes used in combination with a supplementary scale (Lawton-Young Grading System).<sup>18</sup> The SMG includes one ordinal variable that gives 1 to 3 points, depending on the nidus size (divided into three categories), and two nominal variables that give 0 to 1 points, depending on the type of venous drainage and on whether the AVM is eloquently located. (Table 1.) The Lawton-Young scale adds three more variables to the original SMG scale. These are graded with similar logic, age being divided into three categories that give 1 to 3 points; rupture status, and whether the nidus morphology is diffuse or not both give 0 to 1 point (Table 1).

TABLE 1. SPETZLER-MARTIN GRADING (SMG) AND SUPPLEMENTARY GRADING (LAWTON-YOUNG)

| SMG             | Points | Lawton-Young |
|-----------------|--------|--------------|
| Size, cm        |        | Age          |
| <3              | 1      | <20          |
| 3–6             | 2      | 20–40        |
| >6              | 3      | >40          |
| Venous drainage |        | Bleeding     |
| Superficial     | 0      | Yes          |
| Deep            | 1      | No           |
| Eloquence       |        | Compactness  |
| No              | 0      | Yes          |
| Yes             | 1      | No           |

Microsurgical resection is generally recommended for S-M grades 1 and 2 (SPC A). For grades 4 and 5 (SPC C), surgical outcomes are poor and, therefore, surgery alone is generally not recommended, at least with unruptured AVMs. With ruptured grade 4 and 5 AVMs, multimodality treatment is often necessary. Deep-seated high-grade AVMs can be managed with endovascular embolization and stereotactic radiosurgery, especially if repeated ruptures occur. The challenge for the clinician lies in grade 3 (SPC B) cases, as the recommendations vary and therefore multimodality treatment is generally needed. Lawton and Young proposed a supplementary scale to assist in treatment decisions, especially in grade 3 AVMs. This scale, which has proved to be

a valuable additional tool, considers grade 6 a cut-off point for surgery.<sup>155,156</sup> It is adaptable over time since age is clearly not a constant variable, and bleeding status may unfortunately change. Moreover, the size and morphology of the nidus may occasionally be modified by radiosurgery or embolization.

### 1.10 Scales for clinical outcome prediction in AVM-related ICH

Arteriovenous malformation-related ICH is a pathophysiologically different phenomenon from spontaneous intracerebral hemorrhage (sICH), occurring in a very distinct - younger and healthier - population, and generally considered less dangerous.<sup>74,77</sup> Therefore, ICH outcome prediction scales, such as the ICH score,<sup>157</sup> are not necessarily generalizable to AVM hemorrhages. The Hunt and Hess (HH)158 and World Federation of Neurological Surgeons (WFNS)<sup>159</sup> scales (Tables 2 and 3), originally developed for the prognosis assessment of subarachnoid hemorrhage (SAH), have also been used to predict the outcome after AVM rupture.<sup>160,161</sup>

TABLE 2. HUNT & HESS (HH) SCALE

| GRADE |                                                                                     |
|-------|-------------------------------------------------------------------------------------|
| 1     | Asymptomatic or mild headache                                                       |
| 2     | Moderate to severe headache, no neurological deficit other than cranial nerve palsy |
| 3     | Drowsiness, confusion, or mild focal deficit                                        |
| 4     | Localizes or flexion to pain, moderate to severe hemiparesis                        |
| 5     | Extension or no motor response to pain                                              |

TABLE 3. WORLD FEDERATION OF NEUROLOGICAL SURGEONS (WFNS) SCALE

| GRADE | GLASGOW COMA SCALE (GCS) | MOTOR DEFICIT |
|-------|--------------------------|---------------|
| 1     | 15                       | No            |
| 2     | 13-14                    | No            |
| 3     | 13-14                    | Yes           |
| 4     | 7-12                     | Yes or no     |
| 5     | 3-6                      | Yes or no     |

Specific grading systems have recently been developed for AVM hemorrhage. In 2016, the arteriovenous malformation-related intracerebral hemorrhage (AVICH) score was introduced (Table 4).<sup>162</sup> It combines elements of the ICH score (Table 3) with the Lawton-Young grading scale (Table 1). The AVICH score has been further validated in three studies: two reported better prediction power on the functional outcome than the ICH score or the SMG and Lawton-Young scales, and one study reported that the ICH score was more accurate than the AVICH score.<sup>163–165</sup>

TABLE 4. ARTERIOVENOUS MALFORMATION RELATED INTRACEREBRAL HEMORRHAGE (AVICH) SCORE

| PARAMETERS                          | POINTS |
|-------------------------------------|--------|
| LAWTON-YOUNG GRADE WITHOUT BLEEDING | 2-9    |
| GCS >4 AND <13                      | 1      |
| GCS 3-4                             | 2      |
| ICH VOLUME >30 CM <sup>3</sup>      | 1      |
| IVH                                 | 1      |
| MAXIMUM                             | 13     |

## 1.11 Hemorrhagic strokes in childhood

Childhood strokes are relatively uncommon but can result in significant mortality and long-term morbidity. Studies of childhood stroke have reported an incidence of around 2.1-2.5 / 100 000 person-years (excluding neonatal IVH / asphyxia).<sup>166–169</sup> About 50% of pediatric strokes are hemorrhagic compared to 10–30% of adult strokes.<sup>166,170</sup> Childhood hemorrhagic stroke is associated with 15–35% mortality and, of survivors, up to 55% suffer from significant neurological morbidity.<sup>166,171–174</sup> Mortality rates vary considerably, depending on the etiology of the hemorrhage. Moreover, in some studies, the underlying pathology has a greater impact on mortality than the hemorrhage itself. According to the retrospective study by Meyer-Heim et al., mortality rates were 75% in patients with coagulopathy, 40% in those with aneurysms, and 12.5% in those with AVMs.<sup>174</sup> The most common cause of childhood hemorrhagic strokes are AVMs, further

possible causes being other vascular pathologies such as aneurysms and cavernous malformations.<sup>173–175</sup> Other etiologies often found include hematologic disorders and brain tumors.<sup>174,176</sup>

## 1.12 Pediatric AVM patients

Brain arteriovenous malformations account for up to 50% of all pediatric hemorrhagic strokes.<sup>173,174,177–179</sup> Around 12% to 21% of patients presenting with brain AVMs are children.<sup>8,180,181</sup> In modern series, AVM rupture in children is associated with 4–12.5% mortality and up to 28.7% long-term neurological morbidity.<sup>111,174,182</sup> Naturally, the lifetime risk of rupture is higher in patients diagnosed with an AVM in childhood owing to the longer life expectancy and cumulative rupture risk.

Pediatric patients with AVMs differ from adults in clinical presentation, angioarchitecture, morphology, and AVM location.<sup>8,9,183–185</sup>

### 1.12.1 Presentation and characteristics of AVMs in children

Children's AVMs come to clinical attention through intracranial hemorrhage more often than adults' AVMs.<sup>8,9,180</sup> At the same time, children present with seizures (not associated with hemorrhage) less frequently than adults.<sup>8,186</sup> Epilepsy most likely develops due to gradual microhemorrhages from the AVM and consequent irritation of the surrounding cortex by hemosiderin.<sup>187–193</sup> This phenomenon has two consequences: the proportion of ruptured and deep-located AVMs is greater in children than in adults, and; epileptogenic cortical locations<sup>186,194,195</sup> do not often come to clinical attention until later in life. Thus their incidence is relatively lower in the pediatric cohort than in adults. Also, deep venous drainage is often associated with pediatric AVMs,<sup>8,9</sup> but this is probably related to the greater proportion of deep AVMs, as they are more often associated with deep venous drainage.

Neonates and infants may also present with heart failure due to the high degree of arteriovenous shunting relative to cardiac output.<sup>40,41</sup>

### 1.12.2 Annual rupture risk in pediatric patients

Occasionally, pediatric patients have been specu-

lated to have a higher annual rupture risk than adults. However, there is little evidence to support this. Longitudinal studies analyzing the annual rupture risk with Kaplan-Meier life table analyses and Cox proportional hazards regression models have been inconclusive, with many reporting age as an insignificant factor,<sup>19,89,91</sup> while others have noted that older<sup>90,180</sup> or younger<sup>88</sup> age increases the rupture risk. The three studies reporting age as a factor not significant for increased rupture risk all analyzed age as a continuous variable. The study by Mast et al. had a very limited follow-up time (<1 year) and, consequently, a low number of hemorrhagic events (18 in the initially ruptured group and three in the non-ruptured group),<sup>89</sup> whereas that by Halim et al. found borderline significance ( $P=0.056$ ) for increased rupture risk with increasing age.<sup>91</sup> In the third study, by Laakso et al., age was not a significant factor for rupture risk.<sup>19</sup> The study by Yamada et al. reported low age (<20 years) as a risk factor for subsequent hemorrhage in hemorrhagically presenting AVM patients but not in the initially non-hemorrhagic group.<sup>88</sup> In contrast, Stapf et al. reported increasing age as an independent risk factor for subsequent hemorrhage after adjusting for hemorrhagic presentation.<sup>90</sup> To the best of the author's knowledge, only one small study of 19 pediatric AVM patients reported increased rupture risk related to age in unruptured pediatric AVMs,<sup>196</sup> but these patients had undergone treatment for their AVMs and were not therefore representative of the natural disease course. Additionally, one study has reported childhood (<20 years) as a risk factor for subsequent hemorrhage in cerebellar AVMs.<sup>197</sup>

Fullerton et al. analyzed the difference in hemorrhage risk between 214 pediatric (<20 years) and 857 adult patients and observed annual rupture rates of 2.2% and 2.0%, respectively.<sup>180</sup> In multivariate analysis, after adjusting for hemorrhagic presentation, subsequent ICH rates were 90% lower in children than in adults. In contrast to other longitudinal studies, they did not analyze age as a continuous variable. A study by Kim et al. compared ICH rates between birth-to-diagnosis and diagnosis-to-ICH groups. Primarily ruptured AVMs were excluded from the diagnosis-to-ICH group, and patients were censored at the date of the first treatment, last

follow-up, or death. The annual rupture rates between the groups were similar (1.27% vs 1.17%) and comparable to those reported in natural history studies.<sup>7,19,20,76,85</sup> Analysis of ICH rates by decade showed that rupture risk was lower (0.32%) during the first decade of life (<10 years) in the birth-to-diagnosis group.<sup>198</sup>

The annual rupture risk of children's symptomatic AVMs seems to be the same as that of adults, or even slightly lower, perhaps owing to the lower incidence of time-dependent features such as flow-related aneurysms and venous ectasia.<sup>8-10,118,199</sup> Moreover, extracranial AVMs have been shown to progress during puberty<sup>44,200</sup> and pregnancy,<sup>44,201</sup> accompanied by increased hemodynamic lability and bleeding, which have led some researchers to propose that hormonal changes during puberty may also affect intracranial AVM rupture risk.<sup>202</sup> Results regarding the rupture risk of intracranial AVMs during pregnancy have been inconclusive, some reporting higher<sup>203</sup> and others lower<sup>204</sup> risk.

### 1.12.3 Outcome

Pediatric AVM patients present with ICH more often than adults, and the rupture has been reported to be clinically more severe with higher mortality than in adults.<sup>94,181,196,205</sup> Arteriovenous malformation hemorrhage is most likely more severe in children because of their limited cerebrospinal fluid (CSF) spaces and higher incidence of infratentorial AVMs.<sup>181,206</sup> Ruptures of posterior fossa AVMs have been associated with higher mortality than AVMs in general, because the expanding hematoma rapidly fills the limited space, thus easily causing hydrocephalus and brainstem compression.<sup>207,208</sup> Despite the initial insult in children being on average more dangerous than in adults, their long-term prognosis is better than that of older patients.<sup>8</sup> Children's better neural plasticity and, consequently, their greater ability to recover from the hemorrhage if they survive the initial insult is likely a contributing factor.

Microsurgical AVM treatment, small AVM size, and low Spetzler-Martin grade have all been reported to correlate with favorable long-term outcomes in children.<sup>8</sup> In contrast, conservative treatment, deep perforators, coma at admission, ICH volume >30 cm<sup>3</sup>, hydrocephalus, Spet-

zler-Martin grade  $\geq 3$ , and any deep venous drainage have been reported to correlate with unfavorable outcomes.<sup>8,155,209</sup> It is not surprising that microsurgical treatment is associated with favorable long-term outcomes as it is the most reliable way to eliminate the rupture risk immediately. If we consider that most pediatric AVM patients present with hemorrhage and that a previous rupture is the most consistently reported risk factor for a subsequent rupture, and moreover that the cumulative rupture risk predisposes younger patients to a higher life-time rupture risk in any case, the risk/reward ratio is generally favorable for surgery. The increased risk posed by deep perforators is also easy to understand, as these fragile small vessels are difficult to coagulate, often retracting deeper into white matter, which contains potentially eloquent long fiber tracts.<sup>155</sup>

## 1.13 Management of pediatric AVMs

The general principles of AVM treatment were described in Section 5. However, there are some specific considerations that must be addressed when planning the treatment of pediatric AVM patients.

The goal of the treatment is to eliminate rupture risk with minimal neurological complications. Rupture risk will persist until complete AVM obliteration is achieved.<sup>20</sup> There are few data on the annual rupture risk in pediatric patients, but it seems to be approximately the same as in adults.<sup>180</sup> The cumulative rupture risk, combined with children's longer life expectancy and better recovery capacity, favors a more aggressive treatment approach in general.

Selection of the treatment modality in pediatric patients still depends on the same factors as in adults: AVM size, angioarchitecture, morphology, rupture status, lesion location, and the clinical condition of the patient. There are currently no pediatric-specific grading systems for surgical risk evaluation. The scale most widely used is the Spetzler-Martin grading system, but this has some limitations in the assessment of pediatric patients. It does not include the rupture status and age of the patient and so may provide excessively conservative treatment recommendations

for children, who also often present with hemorrhage. The Lawton-Young grading scale is more suitable for children as it includes these two crucial factors.<sup>18</sup> Winkler et al. reported a favorable treatment outcome (mRS score  $\leq 2$ ) in 67.3% of pediatric patients with SM grade IV and V AVMs with a 16.3% complication rate.<sup>112</sup>

The grading scales are, however, intended for surgical risk evaluation and so do not provide guidance on the optimal treatment modality. There is a shortage of scientific research comparing different treatment modalities in pediatric AVM patients. Moreover, as in any disease, but especially in AVMs, the lesions, patients, and circumstances vary greatly, making it very hard to give any firm general treatment recommendations. To achieve the best results, the decision on the optimal treatment modality in pediatric patients as in adult patients should be made by a multidisciplinary team comprising a vascular neurosurgeon, an interventional neuroradiologist, and a radiation oncologist.

Different treatment modalities with emphasis on the special concerns of pediatric AVM patients are presented below.

### 1.13.1 Conservative management

The cumulative rupture risk with long life expectancy rarely justifies conservative treatment in pediatric patients. Even so, some AVMs are too hazardous for any treatment, and conservative management is applied. In a recent single-center study of pediatric AVM patients, conservative treatment was associated with a poor long-term outcome (mRS  $\geq 2$ ), 68% of the conservatively treated patients suffering a hemorrhage from AVM during follow-up and 56% of them having died by the end of the follow-up.<sup>8</sup> The natural history of truly incidental AVMs is not well understood since even the prevalence of the disease is unknown.

### 1.13.2 Microsurgery

Pediatric patients have been reported to have a better outcome than adults after microsurgical AVM resection.<sup>113,196,210</sup> Sanches-Mejia et al. compared functional outcomes between pediatric and adult patients after microsurgical AVM resection, matched by AVM characteristics, clinical status at presentation, rupture status, and

treatment methods. They found that 94% of the mRS scores in the pediatric group improved or remained unchanged (70% in the adult group), while the mean mRS scores improved by 1.31 points (0.14 points in the adult group). The authors concluded that the most probable explanation for children's better recovery capacity is their better neural plasticity. Supporting evidence comes from a comparative study of stroke outcomes between children and adults, in which children recovered significantly better than adults in terms of language and speech scores as well as social skills.<sup>211</sup> In a study of 36 pediatric patients with SMG 1-3 AVMs treated with microsurgery alone or with microsurgery and preoperative embolization (SMG 3 AVMs), full obliteration was achieved in all of the patients, and most (86.1%) of these patients had a favorable outcome (mRS <3).<sup>212</sup> Another study of 94 pediatric patients with SMG 1-4 AVMs (though only two with SMG 4) reported good functional outcomes (mRS <3) in 94% of the patients, and an obliteration rate of 100%.<sup>11</sup> It has sometimes been proposed that Rolandic AVMs are better managed with radiosurgery.<sup>213</sup> However, one study of 11 pediatric patients with Rolandic AVMs reported that the results for SMG 2-3 AVMs were better after microsurgery, with 100% obliteration and no permanent clinically significant neurological deficits.<sup>214</sup>

### 1.13.3 Radiosurgery

In 1989, Altschuler et al. pioneered the use of stereotactic radiosurgery for pediatric AVMs.<sup>215</sup> The main reason for postponing the use of radiosurgery in children was concern about the effect of radiation exposure on the developing brain.

Radiosurgery-induced obliteration rates depend on the marginal dose and AVM size. In pediatric patients with at least three years of follow-up, marginal doses of  $\geq 18$ , 20, and 22 Gy have been associated with obliteration rates of 47.6%, 63%, and 71.3%, respectively.<sup>112,127</sup> In a single-center study of pediatric AVM patients treated with stereotactic radiosurgery, Shin et al. reported a 96% obliteration rate at three years for <1.5 cm AVMs compared to 58.6% for 2-3.3 cm AVMs.<sup>128</sup>

Increased T2 signaling on MRI after stereotactic radiosurgery has been reported in up to

38% of pediatric patients even though most of them were asymptomatic.<sup>129</sup> The data on long-term effects of stereotactic radiosurgery on pediatric AVM patients is scarce. However, rare cases of cognitive impairment, meningiomas, cyst formation, and radiation necrosis have been reported up to 20 years after treatment.<sup>129,133,216</sup> At least one secondary glioblastoma has been reported in a 4-year-old patient 70 months after thalamic AVM radiosurgery.<sup>217</sup>

### 1.13.4 Endovascular embolization

In pediatric patients, the obliteration and complication rates after embolization with intent to cure have ranged from 45% to 91% and from 9% to 15%, respectively.<sup>218-220</sup> At the time of writing, the latest meta-analysis of pediatric AVMs reported a recurrence rate of 36.4% in the curative embolization group, suggesting that embolization alone is not recommended in most cases, at least in pediatric patients.<sup>29</sup> Partial embolization has also been associated with increased rupture risk in pediatric patients.<sup>209</sup>

## 1.14 Recurrent AVMs

Over the last three decades, AVM recurrence after complete treatment is increasingly recognized, notably in the pediatric population.<sup>221,222</sup>

In children, the percentage of patients harboring recurrent AVMs has ranged from 5% to 28%,<sup>221,223-228</sup> the highest rates probably being residuals, not actual recurrences. The latest meta-analysis of 1134 patients had a 4.8% recurrence rate.<sup>29</sup> Reported risk factors for AVM recurrence include diffuse nidus, deep venous drainage, and presentation with rupture.<sup>222,225,226</sup>

The need for follow-up imaging in completely treated pediatric AVM patients is understood. However, there is diversity in recommendations regarding the timing and duration of follow-up as well as the appropriate imaging modality. Some authors recommend the first angiographic follow-up one year after the surgical treatment, with either MRA<sup>223</sup> or DSA<sup>224</sup>, the aim being to find residual AVM missed in the initial postoperative angiography. Others have proposed angiographic follow-up with MRA yearly until adult age<sup>221</sup> or with DSA at one, three, and five years and thereafter every five years.<sup>224</sup>

There are reports of recurrent AVMs seen in DSA performed just a few months after MRA that showed no signs of AVM.<sup>223,224</sup> Jhaveri et al. reported the sensitivity and specificity of a combination of Gd-enhanced MRI and TOF-MRA for detecting recurrent AVMs to be 75% and 91%, respectively.<sup>65</sup> Therefore, MRI/MRA alone cannot rule out recurrence.

Arteriovenous malformations have been demonstrated to have abnormal perinidal capillary networks connected to the adjacent brain parenchyma, capillaries, arterioles, and venules.<sup>12,13,229</sup> Dysplastic vessels in postoperative DS-angiography have been reported in up to 35% of AVM patients.<sup>230</sup> As pointed out in Section 3, somatic activating mutations in endothelial cells have recently been recognized as the causative agent in AVM formation. Most likely, these mutations are present in the perinidal endothelial cells and may lead to recurrent AVM formation. The recent meta-analysis of recurrent AVMs by Lauzier et al. reported the lowest recurrence risk in patients treated with radiosurgery (0.7% in radiosurgery vs 8.5% in microsurgery)<sup>29</sup>, supporting the idea of a pathological perinidal zone. Immature vasculature and higher levels of circulating angiogenic growth factors may play a role in the increased risk of children developing recurrent AVMs.<sup>29,231</sup> Furthermore, recurrent AVMs have been shown to have increased levels of the endothelial progenitor markers CD31, CD34, and CD105 as well as the smooth muscle proliferative marker pERK.<sup>232,233</sup>

## 1.15 Helsinki AVM database

Finland is a suitable country for population-based studies because of the high-quality public health care system, the level of population responsibility, the use of traceable social security numbers unique for every citizen, and the existence of health care record archives available for research purposes. Finland has five university hospitals with neurosurgical departments, the largest of them being the Department of Neurosurgery of Helsinki University Hospital (HUS). No neurosurgical services (other than some spine surgeries) are provided in any other institution. This centralized system improves the reliability of tracing patients for research purposes.

The Helsinki AVM database comprises 805 consecutive AVM patients treated at Töölö Hospital between 1942 and 2014. Here it should be noted that until 1967, Töölö Hospital was the only neurosurgical department in Finland.<sup>234</sup> The database has been gathered retrospectively from the patient archives and is updated regularly with the latest relevant follow-up data. Information obtained from the questionnaire, which included the 15D instrument and was sent to patients in 2016, has also been added. The death certificates of deceased patients were reviewed in 2016. Over the years, the database has thus accumulated a vast amount (hundreds of variables) of patient- and disease-specific information.

