pediatric stroke

The Use of Triptans in Pediatric Vascular Malformations: A Review and Recommendation

Ashley Miller, DO; Eric Remster, MD; Ishani Kumar, MD; Mathew Stokes, MD

Corresponding author: Ashley Miller, DO, 612-210-0674, ashleykay080@gmail.com

5632 Carvel Ave, Indianapolis, IN, 46220, ORCID 0009-0005-2803-1938

Eric Remster: eric.remster@utsouthwestern.edu 0000-0003-0412-6885

Ishani Kumar: ishani.kumar@utsouthwestern.edu 0000-0002-3827-9786

Mathew Stokes: mathew.stokes@utsouthwestern.edu 0000-0001-8655-9814

Competing Interest/Conflict of Interest: none

Introduction

Patients with vascular malformations often have headaches, more specifically, migraine headaches. Many clinicians are uncomfortable prescribing headache abortive medications given possible adverse effects. About 50% of the time over the counter analgesics provide insufficient control of

Cavernous malformation, triptan, headache, migraine, vascular

Pediatr Stroke. 2024;10: 86-102

www.pediatricstrokejournal.com

headache pain and providers find themselves in a difficult position recommending migraine specific medications like triptans[1]. Historically, the concern with triptan usage was risk of ischemia[2, 3].

To better understand why the usage of triptan medications for migraine headaches have been avoided in patients with vascular malformations, it is prudent to understand the pathophysiology of a migraine headache attack. Migraine headaches are described in four phases: premonitory, aura, headache, and postdrome. Migraine headaches can be spontaneous or triggered. Cortical spreading depression activates trigeminal afferents that results in an inflammatory cascade in the meninges. The trigeminal ganglion and cervical dorsal roots project to the vessels, dura, and venous sinuses. The periaqueductal grey and raphe nucleus sends projections to the nucleus caudalis, which then sends projections to the ventral posteromedial nucleus, sensory cortex, and many other parts of the brain. There is a release of substance P, calcitonin gene related peptide (CGRP), and vasoactive intestinal peptide (VIP) that causes neurogenic inflammation and results in sensitization and field expansion[4, 5]. This understanding of pathophysiology was a paradigm shift from the original theory that migraine headaches were a purely vascular phenomenon from blood vessel dilation.

Triptans were a revolutionary addition to the management of migraine headaches in 1992. They are selective 5-hydroxytryptophan 1B/D (5-HT) receptor agonists and were believed to act on intracranial blood vessels as well as the trigeminal sensory nerves to cause vasoconstriction and inhibit release of substance P and CGRP[6, 7].

With further research, we have gained new insights into the mechanism of triptans. 5-HT1B receptors are found in smooth muscle and endothelium of the middle meningeal and cerebral arteries. The triptan effect on vessels has been studied over the years with intra-arterial Xenon[133] blood flow studies, transcranial doppler sonography, and magnetic resonance angiography (MRA) head imaging. In 1981, Oleson et al. studied regional cerebral blood flow changes during migraine attacks and noted that focal hyperemia and spreading oligemia was not vascular territory specific and more likely a neurogenic phenomenon than true ischemia[2, 8]. Transcranial doppler studies from a 1991 study by Fribert et al showed that during spontaneous migraine headache in 10 patients with episodic migraine with and without aura, the middle cerebral artery (MCA) velocity is lower than the non-headache side and returned to normal after treatment with intravenous sumatriptan[9]. A 2003 study by Thomaides et al studied 45 patients with episodic migraine without aura and showed that nitroglycerin-induced migraine attacks resulted in statistically significant vasodilation in migraine patients, but not in the control group that did not have baseline migraine headaches. There was measurable increase in velocities indicating vasoconstriction after being given zolmitriptan or sumatriptan[10]. These studies conclude that triptans act on pathologically distended vessels. A review by Benemei et al in 2017 went on to summarize two points: 1) that during spontaneous and CGRP induced migraine attacks, MRA imaging shows dilation of the middle meningeal artery (MMA) more than the MCA on the painful side of the head and 2) that the MCA and cerebral internal carotid artery (ICA) are unaffected by sumatriptan infusion, and instead, the MMA and superficial temporal artery (STA) showed vasoconstriction[11]. While the latter two studies

do have some conflicting data, they suggest that vasoconstriction caused by triptans is to normalize the dilated vessel, not cause vasoconstriction beyond normal.

Four of the seven triptans have been FDA approved in pediatrics. Rizatriptan dissolving tablets are approved for children six years and older, while sumatriptan/naproxen combination tablets, almotriptan tablets, and zolmitriptan nasal spray are approved for 12 years and above[7, 12]. While highly efficacious, there are also quite a few contraindications that providers must be aware of (see Table 1).

Table 1: Contraindications to triptan usage according to Imitrex (sumatriptan) package insert 2020[13]

Cardiac	Vascular	Medications	Other
Coronary artery disease	Transient ischemic attack	Usage of another ergotamine or 5-HT1 agonist within 24 hours	Allergy to medication
Vasospasm (e.g. Prinzmetal angina)	Hemiplegic/basilar migraine	Concurrent or recent (two weeks) usage of MAO-A inhibitors	Severe hepatic impairment
Accessory conduction pathway disorders (e.g Wolff Parkinson-White syndrome)	Stroke including ischemic, cerebral hemorrhage, and subarachnoid hemorrhage		Do not use more than 10x monthly -increases risk of serotonin syndrome
	Peripheral vascular disease		Caution in history of seizure
	Ischemic bowel disease		
	Uncontrolled hypertension		

Case

An 11-year-old female with no past medical history was seen by neurology for two episodes of left arm jerking, pain, and numbness with retained awareness lasting five minutes followed by weakness. Routine electroencephalogram (EEG) was normal and brain magnetic resonance image (MRI) with and without contrast was notable for bilateral precentral gyrus cavernomas, right > left. The right cavernoma had a recent hemorrhage (see figure 1). She was admitted for neurosurgical observation and levetiracetam was started with reduction of left arm jerking and sensory changes to once monthly. She followed up in neurosurgery clinic six months later and reported seizure

freedom but was having once weekly headaches lasting up to three days with vomiting. Repeat brain MRI showed bleeding and edema of the left cavernoma.

Six months after her neurosurgery clinic appointment, she presented to the emergency department (ED) with altered mental status, headache, and gait difficulty and was found to have left leg numbness and weakness. She also had an episode of right arm numbness and weakness with word finding difficulty and MRI brain showed bleeding of bilateral cavernomas with enlargement of both malformations (see figure 2). Neurosurgery's plan was to move forward with cavernoma resection after edema resolved, monitoring with MRI brain every two to three months.

Due to difficulty with seizure control the decision was made to resect the right cavernoma. One month post procedure she was seizure and headache free on levetiracetam 2500mg/day and oxcarbazepine 1200mg/day. Repeat imaging two months post operatively showed decreased size of the left cavernoma and decreased edema of bilateral cavernomas.

Three years later, at age 15, she was seen in pediatric headache clinic. She described multiple years of headaches with an increase to 20 headache days in the past month. Headaches were described as left moderately severe temporal tightness, neck pain, photophobia and phonophobia, vomiting, and dizziness consistent with migraine without aura. She had a second type of headache described as stabbing occurring daily for two months that resolved with daily extended-release verapamil 240mg. Her MRI brain studies were stable over the previous year and a half. She started amitriptyline 10mg nightly and propranolol 20mg twice daily for migraine headache prevention and was given rizatriptan 10mg for as needed migraine headache rescue usage. At four month follow up headaches had reduced to about two migraine headaches per month and amitriptyline was stopped. Rizatriptan was effective in improving migraine headache within 15 minutes. Genetic testing was recommended but declined by family.

Over 4.5 years this patient had three episodes of symptomatic bleeding of the right CM resulting in resection and three episodes of bleeding of the left CM, one of which was symptomatic. She had a total of 11 MRIs where six showed increased CM size and she was symptomatic about 50% of the time.