The database has provided valuable insight into the epidemiology and natural history of AVMs and has been used in many studies. In 2008, Laakso et al. published a natural history study of AVMs with the longest follow-up to date.<sup>19</sup> It was accompanied by a long-term excess mortality study<sup>87</sup> that is still the only study to have analyzed excess mortality in relation to the matched general population. A few years later, Laakso et al. expanded the natural history with a subpopulation of 63 SM-grade IV-V patients.<sup>235</sup> In addition, the database has been used, among others, for the external validation of the Lawton-Young scale<sup>155</sup>, assessment of the long-term HRQOL of AVM patients<sup>236</sup>, and evaluation of the special characteristics of pediatric AVM patients.<sup>8</sup>

## 1.16 Health-Related Quality Of Life (HRQOL)

Back in 1948 the World Health Organization (WHO) defined health as “a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity”.<sup>237</sup> However, it took several years before the concept was utilized in medical research. As medical treatments evolved, thereby improving survival and reducing morbidity, quality of life (QOL) became more important in health care.<sup>238</sup> Quality of life is an abstract concept that encompasses all aspects of life affecting an individual’s well-being or life satisfaction.<sup>239</sup> Health naturally plays an important role in overall QOL but it is not the only factor; housing, employment, standard of liv-

ing, marital status, social relations, religion, and environmental factors all affect the overall QOL.<sup>240</sup> The healthcare system cannot address all of these individual needs, leading to development of the concept of health-related quality of life (HRQOL).<sup>239</sup> This includes only QOL factors that are related to an individual's health. The HRQOL is composed of physical, emotional, and social domains that may be altered by disease or treatment, while the degree of the impact depends on external factors (such as the functional outcome of the intervention) and on the individual's subjective reaction to these factors.<sup>241</sup>

There are two types of HRQOL instrument: generic and specific.<sup>242</sup> Generic instruments measure all the dimensions of HRQOL (physical, emotional, and social) and therefore can be used to compare different treatments and diseases.<sup>243</sup> They can also be used to measure HRQOL in a certain population and the changes in that population, thus permitting a comparison to be made between specific study cohorts and the general reference population. Specific instruments target issues related to certain diseases, patient populations, or functional domains.<sup>243</sup> For the detection and quantification of small changes in relation to a certain disease or treatment, specific instruments may be more sensitive than generic instruments.<sup>244</sup> If feasible, a generic instrument should be combined with a specific instrument to assess clinically important changes.<sup>245</sup>

Generic instruments can be presented as an HRQOL profile or a single index score. Profiles have the advantage of specifying on which dimensions the difficulties lie and where the possible change occurs. The single index score is typically between 0 and 1 and represents the overall HRQOL: it is calculated by using a utility/preference weight on each dimension obtained from the validated valuation system.<sup>246</sup> The single index score can be used to calculate quality-adjusted life years (QALYs), which take into account both the quantity and quality of life and are most often used for cost-effectiveness analyses of healthcare interventions.<sup>247</sup> The most generally approved generic instruments, such as 15D, NHP, EQ-5D, and SF-20, have incorporated both the HRQOL profile and the single index score.<sup>248–251</sup>

## 1.17 Historical overview of brain AVMs

The first description of a brain AVM was made by the German anatomist Hubert von Luschka in 1854.<sup>252</sup> In 1889, Jules-Émile Péan performed the first documented successful surgical AVM extirpation.<sup>21</sup> However, it took several decades and diagnostic innovations before the procedure was replicated. The x-ray was discovered by Wilhelm Roentgen in 1895. This enabled the development of pneumoencephalography in 1919 by Walter Dandy, thus allowing robust localization of brain lesions.<sup>253</sup> In 1927, the Portuguese neurologist Egas Moniz introduced angiography, performed in the early days by direct carotid puncture.<sup>254</sup> Developments in diagnostics allowed Professor Herbert Olivecrona to perform the second documented AVM extirpation with an improved technique in 1932.<sup>21</sup> In the latter half of the decade, surgical microscopes and more sophisticated diagnostics methods were developed. The first neurosurgeon to use a microscope was Theodore Kurze when, in 1957, he removed the seventh cranial nerve schwannoma from a 5-year-old patient.<sup>255</sup> Later, in the 1960s, with the contribution of pioneering neurosurgeons such as Kurze, Jacobson, Donaghy, and Yasargil, the use of surgical microscopes became standard practice, and microneurosurgery was born.<sup>256</sup> The field was transformed with the entry of computed tomography (CT) into clinical practice in the 1970s.<sup>257</sup> The use of an operating microscope, CT, and angiography allowed a new era in AVM surgery as well as in many other neurosurgical procedures. In 1976, Yasargil published one of the earliest case series of 10 microsurgically treated AVM patients.<sup>258</sup> Further advances were made when MRI, which was developed in 1973 by Paul Lauterbur and Peter Mansfield (who were later awarded the Nobel prize for their discoveries)<sup>259</sup>, came into clinical practice in the early 1980s<sup>260</sup> followed by MRA a few years later.<sup>261</sup> These discoveries allowed the development of intraoperative neuronavigational devices, now routinely used in microneurosurgery, making AVM surgeries even more feasible. The latest development is the hybrid operation room, which offers high-resolution images together with the possibility of endovascular procedures.<sup>262</sup>

### 1.17.1 Helsinki neurosurgery

The Finnish Red Cross Hospital (which later became Töölö hospital) was established on the initiative of Marshal Carl Gustaf Mannerheim in 1932. Neurosurgery as a separate field was established by Aarno Snellman in 1935 on his return to Finland from a six-month training period at Professor Herbert Olivecrona's Neurosurgical Clinic in Stockholm.<sup>263</sup> Later, in 1942, Snellman was appointed Finland's first professor of neurosurgery<sup>264</sup> (Fig. 8). The same year he performed the first AVM surgery in Finland. After Snellman's retirement, Gunnar af Björkesten was appointed professor of neurosurgery in 1962. Having trained for four years under Professor Olof Sjöqvist in Stockholm, he developed a keen interest in vascular and skull base neurosurgery.<sup>265</sup> Since then, Helsinki Neurosurgery has built on the high standards set in vascular neurosurgery.



Fig. 8. Portrait of Professor Snellman

## 2 Aims of the study

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The overall goal of this study was to enhance our knowledge of pediatric AVM patients with a view to improving their treatment. The more specific aims were as follows:

1. To clarify the special characteristics of pediatric AVM patients.
2. To evaluate the long-term outcomes of pediatric AVM patients.
3. To assess the long-term Health-Related Quality of Life measured with the 15D instrument in AVM patients treated in childhood or adolescence.
4. To perform a long-term angiographic follow-up for AVM patients treated in childhood or early adulthood with the intention of establishing the recurrence rate in our cohort.



# 3 Materials and methods

This study was based on the Helsinki AVM database described in section 14. In 2016, questionnaires were sent to all living patients in the database who were over 18 years of age (n = 432). The database was updated with the information obtained from the questionnaires and by reviewing all the relevant medical records, images, and death certificates. The questionnaires contained the 15D HRQOL instrument as well as separate questions on symptoms, comorbid conditions, lifestyle, educational level, and self-sufficiency/independence. Of the 432 patients contacted, 325 (75%) completed the questionnaire.

The diagnosis of AVM was based on digital subtraction angiography. Size, location, angioarchitecture, and associated aneurysms of the AVM were evaluated from angiography, computed tomography (CT), and/or magnetic resonance images (MRI). The AVM was considered deep if it was in paracallosal, basal ganglia, intraventricular, trigonal, temporomesial, pontomesencephalic, or deep cerebellar locations; all other locations were considered superficial. The Spetzler-Martin Grading scale (SMG) was assessed for each AVM. If the CT or MRI performed prior to admission showed signs of bleeding, AVM was regarded as ruptured.

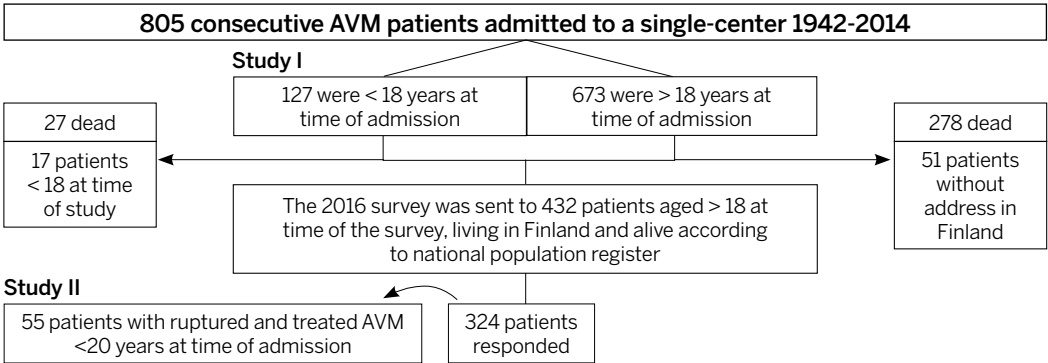
## 3.1 Study population:

For Study I, the patients were defined as children if they were under 18 years of age at the time of admis-

sion. They were extracted from the updated Helsinki AVM database. At the time of admission, 127 patients were under 18 and were thus included in the study. As diagnostics and treatments had evolved greatly during the study period, a subgroup analysis was conducted for patients diagnosed between January 1, 1980, and December 31, 2014.

For Study II, 95 patients under 20 years of age at the time of admission with ruptured and treated AVMs were included from the Helsinki AVM database. Of them, 79 (83%) were alive at the time of the survey; 55 replied to the 2016 questionnaire and formed the study cohort. AVMs were classified according to the SM-grading system, which was converted into the SPC. The 3-tier SPC is based on the original 5-tier SMG (as described previously in Section 1). Two patients who were treated in 1951 and 1962 lacked SPC grades and were thus excluded from the analysis. The deceased patients' SPC grades were A (2 patients, 14%), B (8 patients, 57%), and C (4 patients, 29%). The occurrence of symptomatic epilepsy was measured by the Engel classification. In Engel class I, a patient is asymptomatic from epilepsy with or without antiepileptic drugs (AEDs). In Engel class II or higher, a patient has symptomatic epilepsy despite treatment. The number of AVM ruptures was dichotomized into those with repeated ( $\geq 2$ ) ruptures and those with only one rupture. The admission age was divided into three groups: under 10, 10- $<15$ , and 15-20 years.

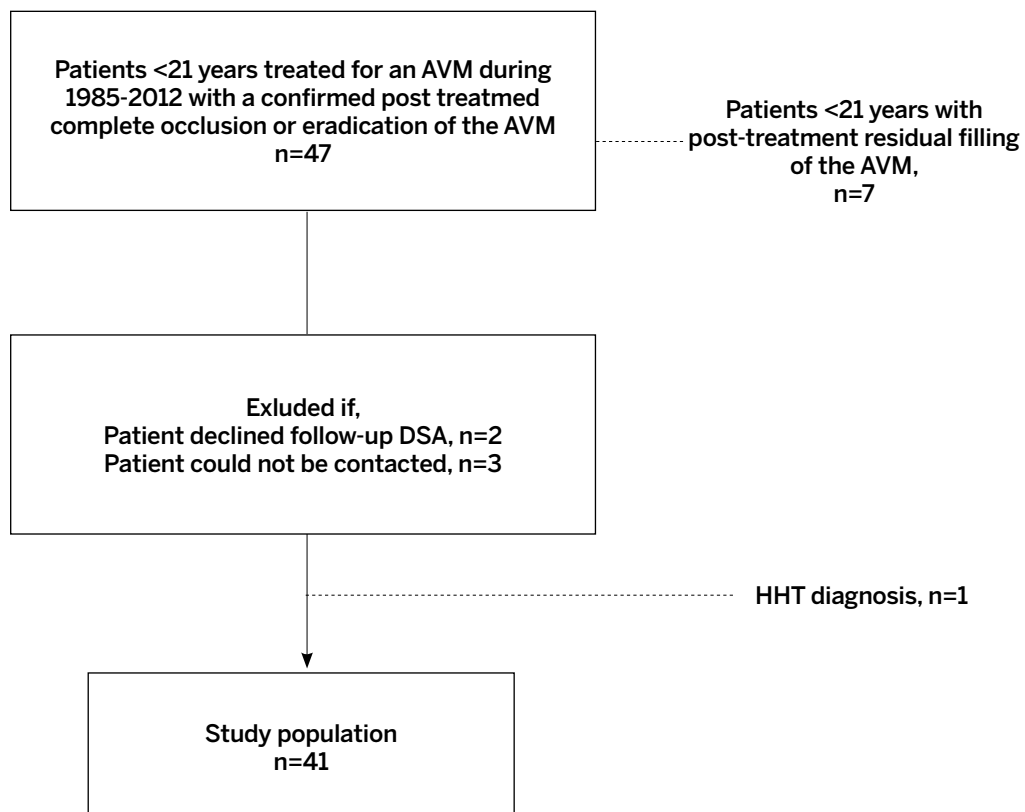
Fig. 9. Flowchart of patient selection in Study I and II



Study III included patients treated at the Department of Neurosurgery of Helsinki University Hospital during 1985–2012. Traditionally, we had not conducted routine long-term follow-up angiographic imaging in asymptomatic patients with AVMs in which complete eradication was verified by post-treatment DSA. In the light of increasing clinical experience of recurrences at the Department of Neurosurgery, it was deemed necessary to continue follow-up for patients treated in childhood or early adulthood (<21 years) due to the risk of AVM recurrence. In January 2021, we introduced a new follow-up protocol comprising a clinical visit and DSA study to evaluate the long-term risk of AVM recurrence. The control DSA study was offered to patients under

50 years of age at the time of follow-up, as possible asymptomatic recurrences would probably not have led to any interventions in those older than 50. Since 2021, the follow-up of AVM patients has been organized according to this protocol. All the patients participating in the late follow-up DSA had had immediate postoperative DS angiography after the primary treatment confirming complete AVM eradication. Forty-two of the 44 patients contacted agreed to participate in the late DSA controls and 41 of them were included in the analyses after excluding the patient with HHT-AVM, who was presented separately. Fig. 10. Patients' medical records, including relevant radiological images (if still existing in digital format), were reviewed.

**Fig. 10. Flowchart of patient selection in Study III**



## 3.2 Follow-up

A follow-up evaluation for Study I was based on the results of the 2016 questionnaire and the updated Helsinki AVM database. Long-term outcome was measured with the modified Ranking Scale (mRS), and short-term outcome (2-4 months) with the Glasgow outcome scale (GOS). The mRS was dichotomized: scores 0 and 1 were considered as favorable, and 2 to 6 as unfavorable outcomes.

The long-term HRQOL for Study II was measured with the 15D instrument included in the 2016 questionnaire. It is a generic, 15-dimensional, standardized, self-administered instrument that generates both a profile and a single index score. It includes 15 health-related questions that have been utility weighted with a reference population. For each dimension (question), the respondent chooses, on an ordinal scale from 1 to 5, the value best describing his/her state of health at that moment (best = 1, worst = 5). On the basis of the answers, the instrument produces life-quality profiles and a single index score that represents the overall HRQOL on a scale of 0 to 1 (1 = full health, 0 = being dead). A difference of 0.015 in the 15D score is considered clinically important.<sup>26</sup>

The educational level of the patients was compared with that of the age-matched general population. The data on the reference population were collected from a public database (Official Statistics of Finland). The educational level was divided into five categories in the written questionnaire: basic, vocational, high school, polytechnic/college, and university. In Finland, educational level is generally divided into basic, secondary (vocational and high school), lowest upper secondary (2-3 years after secondary, e.g., nurse), lower upper secondary (3-4 years after secondary, e.g., Bachelor's), upper secondary (Master's and Licentiate), and doctoral degree (Ph.D.). To ensure good comparability with the reference population, we combined vocational and high school as one variable, "secondary level". Polytechnic/college includes the lowest and lower upper secondary levels, and university includes the upper secondary level and doctoral degree.

## 3.3 Ethical aspects

Studies I and II were approved by the University Hospital ethical committee. All patients who completed and returned the questionnaires in 2016 gave their informed consent for use of their data. Under current Finnish law, ethics committee approval is not required for secondary use of existing clinical registry data, and informed consent is not required for retrospective studies based on hospital records. Study III was approved by the hospital administration. The DSA control was performed as a part of a new clinical follow-up protocol for AVM patients. Patients also had counseling about the possibility of recurrence and its implications. Participation in the control angiographies was voluntary.

## 3.4 Statistical methods

Version 24.0 of the commercial software SPSS (IBM Inc, Armonk, New York) was used for statistical analysis.

*Study I:* The Pearson chi-square test and multivariate analysis using binary logistic regression with the backward Wald method were used. Missing data were excluded. A probability value below 0.05 was considered statistically significant. The Strobe reporting guidelines were applied.

*Study II:* The statistical significance of the differences in the mean HRQOL scores and their dimensions was tested by independent-samples t-test or analysis of covariance (age-standardized), followed by Bonferroni-corrected post hoc tests. The following variables were included in the linear regression model: patient age at admission, number of bleeds, SPC, and refractory epilepsy. The fixed regression model was created to understand which independent variables were associated with a decreased 15D score and the interactions between these variables.

*Study III:* Due to the relatively small number of patients, no statistical intergroup comparisons were made. Categorical variables were presented as absolute numbers with percentages. Continuous data were analyzed for skewness and since all data were non-parametrically distributed, they were presented as medians with interquartile ranges, and minimum and maximum ranges. One patient with an HHT-related AVM was presented separately and excluded from the analyses.



# 4 Results

## 4.1 Study I

### 4.1.1 Demographics

A total of 805 consecutive AVM patients were admitted to a single center between 1942 and 2014. Of these 805 patients, 127 were under 18 years of age at the time of diagnosis. The mean admission age in the pediatric cohort was 12 years (median 13, range 2 months-18 years). The mean follow-up time for these patients was 21 years, ranging from 0 to 62 years of age. In children, 47% of the patients were female and 54% male; in adults, the proportions were 43% and 57%, respectively.

### 4.1.2 Presentation and characteristics of AVMs

Children presented with hemorrhage more often than did adults (76% in children vs 64% in adults,  $P = 0.010$ , modern subgroup: 72% in children vs 57% in adults,  $P = 0.010$ ) but less often with focal epilepsy (33% in adults and 20% in children,  $P = 0.003$ , modern subgroup: 34% in adults vs 19% in children,  $P = 0.009$ ). Children's AVMs were more often deep and posterior fossa-located, while adults had more cortical AVMs. Deep venous drainage was more common in children (31% vs 17%). Flow-related aneurysms were less common in children (6% vs 16%). The size of AVMs was approximately the same in both children and adults. Table 5. Owing to the differences in location and venous drainage patterns the SM grades were higher in children (Table 6).

TABLE 5. ARTERIOVENOUS MALFORMATION CHARACTERISTICS

| Location, venous drainage, associated aneurysm(s) | Number of pediatric patients | %   | Number of adult patients | %   |
|---------------------------------------------------|------------------------------|-----|--------------------------|-----|
| Frontal                                           | 13                           | 17  | 97                       | 22  |
| Parasylvian                                       | 3                            | 3.9 | 32                       | 7.2 |
| Temporal                                          | 7                            | 9.2 | 53                       | 12  |
| Rolandic                                          | 4                            | 5.3 | 38                       | 8.5 |
| Parietal                                          | 4                            | 5.3 | 56                       | 13  |
| Occipital                                         | 8                            | 11  | 47                       | 11  |
| Anterior paracallosal                             | 1                            | 1.3 | 11                       | 2.5 |
| Posterior paracallosal                            | 9                            | 12  | 15                       | 3.4 |
| Basal ganglia                                     | 12                           | 16  | 18                       | 4.0 |
| Intraventricular                                  | 1                            | 1.3 | 6                        | 1.3 |
| Trigonal                                          | 1                            | 1.3 | 7                        | 1.6 |
| Temporomesial                                     | 0                            | 0.0 | 9                        | 2.0 |
| Whole hemispheric                                 | 1                            | 1.3 | 0                        | 0.0 |
| Pontomesencephalic                                | 1                            | 1.3 | 13                       | 2.9 |
| Medulla oblongata                                 | 0                            | 0.0 | 0                        | 0.0 |
| Cerebellar                                        | 11                           | 15  | 39                       | 9.0 |
| Multiple                                          | 0                            | 0.0 | 4                        | 0.9 |
| $p < 0.001$                                       | 76                           | 100 | 445                      | 100 |
| Superficial                                       | 50                           | 66  | 364                      | 80  |
| Deep                                              | 26                           | 34  | 90                       | 20  |
| $p = 0.005$                                       | 76                           | 100 | 454                      | 100 |
| Supratentorial                                    | 64                           | 84  | 400                      | 88  |
| Infratentorial                                    | 12                           | 16  | 54                       | 12  |
| $p = 0.341$                                       | 76                           | 100 | 454                      | 100 |
| Cortical venous drainage                          | 30                           | 41  | 268                      | 61  |
| Deep venous drainage                              | 26                           | 36  | 73                       | 17  |
| Cortical and deep venous drainage                 | 17                           | 23  | 99                       | 23  |
| $p < 0.001$                                       | 73                           | 100 | 440                      | 100 |
| Small nidus size (0-1 inches)                     | 31                           | 41  | 193                      | 43  |
| Medium nidus size (1-2 inches)                    | 34                           | 45  | 196                      | 44  |
| Large nidus size (>2 inches)                      | 10                           | 13  | 60                       | 13  |
| $p = 0.960$                                       | 75                           | 100 | 449                      | 100 |
| Associated aneurysm(s)                            | 4                            | 5.6 | 76                       | 17  |
| $p = 0.012$                                       |                              |     |                          |     |

TABLE 6. SPETZLER-MARTIN GRADES

| Spetzler-Martin grade | Number of pediatric patients | %  | Number of adult patients | %  |
|-----------------------|------------------------------|----|--------------------------|----|
| 1                     | 16                           | 14 | 88                       | 14 |
| 2                     | 23                           | 20 | 209                      | 31 |
| 3                     | 44                           | 37 | 199                      | 32 |
| 4                     | 26                           | 22 | 115                      | 19 |
| 5                     | 9                            | 8  | 22                       | 4  |

4.1.3 Differences in AVM presentation by decade

The proportion of patients presenting with hemorrhage decreased from the 1950s to 2014 (Fig. 11). At the same time, the number of incidentally found AVMs increased (Fig. 12). In adults, the proportion of AVMs diagnosed because of epilepsy remained more or less constant. Children showed a sudden increase in AVMs diagnosed because of epilepsy in the 1970s (Fig. 13). During

the same decade, the proportion of children in all AVM patients also increased (Table 7).

4.1.4 Outcome at 2-4 month follow-up according to GOS

The majority of patients (124 children and 673 adults) had a clinical follow-up in the outpatient department at 2-4 months. GOS was evaluated on the basis of data available from these follow-up visits. (Table 8). Pediatric patients recovered statistically significantly better than adults ( $P = 0.023$ ).

4.1.5 Long-term outcome

The long-term follow-up was evaluated on the basis of the responses of the 324 patients who completed the questionnaire. For patients who did not respond to the questionnaire (108 patients) and for those who were not sent a questionnaire (17 children and 51 patients without an address in Finland), the most recent medical history available was used. For the deceased (305 patients), the last follow-up day was the date of death as determined by death certificates (Fig. 9). (Methods section).

Fig. 11. Proportions of pediatric and adult patients presenting with hemorrhage at admission by decade

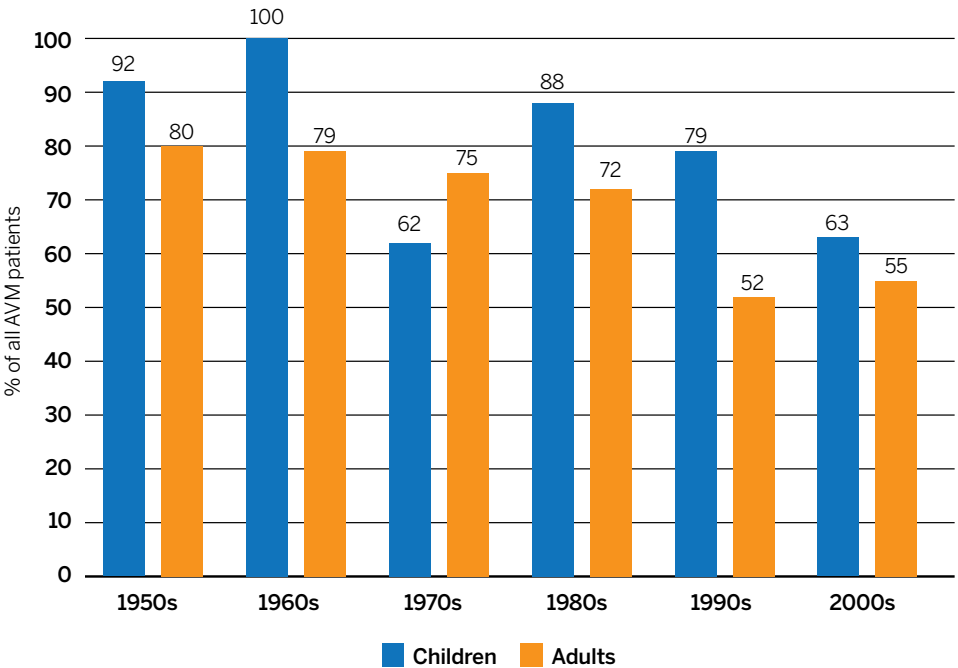


**Fig. 12. Proportion of incidental AVMs in pediatric and adult patient cohorts by decade**

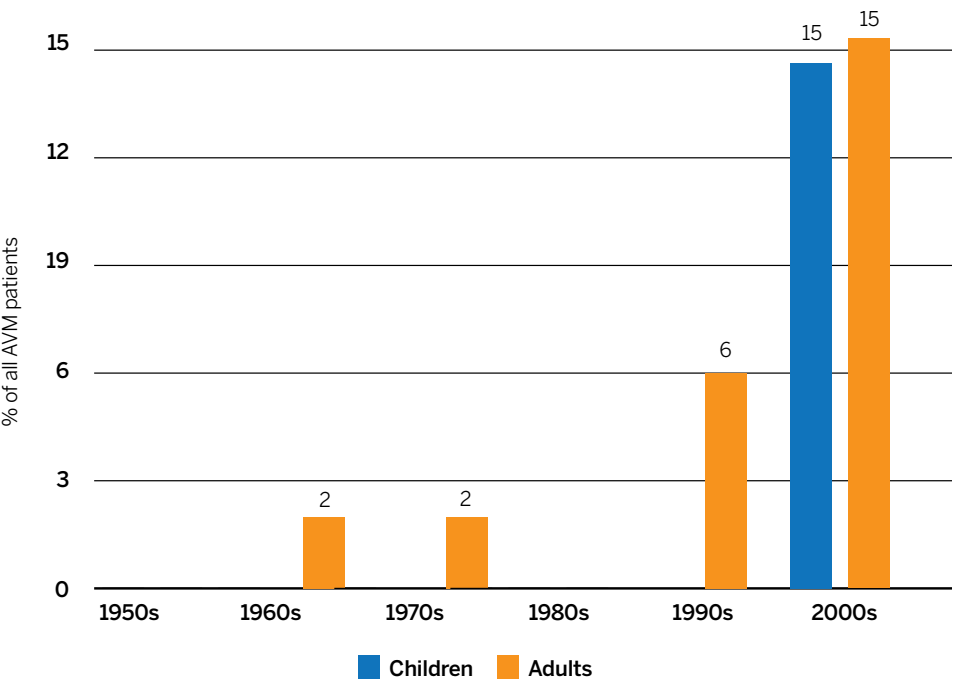
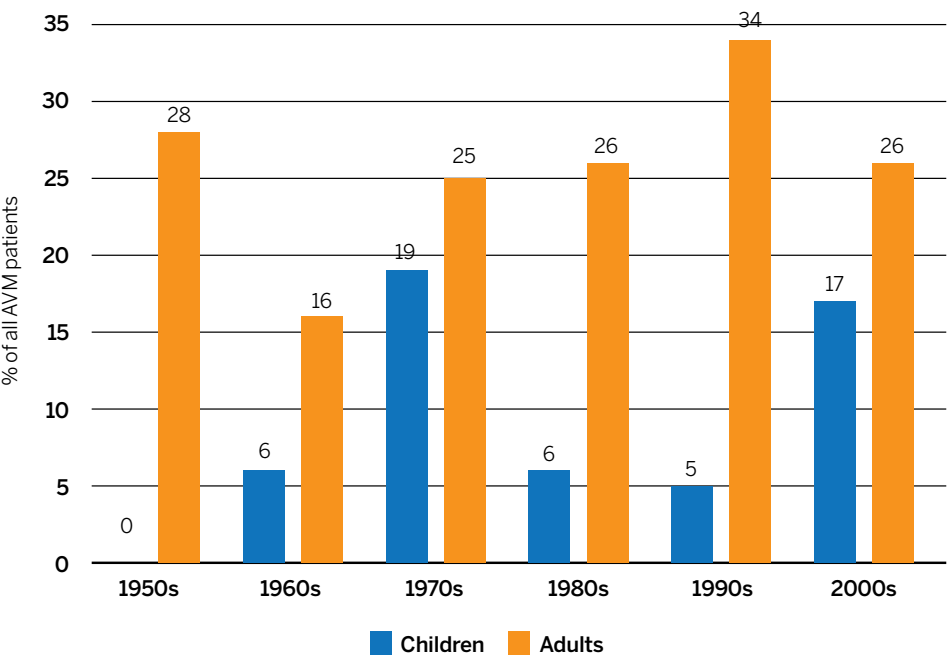


**Fig. 13. Proportion of pediatric and adult AVMs patients presenting with epilepsy (not related to acute bleeding) by decade**



In the pediatric group, 60 patients (48%) had a favorable outcome (mRS <2), while 27 patients (21%) had died by the end of the follow-up period (Table 9). The death of 22 patients (82%) was AVM-related.

TABLE 7. NUMBER AND PERCENTAGE OF PEDIATRIC PATIENTS OUT OF THE TOTAL NUMBER OF AVM PATIENTS FROM THE DATABASE DURING DIFFERENT DECADES

| Years     | Number of pediatric patients | %  |
|-----------|------------------------------|----|
| 1942-1949 | 1                            | 17 |
| 1950-1959 | 12                           | 20 |
| 1960-1969 | 17                           | 13 |
| 1970-1979 | 21                           | 26 |
| 1980-1989 | 16                           | 17 |
| 1990-1999 | 19                           | 14 |
| 2000-2009 | 28                           | 13 |
| 2010-2014 | 13                           | 16 |
|           | 127                          | 16 |

TABLE 8. OUTCOME AT 2-4 MONTHS ACCORDING TO GOS

|                     | Number of pediatric patients | %  | Number of adult patients | %  |
|---------------------|------------------------------|----|--------------------------|----|
| Good recovery       | 87                           | 70 | 373                      | 55 |
| Moderate disability | 26                           | 21 | 181                      | 27 |
| Severe disability   | 2                            | 2  | 56                       | 8  |
| Vegetative state    | 0                            | 0  | 5                        | 1  |
| Death               | 5                            | 4  | 29                       | 4  |

TABLE 9. OUTCOME AT LAST FOLLOW-UP ACCORDING TO MRS

| mRS (score)                        | Number of pediatric patients | %  |
|------------------------------------|------------------------------|----|
| No symptoms (0)                    | 33                           | 26 |
| No disability despite symptoms (1) | 27                           | 21 |
| Slight disability (2)              | 21                           | 17 |
| Moderate disability (3)            | 9                            | 7  |
| Moderately severe disability (4)   | 8                            | 6  |
| Severe disability (5)              | 2                            | 2  |
| Dead (6)                           | 27                           | 21 |

#### 4.1.6 Factors associated with long-term outcome

The most significant factor associated with a favorable long-term outcome in children was whether or not they were surgically treated (P = 0.040; odds ratio [OR] 2.986; 95% confidence interval [CI], 1.049-8.498). Small nidus size also correlated with a favorable long-term outcome (P = 0.031; OR 5.183; 95% CI, 1.166- 23.044).

#### 4.1.7 Data on different treatment modalities

The data on different treatment modalities and their influence on the long-term outcome was evaluated.

*Surgical treatment.* Sixty-seven pediatric and 338 adult patients were treated only surgically. For 57 pediatric and 278 adult patients, the database had information on the reoperations. Eight pediatric (14%) and 12 adult (4%) patients underwent repeated surgery due to residual AVM found immediately after primary surgery.

*Radiosurgery.* Seventeen pediatric patients (13%) received radiosurgery. For three patients (2%) it was the only treatment modality. The most common treatment modality was stereotactic radiosurgery, which was used in 10 children (65%). Four children (25%) were treated with gamma knife radiosurgery, and two (12%) with conventional radiosurgery. The most common reason for radiosurgery in pediatric patients (seven patients, 41%) was unsuccessful embolization, and in adults (25 patients, 46%), the location of AVM. Four children were treated with embolization and radiosurgery, and none of their AVMs were occluded at the end of the follow-up. Seven pediatric patients were treated using all three modalities: embolization, surgery, and radiosurgery. All achieved total occlusion of AVM. One child in this group with SM-grade IV basal ganglia AVM developed a permanent deficit after radiosurgery. At the end of the follow-up, total occlusion was achieved in nine children (53%) but none of them had been treated with radiosurgery alone.

*Embolization.* Twenty-nine (23%) pediatric patients were treated with embolization, but only four of them received embolization alone and no other treatment. Total occlusion was achieved in one of the four patients. To improve their operability, otherwise inoperable AVMs were often submitted to embolization before surgery. Emboliza-

tion caused a permanent deficit in children less often than it did in adults (12% in children versus 25% in adults,  $p = 0.024$ ).

*Conservative.* In the conservatively treated patients, 14 (56%) had died by the end of the follow-up.

TABLE 10. OPERATIVE TECHNIQUES AND OCCLUSION RATES IN PEDIATRIC PATIENTS

| Treatment modality          | N (%)      | Occlusion % |
|-----------------------------|------------|-------------|
| Surgery                     | 67 (53%)   | 81%         |
| Radiosurgery                | 3 (2%)     | 0%          |
| Embolization                | 4 (3%)     | 25%         |
| Surgery + embolization      | 14 (11%)   | 100%        |
| Surgery + radiosurgery      | 3 (2%)     | 67%         |
| Surg. + rad. + emb.         | 7 (6%)     | 100%        |
| Embolization + radiosurgery | 4 (3%)     | 0%          |
| Conservative                | 25 (20)    | 0%          |
|                             | 127 (100%) |             |

## 4.2 Study II

### 4.2.1 Demographics

The patient cohort of Study II was also extracted from the AVM database. The 55 patients included had a mean age of 39.3 (SD 14.4) years at the time of survey and a mean age of 14.7 (SD 4.3) years at the time of diagnosis. The mean follow-up time was 24.6 years (SD 14.7). There was a slight predominance of males over females (55% vs 45%). Eight patients (15%) were active smokers, and 21 patients (38%) smoked or had smoked at some point in their lives.

### 4.2.2 Educational level and occupation

The highest achieved educational levels compared to the age-matched general population were as follows: 9 patients had completed the basic level (16% vs 13% in the matched general population), 25 the secondary level (46% vs 42% in the matched general population), 14 the polytechnic level (26% vs 25% in the matched general population), and 7 the university level (13% vs 20% in the matched general population).

### 4.2.3 Long-term HRQOL

The effect of the SPC, admission age, symptomatic epilepsy diagnosis, and number of rup-

TABLE 11. DISEASE CHARACTERISTICS OF 55 PATIENTS INCLUDED IN STUDY II

|                          |         |
|--------------------------|---------|
| Location of AVM          |         |
| Frontal                  | 11 (20) |
| Parietal                 | 12 (22) |
| Temporal                 | 10 (18) |
| Occipital                | 7 (13)  |
| Cerebellar               | 8 (15)  |
| Deep                     | 7 (13)  |
| Supra- vs infratentorial |         |
| Supratentorial           | 46 (84) |
| Infratentorial           | 9 (16)  |
| SPC grades               |         |
| A                        | 26 (47) |
| B                        | 18 (33) |
| C                        | 11 (20) |
| AVM completely occluded  |         |
| Yes                      | 48 (87) |
| No                       | 7 (13)  |
| Treatment modality       |         |
| Microsurgery             | 50 (91) |
| Embolization             | 10 (18) |
| Radiosurgery             | 7 (13)  |
| Multimodality            | 9 (16)  |
| Symptomatic epilepsy     |         |
| Yes                      | 9 (16)  |
| No                       | 46 (84) |
| Number of ruptures >1    |         |
| Yes                      | 8 (15)  |
| No                       | 47 (85) |

tures on the results of the long-term HRQOL measured with the 15D instrument is presented in Figs. 14-17. The SPC did not predict the long-term 15D score (Fig. 14). Admission age had a significant effect on one dimension. The patients youngest at admission were not able to carry out their usual daily activities later in life as well as the rest of the patients (Fig. 15). Symptomatic epilepsy significantly reduced the long-term HRQOL (Fig. 16). Recurrent AVM ruptures affected the HRQOL in several domains (Fig. 17).

According to the linear regression model analysis, only symptomatic epilepsy significantly reduced the long-term 15D score ( $p=0.033$ ).

**Fig. 14. Correlation between Spetzler-Ponce Classification and 15D HRQOL scores.**  
 The differences in mean 15D scores between the Spetzler-Ponce classes did not reach statistical significance. The mean patient ages of the SPC groups were comparable (class A AVMs, 38.8 years; class B, 37.4 years; and class C, 43.5 years).

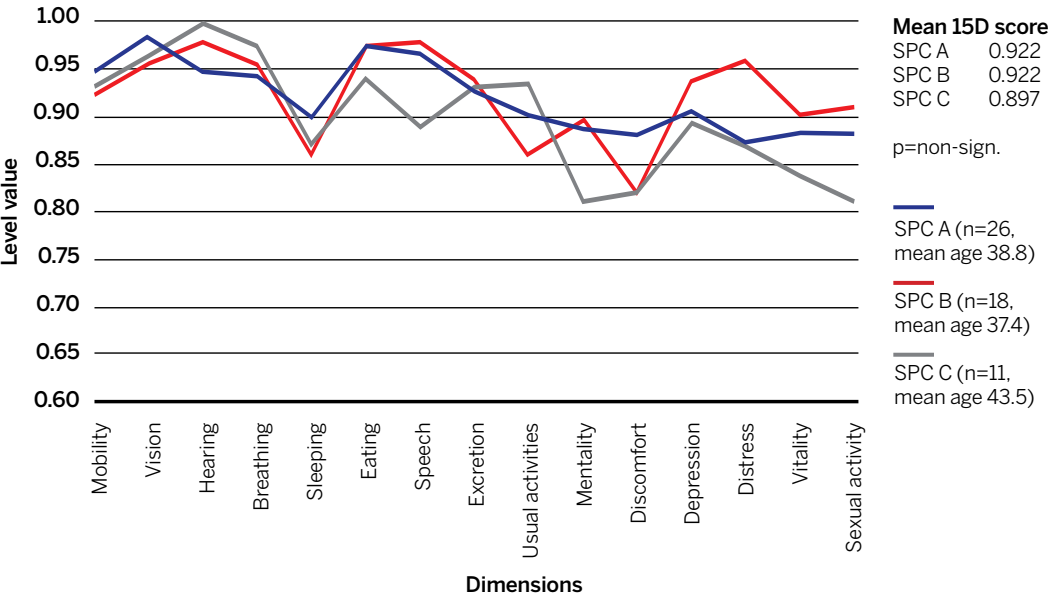


**Fig. 15. Correlation between age on admission and 15D HRQOL scores**  
 The youngest age group (< 10 years at the time of diagnosis) did less well than the older patients on the dimension of usual activities, even though there was little variance in mean age between the groups at the time of the survey.

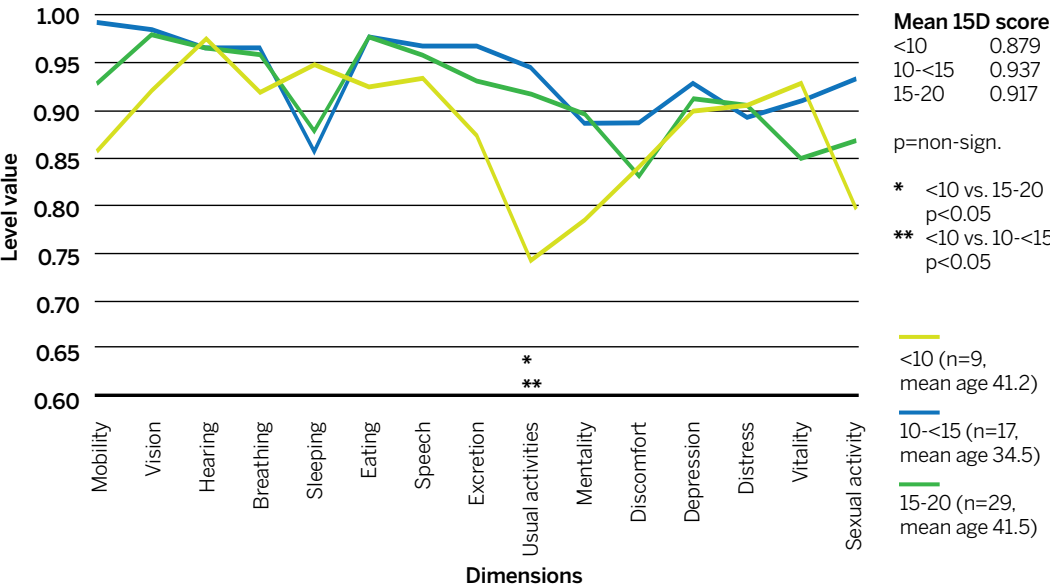


**Fig. 16. Correlation between prevalence of symptomatic epilepsy and 15D HRQOL scores**  
 The presence/diagnosis of symptomatic epilepsy (Engel classes II–IV) significantly reduced the scores on the dimensions of sexual activity and breathing. The mean 15D score was statistically significantly and clinically importantly lower in patients with symptomatic epilepsy.

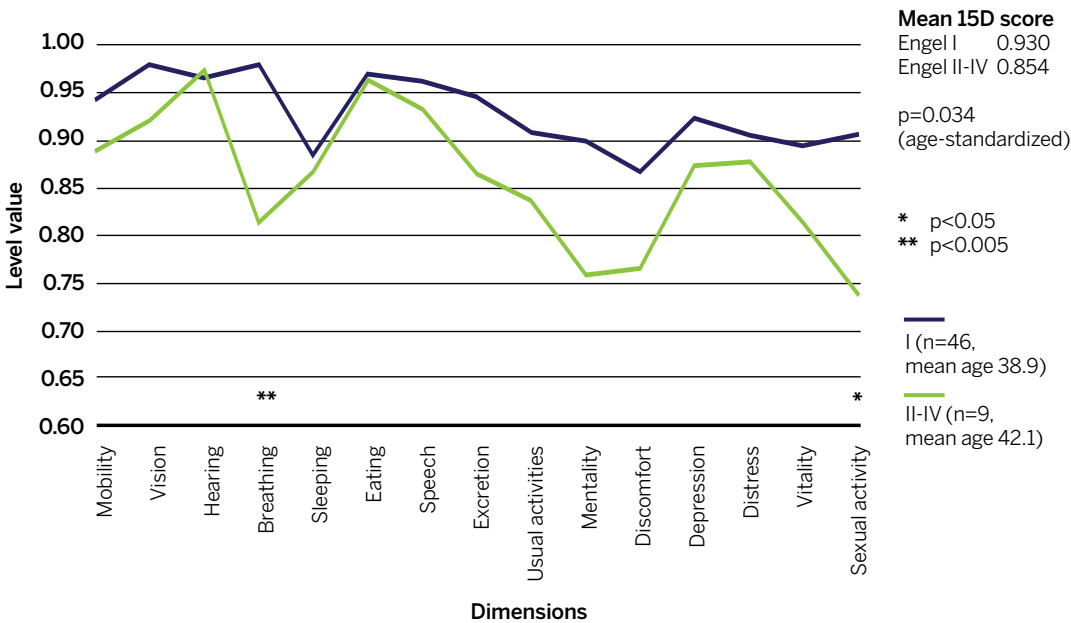
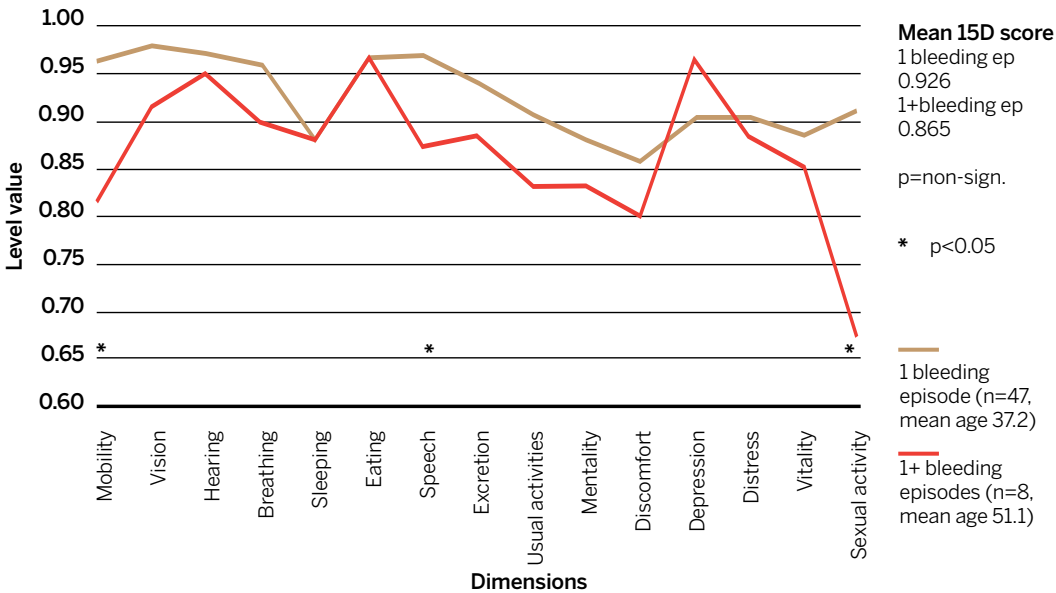


**Fig. 17. Correlation between number of bleeding episodes and 15D HRQOL scores**  
 Multiple hemorrhages significantly reduced the scores on three dimensions: mobility, speech, and sexual activity.



4.3 Study III

Forty-one patients were included in the study (see Methods). In 71% of the patients, AVM rupture occurred before obliteration, whereas 63% presented with a rupture. Focal epilepsy (without signs of acute bleeding) was the presenting symptom in 12 patients (29%). The AVMs of two patients (5%) were found incidentally. In all patients, post-surgery DSA was performed according to the Helsinki protocol.

4.3.1 Follow-up and AVM recurrence

The median time from admission to the late follow-up DSA was 19.1 years (IQR 13.9–22.8, range 8.6–35.7 years). Three out of 42 patients demonstrated AVM recurrence at the late follow-up DSA, of which one was HHT-related AVM (4.9%

recurrence rate for sporadic AVMs and 7.1% for the entire 42-patient cohort including the HHT-related AVM). Of the two patients with a recurrent AVM (excluding the HHT patient), the initial Spetzler-Martin grades were II and III. Both patients were male and active smokers. Patient demographics, AVM characteristics, and treatment modalities are presented in Tables 12 and 13 (Fig. 18) demonstrates one of the patients who developed de-novo AVM.

TABLE 12. PATIENT DEMOGRAPHICS AND AVM CHARACTERISTICS OF STUDY III POPULATION

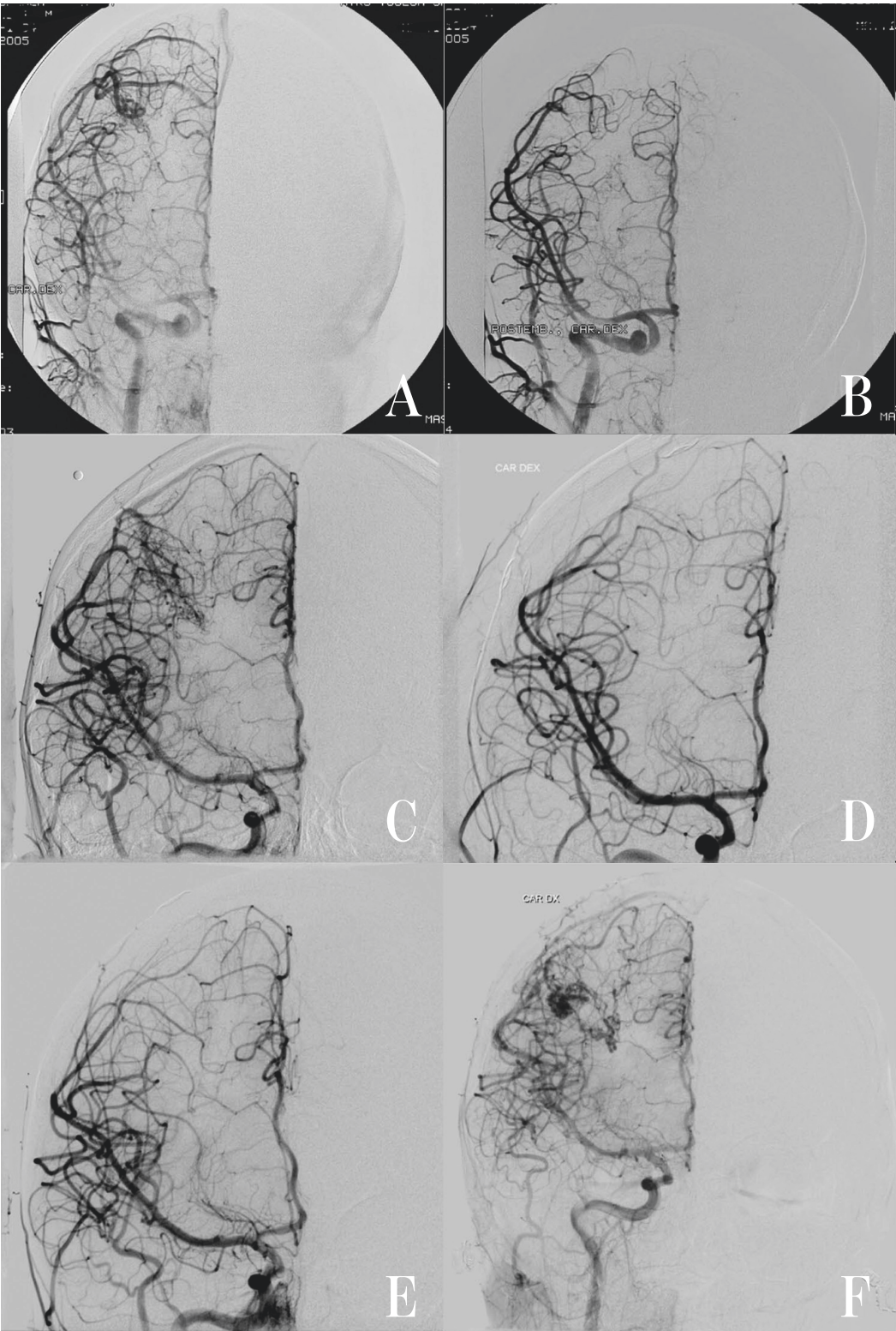
|                                    | Recurrence<br>N=2 | No recurrence<br>N=39 |
|------------------------------------|-------------------|-----------------------|
| <b>PATIENT CHARACTERISTICS</b>     |                   |                       |
| Median age at treatment, y         | 17.0              | 14.4                  |
| Median age at time of study        | 36.5              | 33.0                  |
| Male                               | 2 (100%)          | 25 (64%)              |
| Smoking                            | 2 (100%)          | 8 (21%)               |
| Presentation                       |                   |                       |
| - hemorrhage                       | 2 (100%)          | 27 (69%)              |
| - epilepsy                         | 1 (50%)           | 11 (28%)              |
| <b>AVM CHARACTERISTICS</b>         |                   |                       |
| Exclusive deep venous drainage     | 1 (50%)           | 9 (23%)               |
| Superficial venous drainage        | 1 (50%)           | 25 (64%)              |
| Superficial + deep venous drainage | 0 (0%)            | 5 (13%)               |
| Left side                          | 1 (50%)           | 15 (39%)              |
| Superficial location               | 2 (100%)          | 32 (82%)              |
| Supratentorial location            | 2 (100%)          | 35 (90%)              |
| Spetzler-Martin grade              |                   |                       |
| 1                                  | 0 (0%)            | 8 (21%)               |
| 2                                  | 1 (50%)           | 12 (32%)              |
| 3                                  | 1 (50%)           | 14 (37%)              |
| 4                                  | 0 (0%)            | 3 (8%)                |
| 5                                  | 0 (0%)            | 1 (3%)                |

TABLE 13. TREATMENT MODALITIES IN STUDY III

|                                       | Recurrence<br>N=2 | No recurrence<br>N=39 |
|---------------------------------------|-------------------|-----------------------|
| Microsurgery                          | 1 (50%)           | 23 (59%)              |
| Stereotactic radiosurgery             | 0 (0%)            | 1 (3%)                |
| Embolization                          | 0 (0%)            | 1 (3%)                |
| Embolization + surgery                | 1 (50%)           | 11 (28%)              |
| Embolization + surgery + radiosurgery | 0 (0%)            | 2 (5%)                |
| Embolization + radiosurgery           | 0 (0%)            | 1 (3%)                |

Fig. 18. Digital subtraction angiographies (DSAs) of a patient in Study III. The patient was referred to the Department of Neurosurgery at the age of 14, and surgery with pre-embolization was planned. (A) Pre-embolization DSA shows arteriovenous malformation (AVM) in the parietal Sylvian fissure on the right side. AVM received feeding from the middle cerebral artery (MCA) branches and drained via two large veins to the superior sagittal sinus (SSS). (B) After embolization, AVM did not fill up, and the early venous filling was no longer observed. (C) Six months later the patient suffered a new generalized epileptic seizure. DSA showed recanalized AVM. AVM was operated on a few months later. (D) Post-operative DSA confirming the complete eradication of AVM. (E) Surveillance DSA one year later showed no signs of AVM. The routine follow-up was finished. (F) Fourteen years later, at the age of 30, the patient underwent DSA as part of a new follow-up protocol; it showed de-novo AVM in the same location. An elective operation was scheduled.

**Fig. 18.**





# 5 Discussion

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This study was conducted to evaluate the characteristics, long-term outcomes, and risk of AVM recurrence in pediatric patients with brain AVMs treated during 1942–2014 at the Department of Neurosurgery of Helsinki University Hospital.

The long-term outcomes were assessed with functional scales such as the mRS and GOS while the HRQOL was assessed with the 15D instrument. The effects of different patient- and disease-specific factors on long-term outcomes were evaluated. The AVM recurrence risk was evaluated by DS angiographies performed on 42 patients treated before the age of 21 years.

The main goal of AVM treatment is to prevent future ruptures with minimal neurological morbidity. The rupture risk is cumulative, and the benefit is commonly seen years after treatment, especially in younger patients. It is therefore necessary to evaluate the long-term outcomes of these patients and potential associated factors. This study provides novel insight into pediatric AVM patients with, to our knowledge, the longest published follow-up time.

## 5.1 Methodological considerations

Retrospective studies, including the present one, are inherently limited by selection bias, making it impossible to establish direct causality between treatments and outcomes. This bias is, however, diminished by Finland's comprehensive healthcare record archives and high-quality public healthcare system. The results of the 2016 survey are also subject to selection bias, as only 70% of patients responded, potentially limiting the representativeness of the patient population. In Study I, this bias was limited, since healthcare records were obtained for all patients, and death certificates were obtained for all deceased patients. In the interpretation of the results of Study II, which assessed long-term outcomes using the 15D instrument, survival bias should be considered, especially for patients with Spetzler-Ponce class C AVMs and those with multiple bleeding episodes, as their outcomes may be overly optimistic in our study. Assessing the quality of life poses a

separate challenge, as the survey may not fully reflect the patient's experience. To address this, we focused on the HRQOL and used a well-established and validated method. Moreover, our results may not be directly applicable to all ethnic groups, since the study was performed on a rather homogeneous Finnish population.

The length of follow-up is crucial in the evaluation of treatment outcomes. The strength of our study was the length of the follow-up, which was an average of 21 years in Study I and 24 years in Study II.

## 5.2 Characteristics and long-term outcomes

According to our study, 16% of patients treated for brain AVMs in Helsinki from 1942 to 2014 were children. This is consistent with the generally reported 12–21% of pediatric cases.<sup>180,181</sup> In both patient cohorts, children and adults, males were diagnosed with AVMs somewhat more often than females, which is in line with various other reports,<sup>184,185,212,267,268</sup> but this finding was not statistically significant. Ma et al. also observed male predominance in pediatric AVM patients, especially in periventricular AVMs, which were also more likely to present with ICH.<sup>268</sup> In our study, males presented more often with ICH in the pediatric than in the adult cohort. Nevertheless, many studies have reported equal gender distribution between pediatric patients, and some have even reported female predominance.<sup>9,180,269</sup> The findings regarding gender distribution are therefore inconclusive.

In our single-center consecutive series, more AVMs presented with ICH than has recently been reported.<sup>39,90</sup> This is partly due to the long period during which the cohort was gathered. Our series from earlier years did not include incidentally diagnosed AVMs. They have only been found since the use of modern imaging techniques became more widespread in the early 2000s. The decrease in hemorrhagic AVM presentation rates can also be seen by comparing historical and modern series. We, therefore, analyzed present-

ing symptoms by decade. The results clearly demonstrated the declining rates of hemorrhagic presentation simultaneously with increasing rates of epilepsy and incidentally diagnosed AVMs (Tables 10-12). A decline has also been observed in the rate of the aneurysmatic subarachnoid hemorrhage (SAH) incidence in Finland, although this is more likely related to the reduction in smoking in the population than to the increasing availability of cerebrovascular imaging and diagnostics.<sup>270</sup> Nevertheless, we have also shown that the prevalence of smoking is higher in AVM patients than in the age-, sex-, and admission year-matched general population.<sup>271</sup> The decrease in pediatric rupture rates cannot be related to smoking but rather to the increasing availability of brain imaging and better diagnostics. This has importance for healthcare and population well-being in general since morbidity and mortality are reduced.

Children have been reported to have AVMs with deep venous drainage more often than adults<sup>9</sup>, as was also the case in our study. This is most likely related to the higher proportion of deep AVMs, as they tend to have deep venous drainage. Flow-related aneurysms were, however, less common in children. This finding is not surprising since the shunting of blood creates chronic hemodynamic stress, which can gradually lead to aneurysm formation. This process needs time to develop and thus aneurysms are more frequently found later in life.

### 5.3 Hemorrhagic presentation vs. hemorrhage risk

As in many previous studies, Study I showed that the small AVM nidus size was associated with hemorrhagic presentation. Spetzler et al. reported that small AVMs presented significantly more often with hemorrhage than did large ones (82% vs 21%,  $p < 0.001$ ).<sup>272</sup> They also observed that larger hematoma volumes could be attributed to higher feeding artery pressures in small AVMs. However, small AVM size has not been a risk factor for subsequent hemorrhage in any longitudinal studies using multivariate models, most likely because small AVMs remain asymptomatic unless they bleed. In fact, the Helsinki natural history AVM series reported higher annual hemor-

rhage risk in large AVMs,<sup>19</sup> although others have reported that large size has no effect on rupture risk.<sup>273</sup> In a recent study by our HUS AVM research group, we have also shown that AVM size does not correlate with hematoma volume at the time of rupture.<sup>164</sup>

Similarly, the proportion of children's AVMs that came to clinical attention because of hemorrhage was higher than that of adults (76% in children vs 64% in adults), which is in line with previous studies.<sup>9,118,180,196</sup> Still, the rupture risk in children has not been shown to be higher than in adults.<sup>180</sup> We observed that the proportion of AVMs coming to clinical attention because of epilepsy was lower in children than in adults (20% in children vs 33% in adults). In addition, children's AVMs were more often cerebellar (12% in children vs 7% in adults) or deep-located (30% in children vs 19% in adults) and less often cortical-located (frontal location: 13% in children vs 22% in adults, temporal location: 9% in children vs 12% in adults) than those of adults. We theorized that gradual microhemorrhages from AVMs and the consequent build-up of hemosiderin in the adjacent brain parenchyma may lead to the development of epilepsy over time. Therefore, cortical epileptogenic AVMs<sup>195</sup> come to clinical attention later in life, and their proportion is lower in children than in adults whereas the proportion of hemorrhagically presenting deep AVMs is higher.

### 5.4 Eradication rates

After surgical AVM resection, more residual AVMs leading to re-operation were found on the immediate postoperative imaging in children than in adults (14% in children vs 4% in adults). Children have frequently been reported to have diffuse-type AVMs,<sup>223,227,274</sup> although Hetts et al. did not find a statistically important difference between children's and adults' nidal diffuseness.<sup>9</sup> Chin et al. first described the diffuse type AVM, which is wedge-shaped, involves normal brain tissue between the abnormal vessels, consists of multiple small arterial feeders and draining veins, and is more challenging to remove completely than a compact AVM.<sup>275</sup> Klimo et al. reported diffuse-type AVMs in 18% of pediatric patients, whereas diffuse lesions were observed in 40% of patients whose AVM was not obliterated, in 44%

of those with residual AVMs and in 80% of those with recurrent AVMs.<sup>227</sup> This could explain why residual AVMs leading to reoperations were more common in our pediatric than in our adult patient cohort. Another contributing factor could be that pediatric patients had more deep-located AVMs than adults. Note, however, that we only analyzed immediate residuals leading to reoperation. It is therefore possible that the higher reoperation rate of residual AVMs in pediatric patients might also be related to the more aggressive treatment approach and the effort to avoid exposure to ionizing radiation in radiosurgery. Moreover, the database did not have complete information on re-operations, a subject that should be studied more closely in future research.

Only four out of 127 patients in the Study I cohort were treated with embolization alone. Complete occlusion of AVM was achieved in only one of them, making embolization alone a rather ineffective treatment modality in this group. Four children were treated with a combination of embolization and radiosurgery. None of their AVMs were occluded at the end of the follow-up, which is in line with the lower occlusion rates reported for pediatric AVM patients treated with embolization prior to radiosurgery.<sup>43,44</sup> However, selection bias probably plays a considerable role in this small group.

## 5.5 Mortality rates in acute rupture

Hemorrhage from AVM has been associated with a mortality rate of over 20% in children, and 6% to 10% in adults.<sup>94,181,196,205</sup> In our series, the percentages were 5% (5 out of 96 ruptured AVMs) for children and 7% (29 out of 434 ruptured AVMs) for adults. Note, however, that our series is not population-based in that patients who died before admission due to hemorrhage from previously undiagnosed AVMs were not included. The lower mortality rates associated with hemorrhage in children in our series could be due to the fact that the percentage of infratentorial AVMs in children was similar to that in adult patients. Di Rocco et al., for example, reported a 23% mortality rate in children, but 24% of AVMs in their series were infratentorial versus 13% in our series.<sup>181</sup> Ruptures of posterior fossa AVMs have been associated with higher mortality than AVMs

in general, because the expanding hematoma rapidly fills the limited space, thus easily causing hydrocephalus and brainstem compression.<sup>207,208</sup> Blauwblomme et al., however, reported similar mortality rates (5%) to those in our study.<sup>209</sup>

## 5.6 Long-term HRQOL

Health-related quality-of-life measurements have gained popularity during the last two decades as the focus has shifted from mere disease-oriented to more patient- and family-oriented treatment. This development has coincided with growing interest in happiness and life-quality research.<sup>276</sup> As treatments have evolved and patients with chronic illnesses are able to live longer, it is only natural that life-quality issues should be given greater consideration. Happiness and life satisfaction cover a vast number of aspects of life that cannot be helped by medical practitioners. Hence, the concept of health-related quality of life, which seeks to measure the aspects of life that can be changed by the treatment was introduced.<sup>277,278</sup>

While the functional outcome including possible neurological deficits will usually correlate with the HRQOL, it is not always the case. We know from psychological research that the effect of an event on life satisfaction, be it a lottery win or a car accident causing paraplegia, will diminish with time, and life satisfaction will approach the baseline.<sup>279</sup> The argument against life-quality measurements is always on the reliability of the instruments in reflecting the actual well-being of the subject. However, recently developed instruments, such as the 15D, have been validated with a large set of subjects and, while not perfect, they do at least offer deeper insight into patients' well-being than the traditional outcome measurements. Also, they are able to differentiate between a larger set of outcomes, with greater sensitivity to change and to the areas of health where patients may be facing problems.<sup>248</sup>

We measured how the SPC, admission age, symptomatic epilepsy, and repeated ruptures affect the long-term HRQOL, as measured with the 15D instrument, in 55 patients treated for ruptured AVMs in childhood (<20 years of age at the time of admission) and who replied to the questionnaire sent out in 2016. The mean follow-up time of this study was 24 years from admission,

thus giving time for the patients to recover fully and to adapt and learn to live with any possible disability.

An interesting finding was that the SPC did not predict the results of the long-term 15D score. This could be due to survival bias, adaptation as years go by, and the better recovery capacity of children. It is also possible that the patients in the poorest condition could not reply to the survey (24 out of 79 eligible patients did not reply). The survival bias was assessed with a subanalysis of the deceased patients. It showed that the fewest deaths were in the SPC A group. However, most deaths did not occur in the SPC C group but in the SPC B group. Children's better recovery capacity has been reported earlier by other studies<sup>113</sup>, and could partly explain the lack of differences between the groups. Repeated ruptures (8 patients) affected the HRQOL in several domains, which is to be expected, as repeated ruptures cause more damage. These results reinforce the previous evidence that pediatric patients with ruptured AVMs should be treated aggressively.<sup>146</sup>

Symptomatic epilepsy significantly reduced the long-term HRQOL, which is not surprising due to the continuous possibility of seizures and the necessity for continuous AEDs.

Admission age had a significant effect on one dimension. At the time of the survey, the patients who had been youngest at admission (<10 years) were not able to carry out their usual daily activities in adulthood as well as the patients who had been older at admission. It has been theorized that as early childhood is the critical time for acquiring developmental milestones<sup>280</sup>, the youngest children would be particularly vulnerable to brain insults. In a study of 164 children with brain insults, Anderson et al. observed that neuropsychological problems were more common in the youngest children (<2 years) than in the other patients.<sup>281</sup>

## 5.7 Recurrent AVMs

Evolving knowledge of AVMs as dynamic acquired lesions and the increasing number of reports on AVM recurrence, together with the increasing availability and quality of non-invasive neuroimaging, have encouraged neurosurgeons to establish follow-up protocols for AVM patients,

thus further improving the diagnostics of AVM recurrence.<sup>282</sup>

In our study, we found three de-novo AVMs, but one of the patients had been diagnosed with HHT years after the primary treatment. There were thus two actual recurrent sporadic AVMs. Their recurrence rate was 4.9%, which is in line with the 4.8% reported in the latest meta-analysis of 1134 AVMs.<sup>29</sup> Recurrent sporadic AVMs in our study had ruptured, as has been associated with later recurrence by others, too.<sup>222,282</sup> It has been theorized that the mass effect of the hematoma could cause a falsely negative postoperative angiogram or that hemorrhage could split the nidus, predisposing to suboptimal resection and subsequent AVM recurrence.<sup>222</sup> However, one of the patients in our series developed later recurrence despite having a negative DSA one year after surgical treatment, ruling out the mass effect hematoma theory. This theory also does not explain why children are more prone to develop recurrent AVMs. Nidus splitting makes more sense if we consider that the most likely reason for later recurrence is omission of the pathological vessels harboring the endothelial activating mutations in the KRAS gene or MAPK pathway after the surgery even though the shunting part has been eradicated. The finding of smoking among recurrent sporadic AVM patients is interesting, considering that nicotine (and possibly many other substances in tobacco) promotes activation of the Ras-MAPK pathway.<sup>283</sup>

There is a clear need for follow-up of these patients. Moreover, the imaging modality should probably be DSA, as the sensitivity of MRA is currently insufficient to detect all small recurrences.<sup>65</sup> Some consideration is still needed before performing DSA since it is an invasive procedure involving exposure to ionizing radiation, the risk of post-puncture hematoma, and the possible need for sedation in younger children. The timing of follow-up imaging is unclear, but a recurrent AVM has been found even after a negative four-year postoperative angiogram.<sup>224</sup> Follow-up should therefore be continued at least until adulthood. An optimal follow-up strategy should be individualized, taking into account radiological and intraoperative findings, the patient's age, the opinion of the patient and family, the patient's clinical condition, and the available resources.

## 5.8 General considerations and future perspectives

Arteriovenous malformations seem to develop at early stages of life and usually become symptomatic in the third or fourth decade. One explanation could be that, in most cases, the underlying somatic mutations are acquired during fetal development, as rapid mitoses take place and AVMs “mature” later into their typical morphological form with a nidus. The biological processes in AVM maturation are largely unknown but may relate to children’s vascular development, elevated circulating angiogenic growth factors, and hormonal changes in puberty. Even so, some AVMs do not cause any symptoms during the entire lifetime. Therefore, other unknown intrinsic factors of certain AVMs may lead them to become symptomatic, while others tend to be silent. Truly incidental AVMs thus pose a challenge to clinicians, as typical rupture risk analyses do not appear to include this “silent” group, and their rupture risk is most likely overestimated. Future research is needed to distinguish between these groups. Recent studies have tried to identify the AVMs at risk of rupture by analyz-

ing different circulating factors.<sup>284–287</sup> However, current results already support the idea that incidental AVMs diagnosed after 50 – 60 years of age are probably best left untouched in most patients as they are more likely to belong to the “silent” group and the lifetime risk of hemorrhage is in any case lower.<sup>288,289</sup>

As the causative mutations of AVMs have been identified, they offer a promising target for pharmacological interventions, and the MEK inhibitors on the market are currently being studied for that purpose.<sup>49,290</sup> Even though the effect of MEK inhibitors on fully matured brain AVMs is uncertain, they may still help to prevent AVM recurrence in susceptible patients or could reduce the hemorrhage risk in patients whose AVMs are not amenable to treatment.

In the future, HRQOL instruments will most likely provide more detailed information on the effects of treatments and, consequently, more specific and personalized treatment paths. Further, the impact of the new imaging follow-up protocol for AVM patients treated before the age of 21 reported in the present study should be evaluated.



# 6 Conclusions

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The AVMs of pediatric patients do not differ in any fundamental way from those of adults. The discrepancies between children and adults in presentation, angioarchitecture, and location are most likely related to later onset of epilepsy due to gradual microhemorrhages from AVM. Pediatric AVM patients seem to recover better than adults in general. Moreover, pediatric patients with ruptured high-grade AVMs that have been obliterated can have a long-term HRQOL comparable to that of patients with lower-grade AVMs. Together with children's longer life expectancy and the cumulative rupture risk of AVMs, these results reinforce the previous evidence that pediatric patients with AVMs should be treated aggressively if possible. Patients treated in childhood or early adulthood can develop a recurrent AVM even after angiographically complete obliteration, and thus it is recommended that these patients are submitted to follow-up with control imaging.



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As I write this final chapter of my thesis with a sense of pride and relief that the project is nearing completion, I am aware that it would not have been possible without the support of numerous people.

First and foremost, I am grateful to my supervisors Professor Aki Laakso and Associate Professor Päivi Koroknay-Pál. Without your guidance and support, this thesis would not have been accomplished. Aki, I am continually amazed by your ability to make sense of even the most complex questions. Not only do you possess the knowledge of a top-level neuroscientist, but you have also honed the skills of a leading neurosurgeon. And Päivi, your exceptional achievements such as two PhDs, one in theoretical physics and one in medicine, while excelling as a top-class neurosurgeon at the same time as raising two daughters, are nothing short of remarkable.

It has been my privilege to have you both, Aki and Päivi, as my mentors.

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Finally, I thank my lovely grandmother, Gillian Häkli, for revising the language of this thesis. Your help has been crucial for getting my message across while giving me the opportunity to enjoy your company.

Helsinki,  
May 2023  
Elias Oulasvirta



# Appendices

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## Appendix I: The 2016 Questionnaire

AIVOJEN VALTIMOLASKIMOEPÄMUODOSTUMIEN PITKÄAIKAISSURANTA/LAAKSO  
TIEDOTE TUTKITTAVILLE

Aivojen valtimolaskimoepämuodostumien pitkäaikaissuranta  
Neurokirurgian klinikka, Töölön sairaala  
Helsingin ja Uudenmaan sairaanhoitopiiri

### SAATEKIRJE

---

Lähestymme teitä kirjeitse Töölön sairaalan HYKS Neurokirurgian klinikasta. Olette olleet hoidossa Töölön sairaalassa Neurokirurgian klinikassa vuonna \_\_\_\_\_ aivojen valtimolaskimoepämuodostuman johdosta. Tutkimustyötämme varten toivoisimme saavamme tietoja nykyisestä voinnistanne. Tutkimuksessa selvitämme henkilöiden joilla on todettu aivojen valtimolaskimoepämuodostuma myöhempää sairastavuutta. Ohessa on tiedote tutkittaville, josta saatte tarkempaa tietoa tutkimuksesta.

Tietonne ovat erittäin arvokkaita.

Mikäli teille tulee tutkimuksesta kysyttävää, voitte ottaa yhteyttä.

Aki Laakso  
Apulaisylilääkäri  
p. 050-427 2895

Päivi Koroknay-Pál  
Erikoislääkäri  
p. 050-427 0393

HYKS Neurokirurgian klinikka  
PL 266  
00029 HUS

Jos päättätte osallistua tutkimukseen, pyydämme teitä

1. Vastaamaan kysymyskaavakkeeseen (nelisivuinen).
2. Palauttamaan oheisessa kirjekuoressa kysymyskaavakkeen (postimaksu maksettu).

Aivojen valtimo-laskimoepämuodostumien pitkäaikaissuranta  
Neurokirurgian klinikka, Töölön sairaala  
Helsingin ja Uudenmaan sairaanhoitopiiri

## **TIEDOTE TUTKITTAVALLE**

Olette olleet hoidossa Töölön sairaalassa Neurokirurgian klinikassa. Tuolloin teillä todettiin aivojen valtimo-laskimoepämuodostuma (arteriovenöosi malformaatio, AVM). Osalla potilaista AVM leikattiin, osalla AVM liimattiin suonensisäisesti (embolisatio), osalla AVM sädehoidettiin ja osalla AVM:n suhteen jäätettiin seurantalinjalle.

### **Tutkimuksen tarkoitus**

Tutkimuksen tarkoituksena on selvittää AVM-diagnoosin saaneiden henkilöiden myöhempää terveyttä. Tämän takia tarjoamme teille mahdollisuutta osallistua tähän tutkimukseen. Tämä kyselykaavake lähetetään kaikille Helsingissä Töölön sairaalassa Neurokirurgian klinikassa vuodesta 1932 lähtien hoidetuille henkilöille, joilla on todettu aivojen valtimo-laskimoepämuodostuma.

### **Tutkimuksen toteutus**

Tutkimus suoritetaan kirjallisena kyselytutkimuksena. Operatiivinen eettinen toimikunta on antanut tutkimuksesta puoltavan lausunnon. Tutkimuksen toteuttaja on Helsingin ja Uudenmaan sairaanhoitopiirin (HUS) Neurokirurgian klinikka.

### **Tutkimukseen osallistumisesta mahdollisesti koituva hyöty**

Tutkimuksessa halutaan selvittää, millainen on AVM-diagnoosin saaneiden henkilöiden terveydentila ja elämänlaatu pitkän aikavälin seurannassa, ja onko eri hoitomuotojen välillä eroavaisuuksia potilaiden myöhemmässä voinnissa.

### **Tietojen luottamuksellisuus**

Teidän tietojanne käsitellään täysin luottamuksellisesti ja ne jäävät vain tutkijoiden tietoon. Kaikkia tutkimuksen tekoon osallistuvia koskee vaitiolovelvollisuus. Tietoja ei luovuteta ulkopuolisille. Tutkimuksen tulokset tullaan julkaisemaan tutkimuksen päätyttyä, mutta teidän henkilöllisyyttänne ei tulla missään yhteydessä paljastamaan.

### **Tutkimuksen keskeytys**

Tutkimukseen osallistuminen on täysin vapaaehtoista. Se, päätättekö osallistua tutkimukseen vai ette, ei vaikuta mitenkään muuhun saamaanne hoitoon kuten ei sekään, jos päätätte luopua tutkimuksesta kesken. Mikäli päätätte luopua tutkimuksesta kesken, teidän ei tarvitse ilmoittaa syytä.

### **Lisäinformaatio**

Aivojen valtimolaskimoepämuodostumien pitkäaikaissuranta  
Neurokirurgian klinikka, Töölön sairaala  
Helsingin ja Uudenmaan sairaanhoitopiiri

## KYSELYKAAVAKE

Pyydämme teitä ystävällisesti vastaamaan alla oleviin kysymyksiin ja palauttamaan kaavakkeen oheisessa kirjekuoressa (postimaksu maksettu). Mikäli teille tulee kysyttävää kysymyksistä, voitte ottaa yhteyttä HUS:n Neurokirurgian klinikkaan (erikoislääkäri Päivi Koroknay-Pál, p. 050-427 0393 tai apulaisylilääkäri Aki Laakso p. 050-427 2895).

Nimi: \_\_\_\_\_

Syntymäaika: \_\_\_\_\_

1. Onko teille jäänyt aivojen valtimo-laskimoepämuodostuman diagnosoinnin ja mahdollisen leikkauksen, liimaushoidon (embolisaaation) tai sädehoidon jälkeen jotain pysyviä puutosoireita, kuten halvausoireita tai muistiongelmia?

☐ kyllä ☐ ei

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

|                                                |                                                            |
|------------------------------------------------|------------------------------------------------------------|
| Käden ja/tai jalan halvausoire                 | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Näön heikentyminen                             | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Näkökenttäpuutos                               | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Kaksoiskuvien näkeminen                        | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Kuulon heikentyminen                           | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Hajuaistin heikentyminen                       | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Kasvohermohalvaus                              | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Nielemisvaikeus                                | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Muistiongelma                                  | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Tasapainon heikentyminen                       | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Keskittymiskyvyn heikentyminen                 | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |
| Puheen tuottamisen ja/tai ymmärtämisen vaikeus | <input type="checkbox"/> kyllä <input type="checkbox"/> ei |

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3. Tupakoitteko? ☐ kyllä ☐ ei Kuinka kauan olette tupakoinut? \_\_\_\_\_  
Oletteko aiemmin tupakoinut? ☐ kyllä ☐ ei  
Kuinka kauan tupakoitte ennen tupakoinnin lopettamista? \_\_\_\_\_  
Miten paljoin tupakoitte päivässä (nykyään tai ennen lopettamista)? \_\_\_\_\_

4. Onko seuranta-aikana aivojanne kuvattu?

☐ kyllä ☐ ei

Jos vastasitte kyllä, niin kirjoittakaa missä ja milloin? \_\_\_\_\_

5. Onko teillä seuranta-aikana todettu aivoverenvuotoja?

☐ kyllä ☐ ei

Jos vastasitte kyllä, niin kirjoittakaa missä ja milloin? \_\_\_\_\_

6. Onko teillä todettu jokin pitkäaikaissairaus?

Epilepsia ☐ kyllä ☐ ei

Sydänvika ☐ kyllä ☐ ei

Sepelvaltimotauti/infarkti ☐ kyllä ☐ ei

Verenpainetauti ☐ kyllä ☐ ei

Verenvuoto-/verisairaus ☐ kyllä ☐ ei

Keuhkosairaus ☐ kyllä ☐ ei

Munuaissairaus ☐ kyllä ☐ ei

Sokeritauti ☐ kyllä ☐ ei

Immuunikato ☐ kyllä ☐ ei

Aivoverenkierron häiriö ☐ kyllä ☐ ei

Kasvain (missä) ☐ kyllä ☐ ei

Muu sairaus (kuvatkaa) ☐ kyllä ☐ ei, mikä? \_\_\_\_\_

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7. Jos teillä on todettu epilepsia, onko teillä siihen lääkitystä?

☐ kyllä ☐ ei

Jos vastasitte kyllä, voisitteko kirjoittaa listan epilepsialääkkeistänne ja niiden annostuksen?

8. Onko teillä muuta säännöllistä lääkitystä?

☐ kyllä ☐ ei

Jos vastasitte kyllä, voisitteko kirjoittaa listan lääkkeistänne ja niiden annostuksen?

9. Onko teillä ollut epileptisiä kohtauksia viimeisen kahden vuoden aikana?

☐ kyllä ☐ ei

Jos vastasitte kyllä, voisitteko vastata seuraaviin tarkentaviin kysymyksiin;

Onko teillä tajuttomuuskohtauksia? ☐ kyllä ☐ ei

Onko teillä pieniä paikallisia kohtauksia, joiden aikana tajunta säilyy? ☐ kyllä ☐ ei

Aiheuttaako epilepsia teille merkittävää haittaa tai toimintakyvyn alentumista? ☐ kyllä ☐ ei

Miten usein teillä on kohtauksia? \_\_\_\_\_

Koska viimeksi olette joutuneet sairaalaan epileptisen kohtauksen johdosta? \_\_\_\_\_

---

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

- ☐ olen oireeton
  - ☐ minulla on oireita (esim. päänsärkyä, huimausta, kaksoiskuvien näkemistä, muistiongelmia), mutta oireista huolimatta selviydyn päivittäisistä toiminnoistani omatoimisesti ilman apua
  - ☐ lievä vamma, päivittäistoiminnoissa omatoiminen
  - ☐ kohtalainen vamma, vähäinen avuntarve päivittäistoiminnoissa, kävely ilman apua onnistuu
  - ☐ kohtalaisen vakava vamma, huomattava avuntarve päivittäistoiminnoissa, kävely ilman apua ei onnistu
  - ☐ vakava vamma, vuodepotilas, jatkuva sairaanhoito
- 

11. Johtuuko mahdollinen alentunut toimintakykyne aivojen valtimo-laskimoepämuodostumasta, vaiko muusta sairaudesta?

- ☐ kyllä, johtuu avm:stä
- ☐ ei, johtuu muusta sairaudesta
- ☐ toimintakykyne ei ole alentunut

12. Mikä on koulutuksenne (tarvittaessa voitte laittaa useamman ristin)?

- ☐ Peruskoulu/kansakoulu
- ☐ Ammattikoulu
- ☐ Ylioppilas
- ☐ Opisto/ammattikorkeakoulututkinto
- ☐ Korkeakoulututkinto

Mikä on ammattinne? Oliko aivojen valtimo-laskimoepämuodostumalla tai sen hoidolla vaikutusta ammatinvalintaanne tai koulutukseenne?

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13. Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka **parhaiten kuvaa nykyistä terveydentilaanne**. Menetelkää näin kaikkien kysymysten kohdalla. Kustakin kysymyksestä rastitetaan siis yksi vaihtoehto

#### ITSESTÄÄN HUOLEHTIMINEN

- ☐ Minulla ei ole vaikeuksia peseytyä tai pukeutua itse.
- ☐ Minulla on lieviä vaikeuksia peseytyä tai pukeutua itse.
- ☐ Minulla on kohtalaisia vaikeuksia peseytyä tai pukeutua itse.
- ☐ Minulla on suuria vaikeuksia peseytyä tai pukeutua itse.
- ☐ En kykene peseytymään tai pukeutumaan itse.

#### LIIKUNTAKYKY

- ☐ Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
- ☐ Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
- ☐ Minulla on kohtalaisia vaikeuksia suorittaa tavanomaisia toimintojani.
- ☐ Minulla on suuria vaikeuksia suorittaa tavanomaisia toimintojani.
- ☐ En kykene suorittamaan tavanomaisia toimintojani.

#### NÄKÖ

- ☐ Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).

- ☐ Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
- ☐ Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
- ☐ En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
- ☐ En näe kulkea oppaatta eli olen lähes tai täysin sokea.

## KUULO

- ☐ Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
- ☐ Kuulen normaalia puheääntä pienin vaikeuksin.
- ☐ Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
- ☐ Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
- ☐ Olen täysin kuuro.

## HENGITYS

- ☐ Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
- ☐ Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
- ☐ Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
- ☐ Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
- ☐ Minulla on hengenahdistusta lähes koko ajan, myös levossa.

## NUKKUMINEN

- ☐ Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
- ☐ Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
- ☐ Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.
- ☐ Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
- ☐ Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

## SYÖMINEN

- ☐ Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
- ☐ Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
- ☐ Tarvitsen hieman toisen apua syömisessä.
- ☐ En pysty syömään itse lainkaan, vaan minua pitää syöttää.
- ☐ En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

## PUHUMINEN

- ☐ Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.
- ☐ Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
- ☐ Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
- ☐ Muilla on vaikeuksia ymmärtää puhuttani.
- ☐ Pystyn ilmaisemaan itseäni vain elein.

## ERITYSTOIMINTA

- ☐ Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
- ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa
- ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia

virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.

- ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
- ☐ En hallitse lainkaan virtsaamista ja/tai ulostamista.

## **TAVANOMAISET TOIMINNOT**

- ☐ Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
- ☐ Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
- ☐ Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
- ☐ Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
- ☐ En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

## **HENKINEN TOIMINTA**

- ☐ Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
- ☐ Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti
- ☐ Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä
- ☐ Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä
- ☐ Olen koko ajan sekaisin ja vailla ajan tai paikan tajua

## **VAIVAT JA OIREET**

- ☐ Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
- ☐ Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

## **MASENTUNEISUUS**

- ☐ En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
- ☐ Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

## **AHDISTUNEISUUS**

- ☐ En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- ☐ Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

## **ENERGISYYS**

- ☐ Tunnen itseni terveeksi ja elinvoimaiseksi.
- ☐ Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
- ☐ Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
- ☐ Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
- ☐ Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

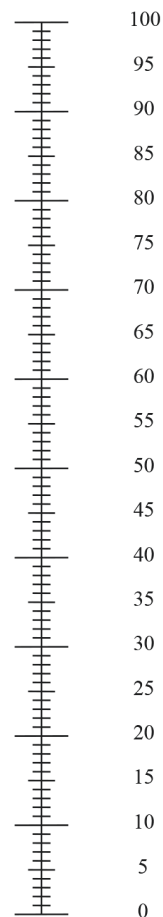
## SUKUPUOLIELÄMÄ

- ☐ Terveystilani ei vaikeuta mitenkään sukupuolielämääni.
- ☐ Terveystilani vaikeuttaa hieman sukupuolielämääni.
- ☐ Terveystilani vaikeuttaa huomattavasti sukupuolielämääni.
- ☐ Terveystilani tekee sukupuolielämäni lähes mahdottomaksi.
- ☐ Terveystilani tekee sukupuolielämäni mahdottomaksi.

- Haluaisimme tietää, miten hyvä tai huono terveytenne on TÄNÄÄN.
- Tämä asteikko on numeroitu 0-100.
- 100 merkitsee parasta terveyttä, jonka voitte kuvitella.  
0 merkitsee huonointa terveyttä, jonka voitte kuvitella.
- Merkitkää X asteikolle osoittamaan kuinka hyvä tai huono terveytenne on TÄNÄÄN.
- Nyt kirjoittakaa asteikolle merkitsemänne numero alla olevaan laatikkoon.

TERVEYTENNE TÄNÄÄN =

Paras terveys,  
jonka voitte  
kuvitella



Kiitos vastauksistanne ja vaivannäöstänne.

Huonoin terveys,  
jonka voitte  
kuvitella



# References

1. Krings T, Kim H, Power S, et al. Neurovascular manifestations in hereditary hemorrhagic telangiectasia: imaging features and genotype-phenotype correlations. *AJNR Am J Neuroradiol*. 2015;36(5):863-870. doi:10.3174/ajnr.A4210
2. Raybaud CA, Strother CM, Hald JK. Aneurysms of the vein of Galen: embryonic considerations and anatomical features relating to the pathogenesis of the malformation. *Neuroradiology*. 1989;31(2):109-128. doi:10.1007/BF00698838
3. Wassef M, Blei F, Adams D, et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics*. 2015;136(1):e203-e214. doi:10.1542/peds.2014-3673
4. null null. Reporting Terminology for Brain Arteriovenous Malformation Clinical and Radiographic Features for Use in Clinical Trials. *Stroke*. 2001;32(6):1430-1442. doi:10.1161/01.STR.32.6.1430
5. Nornes H, Grip A. Hemodynamic aspects of cerebral arteriovenous malformations. *J Neurosurg*. 1980;53(4):456-464. doi:10.3171/jns.1980.53.4.0456
6. Duong DH, Young WL, Vang MC, et al. Feeding Artery Pressure and Venous Drainage Pattern Are Primary Determinants of Hemorrhage From Cerebral Arteriovenous Malformations. *Stroke*. 1998;29(6):1167-1176. doi:10.1161/01.STR.29.6.1167
7. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. *J Neurosurg*. 2013;118(2):437-443. doi:10.3171/2012.10.JNS121280
8. Oulasvirta E, Koroknay-Pál P, Hafez A, Elseoud AA, Lehto H, Laakso A. Characteristics and Long-Term Outcome of 127 Children With Cerebral Arteriovenous Malformations. *Neurosurgery*. 2019;84(1):151-159. doi:10.1093/neuros/nyy008
9. Hetts SW, Cooke DL, Nelson J, et al. Influence of patient age on angioarchitecture of brain arteriovenous malformations. *AJNR*. *RAmerican J Neuroradiol*. 2014;35(7):1376-1380. doi:10.3174/ajnr.A3886 [doi]
10. Hoffman C, Riina HA, Stieg P, et al. Associated aneurysms in pediatric arteriovenous malformations and the implications for treatment. *Neurosurgery*. 2011;69(2):315-322. doi:10.1227/NEU.0b013e31821524a1 [doi]
11. Shakur SF, Hussein AE, Amin-Hanjani S, Valyi-Nagy T, Charbel FT, Alaraj A. Cerebral Arteriovenous Malformation Flow Is Associated With Venous Intimal Hyperplasia. *Stroke*. 2017;48(4):1088-1091. doi:10.1161/STROKEAHA.116.015666
12. Tu J, Stoodley MA, Morgan MK, Storer KP. Ultrastructure of perinidal capillaries in cerebral arteriovenous malformations. *Neurosurgery*. 2006;58(5):961-970; discussion 961-970. doi:10.1227/01.NEU.0000210248.39504.B5
13. Sato S, Kodama N, Sasaki T, Matsumoto M, Ishikawa T. Perinidal dilated capillary networks in cerebral arteriovenous malformations. *Neurosurgery*. 2004;54(1):163-168; discussion 168-170. doi:10.1227/01.neu.0000097518.57741.be
14. Chang SD, Marcellus ML, Marks MP, Levy RP, Do HM, Steinberg GK. Multimodality Treatment of Giant Intracranial Arteriovenous Malformations. *Neurosurgery*. 2003;53(1):1. doi:10.1227/01.NEU.0000068700.68238.84
15. Spetzler RF, Kondziolka DS, Higashida RT, Kalani MYS, eds. *Comprehensive Management of Arteriovenous Malformations of the Brain and Spine*. Cambridge University Press; 2015. doi:10.1017/CBO9781139523943
16. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65(4):476-483. doi:10.3171/jns.1986.65.4.0476 [doi]
17. Spetzler RF, Ponce FA. A 3-tier classification of cerebral arteriovenous malformations. Clinical article. *J Neurosurg*. 2011;114(3):842-849. doi:10.3171/2010.8.JNS10663
18. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A Supplementary Grading Scale for Selecting Patients With Brain Arte-

- rio venous Malformations for Surgery. *Neurosurgery*. 2010;66(4):702-713. doi:10.1227/01.NEU.0000367555.16733.E1
19. Hernesniemi JA, Dashti R, Juvela S, Vaart K, Niemela M, Laakso A. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. *Neurosurgery*. 2008;63(5):823-829; discussion 829-31. doi:10.1227/01.NEU.0000330401.82582.5E [doi]
20. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. *Stroke*. 2009;40(1):100-105. doi:10.1161/STROKEAHA.108.524678
21. Yaşargil M, Duvernoy H. AVM of the brain, history, embryology, pathological considerations, hemodynamics, diagnostic studies, microsurgical anatomy. In: ; 1987. Accessed January 31, 2023. <https://www.semanticscholar.org/paper/AVM-of-the-brain%2C-history%2C-embryology%2C-pathological-Yas-%CC%A6argil-Duvernoy/4f7767aad3d3081fd-ddb3a812f2528d22fef355a?sort=is-influential>
22. McCormick WF. The Pathology of Vascular ("Arteriovenous") Malformations. *J Neurosurg*. 1966;24(4):807-816. doi:10.3171/jns.1966.24.4.0807
23. Deshpande DH, Vidyasagar C. Histology of the persistent embryonic veins in arteriovenous malformations of brain. *Acta Neurochir (Wien)*. 1980;53(3-4):227-236. doi:10.1007/BF02074795
24. Waltimo O. The change in size of intracranial arteriovenous malformations. *J Neurol Sci*. 1973;19(1):21-27. doi:10.1016/0022-510X(73)90052-X
25. Neil JA, Li D, Stiefel MF, Hu YC. Symptomatic de novo arteriovenous malformation in an adult: Case report and review of the literature. *Surg Neurol Int*. 2014;5:148. doi:10.4103/2152-7806.142796
26. Lee SK, Vilela P, Willinsky R, TerBrugge KG. Spontaneous regression of cerebral arteriovenous malformations: clinical and angiographic analysis with review of the literature. *Neuroradiology*. 2002;44(1):11-16. doi:10.1007/s002340100702
27. Lim SL, Foo ASC, Karlsson B, Yeo TT. Spontaneous obliteration highlights the dynamic nature of cerebral arteriovenous malformations: A case report and review of the literature. *Surg Neurol Int*. 2016;7:45. doi:10.4103/2152-7806.180766
28. Nakamura M, Samii A, Lang JM, Götz F, Samii M, Krauss JK. De Novo Arteriovenous Malformation Growth Secondary to Implantation of Genetically Modified Allogeneic Mesenchymal Stem Cells in the Brain. *Neurosurgery*. 2016;78(4):E596. doi:10.1227/NEU.0000000000001025
29. Lauzier DC, Vellimana AK, Chatterjee AR, et al. Return of the lesion: a meta-analysis of 1134 angiographically cured pediatric arteriovenous malformations. *J Neurosurg Pediatr*. Published online 2021:1-8. doi:10.3171/2021.6.PEDS21227
30. Nikolaev SI, Vetiska S, Bonilla X, et al. Somatic Activating KRAS Mutations in Arteriovenous Malformations of the Brain. *N Engl J Med*. 2018;378(3):250-261. doi:10.1056/NEJMoal709449
31. Fish JE, Flores Suarez CP, Boudreau E, et al. Somatic Gain of KRAS Function in the Endothelium Is Sufficient to Cause Vascular Malformations That Require MEK but Not PI3K Signaling. *Circ Res*. 2020;127(6):727-743. doi:10.1161/CIRCRESAHA.119.316500
32. Hong T, Yan Y, Li J, et al. High prevalence of KRAS/BRAF somatic mutations in brain and spinal cord arteriovenous malformations. *Brain*. 2019;142(1):23-34. doi:10.1093/brain/awy307
33. Rodrigues de Oliveira LF, Castro-Afonso LH de, Freitas RK de, Colli BO, Abud DG. De Novo Intracranial Arteriovenous Malformation—Case Report and Literature Review. *World Neurosurg*. 2020;138:349-351. doi:10.1016/j.wneu.2020.03.109
34. Pabaney AH, Rammo RA, Tahir RA, Seyfried D. Development of De Novo Arteriovenous Malformation Following Ischemic Stroke: Case Report and Review of Current Literature. *World Neurosurg*. 2016;96:608.e5-608.e12. doi:10.1016/j.wneu.2016.09.062
35. Morales-Valero SF, Bortolotti C, Sturiale C, Lanzino G. Are parenchymal AVMs congenital lesions? *Neurosurg Focus*. 2014;37(3):E2. doi:10.3171/2014.6.FOCUS14234

36. Jeffree RL, Stoodley MA. Postnatal development of arteriovenous malformations. *Pediatr Neurosurg*. 2009;45(4):296-304. doi:10.1159/000235604
37. Fujimura M, Kimura N, Ezura M, Niizuma K, Uenohara H, Tominaga T. Development of a de novo arteriovenous malformation after bilateral revascularization surgery in a child with moyamoya disease. *J Neurosurg Pediatr*. 2014;13(6):647-649. doi:10.3171/2014.3.PEDS13610
38. Shidoh S, Kobayashi M, Akaji K, Kano T, Tanizaki Y, Mihara B. De Novo Arteriovenous Malformation after Aneurysm Clipping. *NMC Case Rep J*. 2017;4(3):89-92. doi:10.2176/nmccrj.cr.2016-0272
39. Laakso A, Hernesniemi J. Arteriovenous malformations: epidemiology and clinical presentation. *Neurosurg Clin N Am*. 2012;23(1):1-6. doi:10.1016/j.nec.2011.09.012
40. Hara H, Burrows PE, Flodmark O, Terbrugge K, Humphreys R. Neonatal superficial cerebral arteriovenous malformations. *Pediatr Neurosurg*. 1994;20(2):126-136. doi:10.1159/000120775
41. Rodesch G, Malherbe V, Alvarez H, Zerah M, Devictor D, Lasjaunias P. Nongalenic cerebral arteriovenous malformations in neonates and infants. Review of 26 consecutive cases (1982-1992). *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 1995;11(4):231-241. doi:10.1007/BF00277659
42. Potter CA, Armstrong-Wells J, Fullerton HJ, et al. Neonatal Giant Pial Arteriovenous Malformation: Genesis or Rapid Enlargement in the Third Trimester. *J Neurointerventional Surg*. 2009;1(1):151-153.
43. Eguchi S, Aihara Y, Yamaguchi K, Okada Y. Limitations of fetal ultrasonography and magnetic resonance imaging in prenatal diagnosis of congenital cerebral arteriovenous malformations with hemorrhagic onset: Case report. *J Neurosurg Pediatr*. 2012;10(2):154-158. doi:10.3171/2012.4.PEDS11517
44. Kohout MP, Hansen M, Pribaz JJ, Mulliken JB. Arteriovenous malformations of the head and neck: natural history and management. *Plast Reconstr Surg*. 1998;102(3):643-654. doi:10.1097/00006534-199809030-00006
45. Simanshu DK, Nissley DV, McCormick F. RAS Proteins and Their Regulators in Human Disease. *Cell*. 2017;170(1):17-33. doi:10.1016/j.cell.2017.06.009
46. Kranenburg O, Gebbink MFBG, Voest EE. Stimulation of angiogenesis by Ras proteins. *Biochim Biophys Acta*. 2004;1654(1):23-37. doi:10.1016/j.bbcan.2003.09.004
47. Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. *Nat Rev Cancer*. 2003;3(6):459-465. doi:10.1038/nrc1097
48. Al-Olabi L, Polubothu S, Dowsett K, et al. Mosaic RAS/MAPK variants cause sporadic vascular malformations which respond to targeted therapy. *J Clin Invest*. 2018;128(4):1496-1508. doi:10.1172/JCI98589
49. Lekwuttikarn R, Lim YH, Admani S, Choate KA, Teng JMC. Genotype-Guided Medical Treatment of an Arteriovenous Malformation in a Child. *JAMA Dermatol*. 2019;155(2):256-257. doi:10.1001/jamadermatol.2018.4653
50. Walcott BP, Winkler EA, Zhou S, et al. Identification of a rare BMP pathway mutation in a non-syndromic human brain arteriovenous malformation via exome sequencing. *Hum Genome Var*. 2018;5:18001. doi:10.1038/hgv.2018.1
51. Letteboer TGW, Mager JJ, Snijder RJ, et al. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. *J Med Genet*. 2006;43(4):371-377. doi:10.1136/jmg.2005.035451
52. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: An overview of diagnosis, management, and pathogenesis. *Genet Med*. 2011;13(7):607-616. doi:10.1097/GIM.0b013e3182136d32
53. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet*. 1994;8(4):345-351. doi:10.1038/ng1294-345
54. Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet*. 1996;13(2):189-195. doi:10.1038/ng0696-189
55. Gallione CJ, Repetto GM, Legius E, et al. A

- combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *The Lancet*. 2004;363(9412):852-859. doi:10.1016/S0140-6736(04)15732-2
56. Lebrin F, Goumans MJ, Jonker L, et al. Endoglin promotes endothelial cell proliferation and TGF-beta/ALK1 signal transduction. *EMBO J*. 2004;23(20):4018-4028. doi:10.1038/sj.emboj.7600386
  57. Zhang YE. Non-Smad pathways in TGF- $\beta$  signaling. *Cell Res*. 2009;19(1):128-139. doi:10.1038/cr.2008.328
  58. McDonald J, Wooderchak-Donahue W, VanSant Webb C, Whitehead K, Stevenson DA, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. *Front Genet*. 2015;6:1. doi:10.3389/fgene.2015.00001
  59. Brinjikji W, Iyer VN, Wood CP, Lanzino G. Prevalence and characteristics of brain arteriovenous malformations in hereditary hemorrhagic telangiectasia: a systematic review and meta-analysis. *J Neurosurg JNS*. 2017;127(2):302-310. doi:10.3171/2016.7.JNS16847
  60. Revencu N, Boon LM, Mulliken JB, et al. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Hum Mutat*. 2008;29(7):959-965. doi:10.1002/humu.20746
  61. Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Genet*. 2003;73(6):1240-1249. doi:10.1086/379793
  62. Hershkovitz D, Bercovich D, Sprecher E, Lapidot M. RASA1 mutations may cause hereditary capillary malformations without arteriovenous malformations. *Br J Dermatol*. 2008;158(5):1035-1040. doi:10.1111/j.1365-2133.2008.08493.x
  63. Turnbull MM, Humeniuk V, Stein B, Suthers GK. Arteriovenous malformations in Cowden syndrome. *J Med Genet*. 2005;42(8):e50-e50. doi:10.1136/jmg.2004.030569
  64. Weber F, Knopf H. Incidental findings in magnetic resonance imaging of the brains of healthy young men. *J Neurol Sci*. 2006;240(1-2):81-84. doi:10.1016/j.jns.2005.09.008
  65. Jhaveri A, Amirabadi A, Dirks P, et al. Predictive Value of MRI in Diagnosing Brain AVM Recurrence after Angiographically Documented Exclusion in Children. *AJNR Am J Neuroradiol*. 2019;40(7):1227-1235. doi:10.3174/ajnr.A6093
  66. Morris Z, Whiteley WN, Longstreth WT, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2009;339:b3016. doi:10.1136/bmj.b3016
  67. Al-Shahi R, Fang JSY, Lewis SC, Warlow CP. Prevalence of adults with brain arteriovenous malformations: a community based study in Scotland using capture-recapture analysis. *J Neurol Neurosurg Psychiatry*. 2002;73(5):547-551. doi:10.1136/jnnp.73.5.547
  68. Berman MF, Sciacca RR, Pile-Spellman J, et al. The Epidemiology of Brain Arteriovenous Malformations. *Neurosurgery*. 2000;47(2):389.
  69. Wf M. Pathology of vascular malformations of the brain. *Intracranial Arteriovenous Malform*. Published online 1984:234-245.
  70. Karhunen PJ, Penttilä A, Erkinjuntti T. Arteriovenous malformation of the brain: Imaging by postmortem angiography. *Forensic Sci Int*. 1990;48(1):9-19. doi:10.1016/0379-0738(90)90267-3
  71. Friedlander RM. Clinical practice. Arteriovenous malformations of the brain. *N Engl J Med*. 2007;356(26):2704-2712. doi:10.1016/0379-0738(90)90267-3 [pii]
  72. Choi JH, Mohr JP. Brain arteriovenous malformations in adults. *The Lancet Neurology*. 2005;4(5):299-308. doi:10.1016/S1473-0738(05)70073-9 [pii]
  73. ApSimon HT, Reef H, Phadke RV, Popovic EA. A population-based study of brain arteriovenous malformation: long-term treatment outcomes. *Stroke*. 2002;33(12):2794-2800. doi:10.1161/01.str.0000043674.99741.9b
  74. Murthy SB, Merkler AE, Omran SS, et al. Outcomes after intracerebral hemorrhage from arteriovenous malformations. *Neurology*. 2017;88(20):1882-1888. doi:10.1212/WNL.0000000000003935
  75. Boulouis G, Stricker S, Benichi S, et al. Etiology of intracerebral hemorrhage in children:

- cohort study, systematic review, and meta-analysis. *J Neurosurg Pediatr PED*. 2021;27(3):357-363. doi:10.3171/2020.7.PEDS20447
76. Ondra SL, Troupp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. *J Neurosurg*. 1990;73(3):387-391. doi:10.3171/jns.1990.73.3.0387
77. van Beijnum J, Lovelock CE, Cordonnier C, Rothwell PM, Klijn CJM, Al-Shahi Salman R. Outcome after spontaneous and arteriovenous malformation-related intracerebral haemorrhage: population-based studies. *Brain J Neurol*. 2009;132(Pt 2):537-543. doi:10.1093/brain/awn318
78. Choi JH, Mast H, Sciacca RR, et al. Clinical outcome after first and recurrent hemorrhage in patients with untreated brain arteriovenous malformation. *Stroke*. 2006;37(5):1243-1247. doi:10.1161/01.STR.0000217970.18319.7d
79. Hartmann A, Mast H, Mohr JP, et al. Morbidity of intracranial hemorrhage in patients with cerebral arteriovenous malformation. *Stroke*. 1998;29(5):931-934. doi:10.1161/01.str.29.5.931
80. Karlsson B, Jokura H, Yang HC, et al. Clinical outcome following cerebral AVM hemorrhage. *Acta Neurochir (Wien)*. 2020;162(7):1759-1766. doi:10.1007/s00701-020-04380-z
81. Taylor B, Appelboom G, Yang A, et al. Underlying effect of age on outcome differences in arteriovenous malformation-associated intracerebral hemorrhage. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2015;22(3):526-529. doi:10.1016/j.jocn.2014.09.009
82. Mine S, Hirai S, Ono J, Yamaura A. Risk factors for poor outcome of untreated arteriovenous malformation. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2000;7(6):503-506. doi:10.1054/jocn.2000.0743
83. Itoyama Y, Uemura S, Ushio Y, et al. Natural course of unoperated intracranial arteriovenous malformations: study of 50 cases. *J Neurosurg*. 1989;71(6):805-809. doi:10.3171/jns.1989.71.6.0805
84. Forster DM, Steiner L, Håkanson S. Arteriovenous malformations of the brain. A long-term clinical study. *J Neurosurg*. 1972;37(5):562-570. doi:10.3171/jns.1972.37.5.0562
85. Crawford PM, West CR, Chadwick DW, Shaw MD. Arteriovenous malformations of the brain: natural history in unoperated patients. *J Neurol Neurosurg Psychiatry*. 1986;49(1):1-10. doi:10.1136/jnnp.49.1.1
86. Abad JM, Alvarez F, Manrique M, Garcia-Blazquez M. Cerebral arteriovenous malformations. Comparative results of surgical vs conservative treatment in 112 cases. *J Neurosurg Sci*. 1983;27(3):203-210.
87. Laakso A, Dashti R, Seppanen J, et al. Long-term excess mortality in 623 patients with brain arteriovenous malformations. *Neurosurgery*. 2008;63(2):244-253; discussion 253-5. doi:10.1227/01.NEU.0000320439.27895.24 [doi]
88. Yamada S, Takagi Y, Nozaki K, Kikuta K, Ichiro, Hashimoto N. Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. *J Neurosurg*. 2007;107(5):965-972. doi:10.3171/JNS-07/11/0965
89. Mast H, Young WL, Koennecke HC, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. *Lancet Lond Engl*. 1997;350(9084):1065-1068. doi:10.1016/s0140-6736(97)05390-7
90. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology*. 2006;66(9):1350-1355. doi:66/9/1350 [pii]
91. Halim AX, Johnston SC, Singh V, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. *Stroke*. 2004;35(7):1697-1702. doi:10.1161/01.STR.0000130988.44824.29
92. Yang W, Porras JL, Hung AL, et al. Risk of hemorrhage in patients over age 60 with arteriovenous malformations (AVMs). *J Clin Neurosci Off J Neurosurg Soc Australas*. 2016;34:121-127. doi:10.1016/j.jocn.2016.05.010
93. Brown RDJ, Wiebers DO, Torner JC, O'Fallon WM. Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: a population-based study of intrac-

- ranial vascular malformations in Olmsted Country, Minnesota. *J Neurosurg*. 1996;85(1):29-32. doi:10.3171/jns.1996.85.1.0029
94. Hoh BL, Chapman PH, Loeffler JS, Carter BS, Ogilvy CS. Results of multimodality treatment for 141 patients with brain arteriovenous malformations and seizures: factors associated with seizure incidence and seizure outcomes. *Neurosurgery*. 2002;51(2):303-309; discussion 309-311.
  95. Monteiro JM, Rosas MJ, Correia AP, Vaz AR. Migraine and intracranial vascular malformations. *Headache*. 1993;33(10):563-565. doi:10.1111/j.1526-4610.1993.hed3310563.x
  96. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *The Lancet*. 2014;383(9917):614-621. doi:10.1016/S0140-6736(13)62302-8
  97. Miyasaka Y, Kurata A, Tanaka R, et al. Mass effect caused by clinically unruptured cerebral arteriovenous malformations. *Neurosurgery*. 1997;41(5):1060-1063; discussion 1063-1064. doi:10.1097/00006123-199711000-00008
  98. Mast H, Mohr JP, Thompson JL, et al. Transcranial Doppler ultrasonography in cerebral arteriovenous malformations. Diagnostic sensitivity and association of flow velocity with spontaneous hemorrhage and focal neurological deficit. *Stroke*. 1995;26(6):1024-1027. doi:10.1161/01.str.26.6.1024
  99. Meyer B, Schaller C, Frenkel C, Ebeling B, Schramm J. Distributions of local oxygen saturation and its response to changes of mean arterial blood pressure in the cerebral cortex adjacent to arteriovenous malformations. *Stroke*. 1999;30(12):2623-2630. doi:10.1161/01.str.30.12.2623
  100. Iwama T, Hayashida K, Takahashi JC, Nagata I, Hashimoto N. Cerebral hemodynamics and metabolism in patients with cerebral arteriovenous malformations: an evaluation using positron emission tomography scanning. *J Neurosurg*. 2002;97(6):1314-1321. doi:10.3171/jns.2002.97.6.1314
  101. Mast H, Mohr JP, Osipov A, et al. "Steal" is an unestablished mechanism for the clinical presentation of cerebral arteriovenous malformations. *Stroke*. 1995;26(7):1215-1220. doi:10.1161/01.str.26.7.1215
  102. Huang Y, Singer TG, Iv M, et al. Ferumoxytol-enhanced MRI for surveillance of pediatric cerebral arteriovenous malformations. *J Neurosurg Pediatr*. Published online July 19, 2019:1-8. doi:10.3171/2019.5.PEDS1957
  103. Latchaw RE, Hu X, Ugurbil K, Hall WA, Madison MT, Heros RC. Functional magnetic resonance imaging as a management tool for cerebral arteriovenous malformations. *Neurosurgery*. 1995;37(4):619-625; discussion 625-626. doi:10.1227/00006123-199510000-00003
  104. Vates GE, Lawton MT, Wilson CB, et al. Magnetic source imaging demonstrates altered cortical distribution of function in patients with arteriovenous malformations. *Neurosurgery*. 2002;51(3):614-623; discussion 623-627.
  105. Soldozy S, Akyeampong DK, Barquin DL, et al. Systematic Review of Functional Mapping and Cortical Reorganization in the Setting of Arteriovenous Malformations, Redefining Anatomical Eloquence. *Front Surg*. 2020;7:514247-514247. doi:10.3389/fsurg.2020.514247
  106. Kato N, Schilt S, Schneider H, et al. Functional brain mapping of patients with arteriovenous malformations using navigated transcranial magnetic stimulation: first experience in ten patients. *Acta Neurochir (Wien)*. 2014;156(5):885-895. doi:10.1007/s00701-014-2043-7
  107. Berntsen EM, Gulati S, Solheim O, Kvistad KA, Lindseth F, Unsgaard G. Integrated pre- and intraoperative imaging in a patient with an arteriovenous malformation located in eloquent cortex. *Minim Invasive Neurosurg MIN*. 2009;52(2):83-85. doi:10.1055/s-0028-1124104
  108. Chen Y, Li R, Ma L, et al. Long-term outcomes of brainstem arteriovenous malformations after different management modalities: a single-centre experience. *Stroke Vasc Neurol*. 2020;6(1):65-73. doi:10.1136/svn-2020-000407
  109. Hademenos GJ, Massoud TF. Risk of Intracranial Arteriovenous Malformation Rupture Due to Venous Drainage Impairment. *Stroke*. 1996;27(6):1072-1083. doi:10.1161/01.STR.27.6.1072

110. van Beijnum J, van der Worp HB, Buis DR, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. *JAMA*. 2011;306(18):2011-2019. doi:10.1001/jama.2011.1632
111. Gross BA, Storey A, Orbach DB, Scott RM, Smith ER. Microsurgical treatment of arteriovenous malformations in pediatric patients: the Boston Children's Hospital experience. *J Neurosurg Pediatr PED*. 2015;15(1):71-77. doi:10.3171/2014.9.PEDS146
112. Winkler EA, Lu A, Morshed RA, et al. Bringing high-grade arteriovenous malformations under control: clinical outcomes following multimodality treatment in children. *J Neurosurg Pediatr*. 2020;26(1):82-91. doi:10.3171/2020.1.PEDS19487
113. Sanchez-Mejia RO, Chennupati SK, Gupta N, Fullerton H, Young WL, Lawton MT. Superior outcomes in children compared with adults after microsurgical resection of brain arteriovenous malformations. *J Neurosurg*. 2006;105(2 Suppl):82-87. doi:10.3171/ped.2006.105.2.82 [doi]
114. Potts MB, Lau D, Abila AA, et al. Current surgical results with low-grade brain arteriovenous malformations. *J Neurosurg*. 2015;122(4):912-920. doi:10.3171/2014.12.JNS14938
115. Kiriş T, Sencer A, Sahinbaş M, Sencer S, Imer M, İzgi N. Surgical results in pediatric Spetzler-Martin grades I-III intracranial arteriovenous malformations. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 2005;21(1):69-74; discussion 75-76. doi:10.1007/s00381-004-1025-0
116. De Leacy R, Ansari SA, Schirmer CM, et al. Endovascular treatment in the multimodality management of brain arteriovenous malformations: report of the Society of NeuroInterventional Surgery Standards and Guidelines Committee. *J Neurointerventional Surg*. 2022;14(11):1118-1124. doi:10.1136/neurint-surg-2021-018632
117. Hauck EF, Welch BG, White JA, Purdy PD, Pride LG, Samson D. Preoperative Embolization of Cerebral Arteriovenous Malformations with Onyx. *AJNR Am J Neuroradiol*. 2009;30(3):492-495. doi:10.3174/ajnr.A1376
118. Yang W, Anderson-Keightly H, Westbroek EM, et al. Long-term hemorrhagic risk in pediatric patients with arteriovenous malformations. *J Neurosurgery Pediatrics*. 2016;18(3):329-338. doi:10.3171/2016.3.PEDS15715 [doi]
119. Abila AA, Rutledge WC, Seymour ZA, et al. A treatment paradigm for high-grade brain arteriovenous malformations: volume-staged radiosurgical downgrading followed by microsurgical resection. *J Neurosurg*. 2015;122(2):419-432. doi:10.3171/2014.10.JNS1424
120. Niini T, Laakso A, Tanskanen P, Niemelä M, Luostarinen T. Perioperative Treatment of Brain Arteriovenous Malformations Between 2006 and 2014: The Helsinki Protocol. *Neurocrit Care*. 2019;31(2):346-356. doi:10.1007/s12028-019-00674-y
121. Lehecka M, Laakso A, Hernesniemi J. Helsinki Microneurosurgery Basics and Tricks.
122. Hoh BL, Carter BS, Ogilvy CS. Incidence of residual intracranial AVMs after surgical resection and efficacy of immediate surgical re-exploration. *Acta Neurochir (Wien)*. 2004;146(1):1-7; discussion 7. doi:10.1007/s00701-003-0164-5
123. Shimamoto Y, Asada H, Onozuka S, et al. [Natural history for residual intracranial AVM: compared with that for conservatively treated AVM]. *No Shinkei Geka*. 1992;20(9):931-936.
124. Bendok BR, Getch CC, Ali MJ, Parish T, Batter HH. Spontaneous thrombosis of a residual arteriovenous malformation in eloquent cortex after surgery: case report. *Neurosurgery*. 2002;50(5):1142-1145; discussion 1145-1146. doi:10.1097/00006123-200205000-00038
125. Kano H, Lunsford LD, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations, Part 1: management of Spetzler-Martin Grade I and II arteriovenous malformations. *J Neurosurg*. 2012;116(1):11-20. doi:10.3171/2011.9.JNS101740
126. Russell D, Peck T, Ding D, et al. Stereotactic radiosurgery alone or combined with embolization for brain arteriovenous malformations: a systematic review and meta-analysis. *J Neurosurg*. 2018;128(5):1338-1348. doi:10.3171/2016.11.JNS162382
127. Starke RM, Ding D, Kano H, et al. Interna-

- tional multicenter cohort study of pediatric brain arteriovenous malformations. Part 2: Outcomes after stereotactic radiosurgery. *J NeurosurgeryPediatrics*. 2017;19(2):136-148. doi:10.3171/2016.9.PEDS16284 [doi]
128. Shin M, Kawamoto S, Kurita H, et al. Retrospective analysis of a 10-year experience of stereotactic radio surgery for arteriovenous malformations in children and adolescents. *J Neurosurg*. 2002;97(4):779-784. doi:10.3171/jns.2002.97.4.0779
  129. Yen CP, Monteith SJ, Nguyen JH, Rainey J, Schlesinger DJ, Sheehan JP. Gamma Knife surgery for arteriovenous malformations in children. *J Neurosurg Pediatr*. 2010;6(5):426-434. doi:10.3171/2010.8.PEDS10138
  130. Fujimoto M, Uno J, Ikai Y, et al. Risk of rebleeding in arteriovenous malformations due to impaired venous drainage after radiosurgery. *Neurol Med Chir (Tokyo)*. 2011;51(8):585-587. doi:10.2176/nmc.51.585
  131. Glazener EM, Lodin K, Miller MJ, et al. Pediatric Intracranial Arteriovenous Malformation: Long-Term Outcomes with Linear Accelerator (LINAC)-Based Radiosurgery. *Adv Radiat Oncol*. 2020;5(5):850-855. doi:10.1016/j.adro.2020.03.018
  132. Kano H, Flickinger JC, Tonetti D, et al. Estimating the Risks of Adverse Radiation Effects After Gamma Knife Radiosurgery for Arteriovenous Malformations. *Stroke*. 2017;48(1):84-90. doi:10.1161/STROKEAHA.116.014825
  133. Hanakita S, Koga T, Shin M, Igaki H, Saito N. The long-term outcomes of radiosurgery for arteriovenous malformations in pediatric and adolescent populations. *J Neurosurg Pediatr*. 2015;16(2):222-231. doi:10.3171/2015.1.PEDS14407
  134. Luessenhop AJ, Spence WT. ARTIFICIAL EMBOLIZATION OF CEREBRAL ARTERIES: REPORT OF USE IN A CASE OF ARTERIOVENOUS MALFORMATION. *J Am Med Assoc*. 1960;172(11):1153-1155. doi:10.1001/jama.1960.63020110001009
  135. Vollherbst DF, Chapot R, Bendszus M, Möhlenbruch MA. Glue, Onyx, Squid or PHIL? Liquid Embolic Agents for the Embolization of Cerebral Arteriovenous Malformations and Dural Arteriovenous Fistulas. *Clin Neuroradiol*. 2022;32(1):25-38. doi:10.1007/s00062-021-01066-6
  136. Wu EM, El Ahmadieh TY, McDougall CM, et al. Embolization of brain arteriovenous malformations with intent to cure: a systematic review. *J Neurosurg*. 2019;132(2):388-399. doi:10.3171/2018.10.JNS181791
  137. Baharvahdat H, Blanc R, Fahed R, et al. Endovascular Treatment for Low-Grade (Spetzler-Martin I-II) Brain Arteriovenous Malformations. *AJNR Am J Neuroradiol*. 2019;40(4):668-672. doi:10.3174/ajnr.A5988
  138. Hartmann A, Pile-Spellman J, Stapf C, et al. Risk of endovascular treatment of brain arteriovenous malformations. *Stroke*. 2002;33(7):1816-1820. doi:10.1161/01.str.0000020123.80940.b2
  139. Weber W, Kis B, Siekmann R, Kuehne D. *Endovascular Treatment of Intracranial Arteriovenous Malformations with Onyx: Technical Aspects.*; 2007:371-377.
  140. Söderman M, Andersson T, Karlsson B, Wallace MC, Edner G. Management of patients with brain arteriovenous malformations. *Eur J Radiol*. 2003;46(3):195-205. doi:10.1016/s0720-048x(03)00091-3
  141. Bauer AM, Bain MD, Rasmussen PA. Onyx resorbition with AVM recanalization after complete AVM obliteration. *Interv Neuroradiol J Peritherapeutic Neuroradiol Surg Proced Relat Neurosci*. 2015;21(3):351-356. doi:10.1177/1591019915581985
  142. Jafar JJ, Davis AJ, Berenstein A, Choi IS, Kupersmith MJ. The effect of embolization with N-butyl cyanoacrylate prior to surgical resection of cerebral arteriovenous malformations. *J Neurosurg*. 1993;78(1):60-69. doi:10.3171/jns.1993.78.1.0060
  143. Valavanis A, Yaşargil MG. The endovascular treatment of brain arteriovenous malformations. *Adv Tech Stand Neurosurg*. 1998;24:131-214. doi:10.1007/978-3-7091-6504-1\_4
  144. Taylor CL, Dutton K, Rappard G, et al. Complications of preoperative embolization of cerebral arteriovenous malformations. *J Neurosurg*. 2004;100(5):810-812. doi:10.3171/jns.2004.100.5.0810
  145. Gobin YP, Laurent A, Merienne L, et al. Treatment of brain arteriovenous malformations by embolization and radiosurgery. *J*

- Neurosurg*. 1996;85(1):19-28. doi:10.3171/jns.1996.85.1.0019
146. Ogilvy CS, Stieg PE, Awad I, et al. AHA Scientific Statement: Recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. *Stroke*. 2001;32(6):1458-1471. doi:10.1161/01.str.32.6.1458
  147. Blackburn SL, Ashley WW, Rich KM, et al. Combined endovascular embolization and stereotactic radiosurgery in the treatment of large arteriovenous malformations. *J Neurosurg*. 2011;114(6):1758-1767. doi:10.3171/2011.1.JNSI0571
  148. Meisel HJ, Mansmann U, Alvarez H, Rodesch G, Brock M, Lasjaunias P. Effect of partial targeted N-butyl-cyano-acrylate embolization in brain AVM. *Acta Neurochir (Wien)*. 2002;144(9):879-887; discussion 888. doi:10.1007/s00701-002-0978-6
  149. Fox AJ, Girvin JP, Viñuela F, Drake CG. Rolandic arteriovenous malformations: improvement in limb function by IBC embolization. *AJNR Am J Neuroradiol*. 1985;6(4):575-582.
  150. Hung YC, Mohammed N, Muttikkal TJE, et al. The impact of preradiosurgery embolization on intracranial arteriovenous malformations: a matched cohort analysis based on de novo lesion volume. *J Neurosurg*. 2019;133(4):1156-1167. doi:10.3171/2019.5.JNSI9722
  151. Sure U, Butz N, Siegel AM, Mennel HD, Bien S, Bertalanffy H. Treatment-induced neoangiogenesis in cerebral arteriovenous malformations. *Clin Neurol Neurosurg*. 2001;103(1):29-32. doi:10.1016/s0303-8467(01)00112-3
  152. Redekop G, TerBrugge K, Montanera W, Wilinsky R. Arterial aneurysms associated with cerebral arteriovenous malformations: classification, incidence, and risk of hemorrhage. *J Neurosurg*. 1998;89(4):539-546. doi:10.3171/jns.1998.89.4.0539
  153. Crowley RW, Ducruet AF, McDougall CG, Albuquerque FC. Endovascular advances for brain arteriovenous malformations. *Neurosurgery*. 2014;74 Suppl 1:S74-82. doi:10.1227/NEU.0000000000000176
  154. Kano H, Kondziolka D, Flickinger JC, et al. Aneurysms increase the risk of rebleeding after stereotactic radiosurgery for hemorrhagic arteriovenous malformations. *Stroke*. 2012;43(10):2586-2591. doi:10.1161/STROKEAHA.112.664045
  155. Hafez A, Koroknay-Pál P, Oulasvirta E, et al. The Application of the Novel Grading Scale (Lawton-Young Grading System) to Predict the Outcome of Brain Arteriovenous Malformation. *Neurosurgery*. 2019;84(2):529-536. doi:10.1093/neuros/nyy153
  156. Frisoli FA, Catapano JS, Farhadi DS, et al. Spetzler-Martin Grade III Arteriovenous Malformations: A Comparison of Modified and Supplemented Spetzler-Martin Grading Systems. *Neurosurgery*. 2021;88(6):1103-1110. doi:10.1093/neuros/nyab020
  157. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH Score. *Stroke*. 2001;32(4):891-897. doi:10.1161/01.STR.32.4.891
  158. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg*. 1968;28(1):14-20. doi:10.3171/jns.1968.28.1.0014 [doi]
  159. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. *J Neurosurg*. 1988;68(6):985-986. doi:10.3171/jns.1988.68.6.0985
  160. Hafez A, Oulasvirta E, Koroknay-Pál P, Niemelä M, Hernesniemi J, Laakso A. Timing of surgery for ruptured supratentorial arteriovenous malformations. *Acta Neurochir (Wien)*. 2017;159(11):2103-2112. doi:10.1007/s00701-017-3315-9
  161. Dinc N, Won SY, Quick-Weller J, Berkefeld J, Seifert V, Marquardt G. Prognostic variables and outcome in relation to different bleeding patterns in arteriovenous malformations. *Neurosurg Rev*. 2019;42(3):731-736. doi:10.1007/s10143-019-01091-7
  162. Neidert MC, Lawton MT, Mader M, et al. The AVICH Score: A Novel Grading System to Predict Clinical Outcome in Arteriovenous Malformation-Related Intracerebral Hemorrhage. *World Neurosurg*. 2016;92:292-297. doi:10.1016/j.wneu.2016.04.080
  163. Neidert MC, Lawton MT, Kim LJ, et al. Inter-

- national multicentre validation of the arteriovenous malformation-related intracerebral haemorrhage (AVICH) score. *J Neurol Neurosurg Psychiatry*. 2018;89(11):1163-1166. doi:10.1136/jnnp-2017-316259
164. Oulasvirta E, Niini T, Hafez A, et al. Correlation between arteriovenous malformation nidus size and intraparenchymal hematoma volume in the event of rupture. *Brain Spine*. 2022;2:101663. doi:10.1016/j.bas.2022.101663
  165. Taweel BA, Gillespie CS, Richardson GE, et al. External validation of brain arteriovenous malformation haemorrhage scores, AVICH, ICH and R2eD. *Acta Neurochir (Wien)*. 2022;164(6):1685-1692. doi:10.1007/s00701-022-05190-1
  166. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. *Neurology*. 2003;61(2):189-194. doi:10.1212/01.wnl.0000078894.79866.95
  167. Eeg-Olofsson O, Ringheim Y. Stroke in children. Clinical characteristics and prognosis. *Acta Paediatr Scand*. 1983;72(3):391-395. doi:10.1111/j.1651-2227.1983.tb09734.x
  168. Schoenberg BS, Mellinger JF, Schoenberg DG. Cerebrovascular disease in infants and children: a study of incidence, clinical features, and survival. *Neurology*. 1978;28(8):763-768. doi:10.1212/wnl.28.8.763
  169. Broderick J, Talbot GT, Prenger E, Leach A, Brott T. Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage. *J Child Neurol*. 1993;8(3):250-255. doi:10.1177/088307389300800308
  170. González-Pérez A, Gaist D, Wallander MA, McFeat G, García-Rodríguez LA. Mortality after hemorrhagic stroke. *Neurology*. 2013;81(6):559. doi:10.1212/WNL.0b013e31829e6eff
  171. Beslow LA, Licht DJ, Smith SE, et al. Predictors of Outcome in Childhood Intracerebral Hemorrhage. *Stroke*. 2010;41(2):313-318. doi:10.1161/STROKEAHA.109.568071
  172. Blom I, De Schryver ELLM, Kappelle LJ, Rinkel GJE, Jennekens-Schinkel A, Peters ACB. Prognosis of haemorrhagic stroke in childhood: a long-term follow-up study. *Dev Med Child Neurol*. 2003;45(4):233-239. doi:10.1017/s001216220300046x
  173. Lo WD, Lee J, Rusin J, Perkins E, Roach ES. Intracranial Hemorrhage in Children: An Evolving Spectrum. *Arch Neurol*. 2008;65(12):1629-1633. doi:10.1001/archneurol.2008.502
  174. Meyer-Heim AD, Boltshauser E. Spontaneous intracranial haemorrhage in children: aetiology, presentation and outcome. *Brain Dev*. 2003;25(6):416-421. doi:S0387760403000299 [pii]
  175. Adil MM, Qureshi AI, Beslow LA, Malik AA, Jordan LC. Factors Associated With Increased In-Hospital Mortality Among Children With Intracerebral Hemorrhage. *J Child Neurol*. 2015;30(8):1024-1028. doi:10.1177/0883073814552191
  176. Laurent JP, Bruce DA, Schut L. Hemorrhagic Brain Tumors in Pediatric Patients. *Pediatr Neurosurg*. 1981;8(4):263-270. doi:10.1159/000119989
  177. Williams V, Jayashree M, Bansal A, et al. Spontaneous intracranial haemorrhage in children-intensive care needs and predictors of in-hospital mortality: a 10-year single-centre experience. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 2019;35(8):1371-1379. doi:10.1007/s00381-019-04209-w
  178. Jordan LC, Johnston SC, Wu YW, Sidney S, Fullerton HJ. The importance of cerebral aneurysms in childhood hemorrhagic stroke: a population-based study. *Stroke*. 2009;40(2):400-405. doi:10.1161/STROKEAHA.108.518761
  179. Beslow LA, Licht DJ, Smith SE, et al. Predictors of outcome in childhood intracerebral hemorrhage: a prospective consecutive cohort study. *Stroke*. 2010;41(2):313-318. doi:10.1161/STROKEAHA.109.568071
  180. Fullerton HJ, Achrol AS, Johnston SC, et al. Long-term hemorrhage risk in children versus adults with brain arteriovenous malformations. *Stroke J Cereb Circ*. 2005;36(10):2099-2104. doi:01.STR.0000181746.77149.2b [pii]
  181. Rocco CD, Tamburrini G, Rollo M. Cerebral Arteriovenous Malformations in Children. *Acta Neurochir (Wien)*. 2000;142(2):145-158. doi:10.1007/s007010050017
  182. Stricker S, Boulouis G, Benichi S, et al. Acute surgical management of children with rup-

- tured brain arteriovenous malformation. *J Neurosurg Pediatr*. Published online January 22, 2021;1-9. doi:10.3171/2020.8.PEDS20479
183. C.Bills D, Rosenfeld JV, Phelan EM, Klug GL. Intracranial arteriovenous malformations in childhood: presentation, management and outcome. *J Clin Neurosci*. 3(3):220-228. doi:10.1016/S0967-5868(96)90054-5
  184. Ellis MJ, Armstrong D, Vachhrajani S, et al. Angioarchitectural features associated with hemorrhagic presentation in pediatric cerebral arteriovenous malformations. *J Neurointerventional Surg*. 2013;5(3):191-195. doi:10.1136/neurintsurg-2011-010198 [doi]
  185. Zheng T, Wang QJ, Liu YQ, et al. Clinical features and endovascular treatment of intracranial arteriovenous malformations in pediatric patients. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 2014;30(4):647-653. doi:10.1007/s00381-013-2277-3 [doi]
  186. Tong X, Wu J, Lin F, et al. The Effect of Age, Sex, and Lesion Location on Initial Presentation in Patients with Brain Arteriovenous Malformations. *World Neurosurg*. 2016;87:598-606. doi:10.1016/j.wneu.2015.10.060 [doi]
  187. Mori A, Yokoi I, Noda Y, Willmore LJ. Natural antioxidants may prevent posttraumatic epilepsy: a proposal based on experimental animal studies. *Acta Med Okayama*. 2004;58(3):111-118. doi:10.18926/AMO/32111
  188. Kraemer DL, Awad IA. Vascular malformations and epilepsy: clinical considerations and basic mechanisms. *Epilepsia*. 1994;35 Suppl 6:S30-43. doi:10.1111/j.1528-1157.1994.tb05987.x
  189. Singh R, Pathak DN. Lipid peroxidation and glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase, and glucose-6-phosphate dehydrogenase activities in FeCl<sub>3</sub>-induced epileptogenic foci in the rat brain. *Epilepsia*. 1990;31(1):15-26. doi:10.1111/j.1528-1157.1990.tb05354.x
  190. Ronne Engström E, Hillered L, Flink R, et al. Extracellular amino acid levels measured with intracerebral microdialysis in the model of posttraumatic epilepsy induced by intracortical iron injection. *Epilepsy Res*. 2001;43(2):135-144. doi:10.1016/s0920-1211(00)00191-1
  191. Ueda Y, Yokoyama H, Nakajima A, et al. In vivo EPR estimation of bilateral hippocampal antioxidant ability of rats with epileptogenesis induced by amygdalar FeCl<sub>3</sub> microinjection. *Epilepsia*. 2007;48(10):1947-1951. doi:10.1111/j.1528-1167.2007.01141.x
  192. Ueda Y, Willmore LJ, Triggs WJ. Amygdalar injection of FeCl<sub>3</sub> causes spontaneous recurrent seizures. *Exp Neurol*. 1998;153(1):123-127. doi:10.1006/exnr.1998.6869
  193. Williamson A, Patrylo PR, Lee S, Spencer DD. Physiology of Human Cortical Neurons Adjacent to Cavernous Malformations and Tumors. *Epilepsia*. 2003;44(11):1413-1419. doi:10.1046/j.1528-1157.2003.23603.x
  194. Ding D, Starke RM, Quigg M, et al. Cerebral Arteriovenous Malformations and Epilepsy, Part 1: Predictors of Seizure Presentation. *World Neurosurg*. 2015;84(3):645-652. doi:10.1016/j.wneu.2015.02.039
  195. Crawford PM, West CR, Shaw MD, Chadwick DW. Cerebral arteriovenous malformations and epilepsy: factors in the development of epilepsy. *Epilepsia*. 1986;27(3):270-275.
  196. Celli P, Ferrante L, Palma L, Cavedon G. Cerebral arteriovenous malformations in children. Clinical features and outcome of treatment in children and in adults. *Surg Neurol*. 1984;22(1):43-49.
  197. Tong X, Wu J, Lin F, et al. Risk Factors for Subsequent Hemorrhage in Patients with Cerebellar Arteriovenous Malformations. *World Neurosurg*. 2016;92:47-57. doi:10.1016/j.wneu.2016.04.082
  198. Kim H, McCulloch CE, Johnston SC, Lawton MT, Sidney S, Young WL. Comparison of 2 Approaches for Determining the Natural History Risk of Brain Arteriovenous Malformation Rupture. *Am J Epidemiol*. 2010;171(12):1317-1322. doi:10.1093/aje/kwq082
  199. Stefani MA, Porter PJ, terBrugge KG, Montanera W, Willinsky RA, Wallace MC. Angioarchitectural factors present in brain arteriovenous malformations associated with hemorrhagic presentation. *Stroke*. 2002;33(4):920-924. doi:10.1161/01.str.0000014582.03429.f7
  200. Liu AS, Mulliken JB, Zurakowski D, Fishman SJ, Greene AK. Extracranial Arteriovenous Malformations: Natural Progression and Recurrence after Treatment. *Plast Reconstr Surg*. 2010;125(4):1185. doi:10.1097/

PRS.0b013e3181d18070

201. Azis KA, Koh KL, Wan Sulaiman WA, Al-Chalabi MMM. Extracranial Arteriovenous Malformations Rupture in Pregnancy. *Cureus*. 14(3):e22798. doi:10.7759/cureus.22798
202. Derdeyn CP, Zipfel GJ, Albuquerque FC, et al. Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2017;48(8):e200-e224. doi:10.1161/STR.0000000000000134
203. Porras JL, Yang W, Philadelphia E, et al. Hemorrhage Risk of Brain Arteriovenous Malformations During Pregnancy and Puerperium in a North American Cohort. *Stroke*. 2017;48(6):1507-1513. doi:10.1161/STROKEAHA.117.016828
204. Liu X ju, Wang S, Zhao Y li, et al. Risk of cerebral arteriovenous malformation rupture during pregnancy and puerperium. *Neurology*. 2014;82(20):1798-1803. doi:10.1212/WNL.0000000000000436
205. Singhal A, Adirim T, Cochrane D, Steinbok P. Pediatric patients with poor neurological status and arteriovenous malformation hemorrhage: an outcome analysis. *J Neurosurgery-Pediatrics*. 2011;7(5):462-467. doi:10.3171/2011.2.PEDS10355 [doi]
206. Kondziolka D, Humphreys RP, Hoffman HJ, Hendrick EB, Drake JM. Arteriovenous malformations of the brain in children: a forty year experience. *Can J Neurol Sci J Can Sci Neurol*. 1992;19(1):40-45.
207. Torne R, Rodriguez-Hernandez A, Arikian F, et al. Posterior fossa arteriovenous malformations: Significance of higher incidence of bleeding and hydrocephalus. *Clin Neurol Neurosurg*. 2015;134:37-43. doi:10.1016/j.clineuro.2015.04.003 [doi]
208. Abila AA, Nelson J, Rutledge WC, Young WL, Kim H, Lawton MT. The natural history of AVM hemorrhage in the posterior fossa: comparison of hematoma volumes and neurological outcomes in patients with ruptured infra- and supratentorial AVMs. *Neurosurg Focus*. 2014;37(3):E6-E6. doi:10.3171/2014.7.FOCUS14211
209. Blauwblomme T, Bourgeois M, Meyer P, et al. Long-Term Outcome of 106 Consecutive Pediatric Ruptured Brain Arteriovenous Malformations After Combined Treatment. *Stroke*. 2014;45(6):1664-1671. doi:10.1161/STROKEAHA.113.004292
210. D'Aliberti G, Talamonti G, Versari PP, et al. Comparison of pediatric and adult cerebral arteriovenous malformations. *J Neurosurg Sci*. 1997;41(4):331-336.
211. Mosch SC, Max JE, Tranel D. A matched lesion analysis of childhood versus adult-onset brain injury due to unilateral stroke: another perspective on neural plasticity and recovery of social functioning. *Cogn Behav Neurol Off J Soc Behav Cogn Neurol*. 2005;18(1):5-17. doi:10.1097/01.wnn.0000152207.80819.3c
212. Nair AP, Kumar R, Mehrotra A, Srivastava AK, Sahu RN, Nair P. Clinical, radiological profile and outcome in pediatric Spetzler-Martin grades I-III arteriovenous malformations. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 2012;28(4):593-598. doi:10.1007/s00381-011-1668-6 [doi]
213. Andrade-Souza YM, Ramani M, Scora D, Tsao MN, TerBrugge K, Schwartz ML. Radiosurgical treatment for rolandic arteriovenous malformations. *J Neurosurg*. 2006;105(5):689-697. doi:10.3171/jns.2006.105.5.689
214. Cho N, Nga VDW, Ahmed R, et al. Surgical management of pediatric rolandic arteriovenous malformations: a single-center case series. *J Neurosurg Pediatr*. 2020;27(1):62-68. doi:10.3171/2020.6.PEDS18547
215. Altschuler EM, Lunsford LD, Coffey RJ, Bissonette DJ, Flickinger JC. Gamma knife radiosurgery for intracranial arteriovenous malformations in childhood and adolescence. *Pediatr Neurosci*. 1989;15(2):53-61. doi:10.1159/000120443
216. Chen CJ, Lee CC, Kano H, et al. Stereotactic radiosurgery for pediatric brain arteriovenous malformations: long-term outcomes. *J Neurosurg Pediatr*. 2020;25(5):497-505. doi:10.3171/2019.12.PEDS19595
217. Yoshida K, Ichikawa T, Kurozumi K, Yanai H, Onoda K, Date I. Fatal glioblastoma after Gamma Knife radiosurgery for arteriovenous malformation in a child. *J Clin Neurosci*. 2014;21(8):1453-1455. doi:10.1016/j.

jocn.2013.10.039

218. Curative embolization of pediatric intracranial arteriovenous malformations using Onyx: the role of new embolization techniques on patient outcomes | SpringerLink. Accessed February 13, 2023. <https://link.springer.com/article/10.1007/s00234-016-1666-1>
219. Rodriguez-Calienes A, Bustamante-Paytan D, Camacho-Caballero K, Mayoria-Vargas A, Rodríguez-Varela R, Saal-Zapata G. Single-center experience with endovascular treatment of cerebral arteriovenous malformations with intent to cure in pediatric patients. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 2022;38(2):343-351. doi:10.1007/s00381-021-05376-5
220. Rodriguez-Calienes A, Bustamante-Paytan D, Camacho K, Mayoria-Vargas A, Saal-Zapata G, Rodriguez-Varela R. Early Outcomes and Complications of Endovascular Treatment of Cerebral Arteriovenous Malformations in Pediatric Patients. *Pediatr Neurosurg*. 2021;56(2):116-124. doi:10.1159/000513577
221. Aboukais R, Vinchon M, Quidet M, Bourgeois P, Leclerc X, Lejeune JP. Reappearance of arteriovenous malformations after complete resection of ruptured arteriovenous malformations: true recurrence or false-negative early postoperative imaging result? *J Neurosurg*. 2017;126(4):1088-1093. doi:10.3171/2016.3.JNS152846 [doi]
222. Copelan A, Drocton G, Caton MT, et al. Brain Arteriovenous Malformation Recurrence After Apparent Microsurgical Cure. *Stroke*. 2020;51(10):2990-2996. doi:10.1161/STROKEAHA.120.030135
223. Lang SS, Beslow LA, Bailey RL, et al. Follow-up imaging to detect recurrence of surgically treated pediatric arteriovenous malformations. *J NeurosurgeryPediatrics*. 2012;9(5):497-504. doi:10.3171/2012.1.PEDS11453 [doi]
224. Morgenstern PF, Hoffman CE, Kocharian G, Singh R, Stieg PE, Souweidane MM. Postoperative imaging for detection of recurrent arteriovenous malformations in children. *J NeurosurgeryPediatrics*. Published online October 30, 2015:1-7. doi:10.3171/2015.6.PEDS14708 [doi]
225. Morgan MK, Patel NJ, Simons M, Ritson EA, Heller GZ. Influence of the combination of patient age and deep venous drainage on brain arteriovenous malformation recurrence after surgery. *J Neurosurg*. 2012;117(5):934-941. doi:10.3171/2012.8.JNS12351 [doi]
226. Bristol RE, Albuquerque FC, Spetzler RF, Rekate HL, McDougall CG, Zabramski JM. Surgical management of arteriovenous malformations in children. *J Neurosurg*. 2006;105(2 Suppl):88-93. doi:10.3171/ped.2006.105.2.88
227. Jr PK, Rao G, Brockmeyer D. Pediatric arteriovenous malformations: a 15-year experience with an emphasis on residual and recurrent lesions. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 2007;23(1):31-37. doi:10.1007/s00381-006-0245-x [doi]
228. Andaluz N, Myseros JS, Sathi S, Crone KR, Jr JMT. Recurrence of cerebral arteriovenous malformations in children: report of two cases and review of the literature. *Surg Neurol*. 2004;62(4):324-330; discussion 330-1. doi:10.1016/j.surneu.2003.11.030 [doi]
229. Attia W, Tada T, Hongo K, et al. Microvascular pathological features of immediate perinatal parenchyma in cerebral arteriovenous malformations: giant bed capillaries. *J Neurosurg*. 2003;98(4):823-827. doi:10.3171/jns.2003.98.4.0823
230. Stapf C, Connolly E s., Schumacher H c., et al. Dysplastic Vessels After Surgery for Brain Arteriovenous Malformations. *Stroke*. 2002;33(4):1053-1056. doi:10.1161/hs0402.105319
231. Sonstein WJ, Kader A, Michelsen WJ, Llena JF, Hirano A, Casper D. Expression of vascular endothelial growth factor in pediatric and adult cerebral arteriovenous malformations: an immunocytochemical study. *J Neurosurg*. 1996;85(5):838-845. doi:10.3171/jns.1996.85.5.0838
232. Takagi Y, Kikuta KI, Sadamasa N, Nozaki K, Hashimoto N. Proliferative activity through extracellular signal-regulated kinase of smooth muscle cells in vascular walls of cerebral arteriovenous malformations. *Neurosurgery*. 2006;58(4):740-748; discussion 740-748. doi:10.1227/01.NEU.0000192167.54627.3A

233. Takagi Y, Kikuta K ichiro, Nozaki K, Hashimoto N. Early regrowth of juvenile cerebral arteriovenous malformations: report of 3 cases and immunohistochemical analysis. *World Neurosurg.* 2010;73(2):100-107. doi:10.1016/j.surneu.2009.07.008
234. Veldeman M, Rossmann T, Korja M, Laakso A, Lehecka M, Niemelä M. A new home for the Helsinki Neurosurgical Department — closure of Töölö Hospital after 90 years of neurosurgical history. *Acta Neurochir (Wien).* 2022;164(6):1447-1452. doi:10.1007/s00701-022-05202-0
235. Laakso A, Dashti R, Juvela S, Isarakul P, Niemelä M, Hernesniemi J. Risk of hemorrhage in patients with untreated Spetzler-Martin grade IV and V arteriovenous malformations: a long-term follow-up study in 63 patients. *Neurosurgery.* 2011;68(2):372-377; discussion 378. doi:10.1227/NEU.0b013e-3181ffe931
236. Pohjola A, Oulasvirta E, Roine RP, et al. Long-term health-related quality of life in 262 patients with brain arteriovenous malformation. *Neurology.* 2019;93(14):e1374-e1384. doi:10.1212/WNL.00000000000008196
237. Conference IH. Constitution of the World Health Organization. 1946. *Bull World Health Organ.* 2002;80(12):983-984.
238. Kaplan RM, Bush JW. Health-related quality of life measurement for evaluation research and policy analysis. *Health Psychol.* 1982;1:61-80. doi:10.1037/0278-6133.1.1.61
239. Patrick DL, Erickson P. Assessing health-related quality of life for clinical decision-making. In: Walker SR, Rosser RM, eds. *Quality of Life Assessment: Key Issues in the 1990s.* Springer Netherlands; 1993:11-63. doi:10.1007/978-94-011-2988-6\_2
240. Campbell A, Converse PE, Rodgers WL. *The Quality of American Life: Perceptions, Evaluations, and Satisfactions.* Russell Sage Foundation; 1976.
241. Sajid MS, Tonsi A, Baig MK. Health-related quality of life measurement. *Int J Health Care Qual Assur.* 2008;21(4):365-373. doi:10.1108/09526860810880162
242. Hennessy CH, Moriarty DG, Zack MM, Scherr PA, Brackbill R. Measuring health-related quality of life for public health surveillance. *Public Health Rep Wash DC* 1974. 1994;109(5):665-672.
243. Guyatt GH, Feeny DH, Patrick DL. Measuring Health-Related Quality of Life. *Ann Intern Med.* 1993;118(8):622-629. doi:10.7326/0003-4819-118-8-199304150-00009
244. Patrick DL, Deyo RA. Generic and Disease-Specific Measures in Assessing Health Status and Quality of Life. *Med Care.* 1989;27(3):S217.
245. Guyatt GH, Bombardier C, Tugwell PX. Measuring disease-specific quality of life in clinical trials. *CMAJ Can Med Assoc J.* 1986;134(8):889-895.
246. Bullinger M. Indices versus profiles — advantages and disadvantages. In: Walker SR, Rosser RM, eds. *Quality of Life Assessment: Key Issues in the 1990s.* Springer Netherlands; 1993:209-220. doi:10.1007/978-94-011-2988-6\_12
247. Shan LL, Wang J, Westcott MJ, Tew M, Davies AH, Choong PF. A Systematic Review of Cost-Utility Analyses in Chronic Limb-Threatening Ischemia. *Ann Vasc Surg.* 2022;85:9-21. doi:10.1016/j.avsg.2022.04.036
248. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. *Ann Med.* 2001;33(5):328-336. doi:10.3109/07853890109002086
249. Brooks R. EuroQol: the current state of play. *Health Policy Amst Neth.* 1996;37(1):53-72. doi:10.1016/0168-8510(96)00822-6
250. Stewart AL, Hays RD, Ware JE. The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care.* 1988;26(7):724-735. doi:10.1097/00005650-198807000-00007
251. Hunt SM, McKenna SP, McEwen J, Williams J, Papp E. The Nottingham Health Profile: subjective health status and medical consultations. *Soc Sci Med [A].* 1981;15(3 Pt 1):221-229. doi:10.1016/0271-7123(81)90005-5
252. Luschka H von. *Die Adergeflechte Des Menschlichen Gehirnes: Eine Monographie.* G. Reimer; 1855. Accessed February 13, 2023. <https://catalog.hathitrust.org/Record/000911130>
253. Dandy We. Rontgenography of the brain after the injection of air into the spinal canal. *Ann Surg.* 1919;70(4):397-403.

- doi:10.1097/00000658-191910000-00004
254. Leeds NE, Kieffer SA. Evolution of diagnostic neuroradiology from 1904 to 1999. *Radiology*. 2000;217(2):309-318. doi:10.1148/radiology-217.2.r00nv45309
  255. Donaghy RM. The history of microsurgery in neurosurgery. *Clin Neurosurg*. 1979;26:619-625. doi:10.1093/neurosurgery/26.cn\_suppl\_1.619
  256. Kriss TC, Kriss VM. History of the Operating Microscope: From Magnifying Glass to Microneurosurgery. *Neurosurgery*. 1998;42(4):899.
  257. Ambrose J. Computerized transverse axial scanning (tomography). 2. Clinical application. *Br J Radiol*. 1973;46(552):1023-1047. doi:10.1259/0007-1285-46-552-1023
  258. Yaşargil MG, Jain KK, Antic J, Laciga R. Arteriovenous malformations of the splenium of the corpus callosum: microsurgical treatment. *Surg Neurol*. 1976;5(1):5-14.
  259. Ringertz H, Hamberger B, Terenius L. [Peter C Lauterbur and Peter Mansfield. Winners of the 2003 Nobel Prize in medicine or physiology. Magnetic resonance imaging—a breakthrough in clinical medicine and research]. *Lakartidningen*. 2003;100(41):3198-3201.
  260. Hawkes RC, Holland GN, Moore WS, Worthington BS. Nuclear magnetic resonance (NMR) tomography of the brain: a preliminary clinical assessment with demonstration of pathology. *J Comput Assist Tomogr*. 1980;4(5):577-586. doi:10.1097/00004728-198010000-00001
  261. Da F, L C, J H, M A, J W. Pulsatile blood velocity in human arteries displayed by magnetic resonance imaging. *Radiology*. 1984;153(1). doi:10.1148/radiology.153.1.6473779
  262. Iihara K, Satow T, Matsushige T, et al. Hybrid operating room for the treatment of complex neurovascular and brachiocephalic lesions. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc*. 2013;22(8):e277-285. doi:10.1016/j.jstrokecerebrovasdis.2012.07.014
  263. Törmä T. [Aarno Snellman, the pioneer of modern neurosurgery in Finland and the founder of the Neurosurgical Clinic of Helsinki University Hospital]. *Hippokrates Hels Finl*. 1994;11:84-94.
  264. Törmä T. Perspectives in International Neurosurgery: Neurosurgery in Finland. *Neurosurgery*. 1981;9(4):479.
  265. Troupp H. Gunnar af Björkesten in Memoriam. *Acta Neurochir (Wien)*. 1974;31(1):139-142. doi:10.1007/BF01432790
  266. Alanne S, Roine RP, Räsänen P, Vainiola T, Sintonen H. Estimating the minimum important change in the 15D scores. *Qual Life Res*. 2015;24(3):599-606. doi:10.1007/s11136-014-0787-4
  267. Kellner CP, McDowell MM, Phan MQ, et al. Number and location of draining veins in pediatric arteriovenous malformations: association with hemorrhage. *J Neurosurgery Pediatrics*. 2014;14(5):538-545. doi:10.3171/2014.7.PEDS13563 [doi]
  268. Ma L, Huang Z, Chen XL, et al. Periventricular Location as a Risk Factor for Hemorrhage and Severe Clinical Presentation in Pediatric Patients with Untreated Brain Arteriovenous Malformations. *AJNR American J Neuroradiol*. 2015;36(8):1550-1557. doi:10.3174/ajnr.A4300 [doi]
  269. Fok EW, Poon WL, Tse KS, et al. Angiographic factors associated with haemorrhagic presentation of brain arteriovenous malformation in a Chinese paediatric population. *Hong Kong Med J Xianggang Yi Xue Za Zhi Hong Kong Acad Med*. 2015;21(5):401-406. doi:10.12809/hkmj144339 [doi]
  270. Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. *Neurology*. 2016;87(11):1118-1123. doi:10.1212/WNL.00000000000003091
  271. Pohjola A, Lindbohm JV, Oulasvirta E, et al. Cigarette Smoking Is More Prevalent in Patients With Brain Arteriovenous Malformations Compared to General Population: A Cross-Sectional Population-Based Study. *Neurosurgery*. 2020;87(6):E657-E662. doi:10.1093/neuros/nyaa281
  272. Spetzler RF, Hargraves RW, McCormick PW, Zabramski JM, Flom RA, Zimmerman RS. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. *J Neurosurg*. 1992;76(6):918-923. doi:10.3171/jns.1992.76.6.0918 [doi]
  273. Kim H, Salman RAS, McCulloch CE, Stapf C, Young WL, Coinvestigators M. Untreated

- brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. *Neurology*. 2014;83(7):590-597. doi:10.1212/WNL.0000000000000688 [doi]
274. LoPresti MA, Ravindra VM, Pyarali M, et al. Pediatric intracranial arteriovenous malformations: a single-center experience. *J Neurosurg Pediatr*. 2019;25(2):151-158. doi:10.3171/2019.9.PEDS19235
  275. Chin LS, Raffel C, Gonzalez-Gomez I, Giannotta SL, McComb JG. Diffuse arteriovenous malformations: a clinical, radiological, and pathological description. *Neurosurgery*. 1992;31(5):863-868; discussion 868-9.
  276. Tay L, Kuykendall L, Diener E. Satisfaction and Happiness – The Bright Side of Quality of Life. In: Glatzer W, Camfield L, Møller V, Rojas M, eds. *Global Handbook of Quality of Life: Exploration of Well-Being of Nations and Continents*. International Handbooks of Quality-of-Life. Springer Netherlands; 2015:839-853. doi:10.1007/978-94-017-9178-6\_39
  277. Ebrahim S. Clinical and public health perspectives and applications of health-related quality of life measurement. *Soc Sci Med* 1982. 1995;41(10):1383-1394. doi:10.1016/0277-9536(95)00116-o
  278. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? *Pharmacoeconomics*. 2016;34(7):645-649. doi:10.1007/s40273-016-0389-9
  279. Kettlewell N, Morris RW, Ho N, Cobb-Clark DA, Cripps S, Glozier N. The differential impact of major life events on cognitive and affective wellbeing. *SSM - Popul Health*. 2020;10:100533. doi:10.1016/j.ssmph.2019.100533
  280. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioral plasticity after early brain insult. *Brain*. 2011;134(8):2197-2221. doi:10.1093/brain/awr103
  281. Anderson V, Jacobs R, Spencer-Smith M, et al. Does early age at brain insult predict worse outcome? Neuropsychological implications. *J Pediatr Psychol*. 2010;35(7):716-727. doi:10.1093/jpepsy/jsp100
  282. Sorenson TJ, Brinjikji W, Bortolotti C, Kaufmann G, Lanzino G. Recurrent Brain Arteriovenous Malformations (AVMs): A Systematic Review. *World Neurosurg*. 2018;116:e856-e866. doi:10.1016/j.wneu.2018.05.117
  283. Chu M, Guo J, Chen CY. Long-term Exposure to Nicotine, via Ras Pathway, Induces Cyclin D1 to Stimulate G1 Cell Cycle Transition\*. *J Biol Chem*. 2005;280(8):6369-6379. doi:10.1074/jbc.M408947200
  284. Pawlikowska L, Poon KYT, Achrol AS, et al. Apolipoprotein E epsilon 2 is associated with new hemorrhage risk in brain arteriovenous malformations. *Neurosurgery*. 2006;58(5):838-843; discussion 838-843. doi:10.1227/01.NEU.0000209605.18358.E5
  285. Kim H, Hysi PG, Pawlikowska L, et al. Common variants in interleukin-1-Beta gene are associated with intracranial hemorrhage and susceptibility to brain arteriovenous malformation. *Cerebrovasc Dis Basel Switz*. 2009;27(2):176-182. doi:10.1159/000185609
  286. Weinsheimer SM, Xu H, Achrol AS, et al. Gene expression profiling of blood in brain arteriovenous malformation patients. *Transl Stroke Res*. 2011;2(4):575-587. doi:10.1007/s12975-011-0103-3
  287. Cheng P, Ma L, Shaligram S, et al. Effect of elevation of vascular endothelial growth factor level on exacerbation of hemorrhage in mouse brain arteriovenous malformation. *J Neurosurg*. 2019;132(5):1566-1573. doi:10.3171/2019.1.JNS183112
  288. Burkhardt JK, Lasker GF, Winkler EA, Kim H, Lawton MT. Microsurgical resection of brain arteriovenous malformations in the elderly: outcomes analysis and risk stratification. *J Neurosurg*. 2018;129(5):1107-1113. doi:10.3171/2017.6.JNS17392
  289. Pabaney AH, Reinard KA, Kole MK, Seyfried DM, Malik GM. Management of arteriovenous malformations in the elderly: a single-center case series and analysis of outcomes. *J Neurosurg*. 2016;125(1):145-151. doi:10.3171/2015.6.JNS15293
  290. Cooke DL, Frieden IJ, Shimano KA. Angiographic Evidence of Response to Trametinib Therapy for a Spinal Cord Arteriovenous Malformation. *J Vasc Anom*. 2021;2(3):e018. doi:10.1097/JOVA.0000000000000018