Cavernous malformation, triptan, headache, migraine, vascular

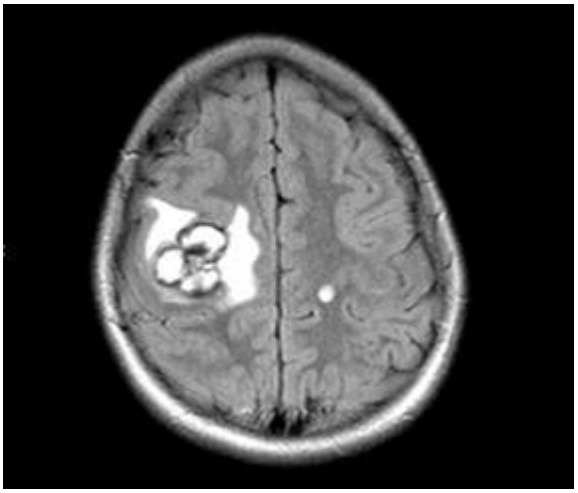

Figure 1: Initial brain MRI T2 flair with contrast image of bilateral cavernomas.

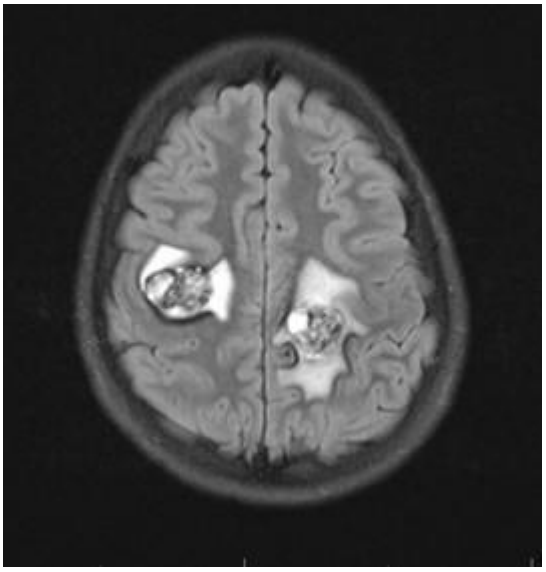

Figure 2: Pre-operative brain MRI T2 image

Discussion

While the prevalence of vascular malformations is small, migraine headaches are common in children (10%)[14]. It is often challenging for clinicians to differentiate between a primary headache like migraine and migraine-like headaches from a vascular entity. Given this difficulty, it is important

to discuss the pathophysiology of each vascular entity and understand the benefits, consequences, and unknowns of prescribing migraine specific medications like triptans.

Cavernous Malformations

Cavernous malformations (CMs) are characterized by low flow sinusoidal channels that do not have brain parenchyma between the vessels. CMs occur in 0.5% of the pediatric population, similar to adults, with 65% CMs being asymptomatic. Most CMs arise in the supratentorial and subcortical regions[15, 16, 17]. Due to the lack of elastin and smooth muscle they are at high risk of bleeding, which can result in parenchymal inflammation, gliosis, and hemosiderin deposition. Pediatric annual hemorrhage rates have been noted to range between 0.7-6% with an overall rate of 3.3% in comparison to a 2.5% risk of hemorrhage in the adult population[15, 16].

CMs are often sporadic, but in patients with multiple CMs, there is a possibility of autosomal dominant inheritance occurring around 84% of the time. There are three genes known to cause familial CM: CCM1, CCM2, and CCM3[15, 16, 18].

In the pediatric population, the mean age of diagnosis is 10 years old and 45% develop symptoms. Symptomatic patients typically present with headache, seizure, altered mental status, or other focal neurologic deficits[19]. Hemorrhagic clustering, dural venous anomalies, and brain stem location are the greatest risk factors for prospective hemorrhage, whereas family history, number of CMs, age, and sex does not appear to increase risk.

CMs are typically managed conservatively as was initially done in our patient case. However, in patients with frequent bleeds, higher symptom burden; particularly medically refractory seizures, location, and size; then microsurgery or stereotactic radiosurgery should be considered[20].

The concern with the usage of triptans, especially in patients with vascular malformations, is ischemic events. For patients with CMs, the goal of management is to limit intracranial bleeding, both symptomatic and asymptomatic. In a prospective study from 2015-2020, Flemming et al. identified 329 adult patients with CMs of which 50% were female, 28.6% had multiple CMs, and 27.5% had headache. 8.8% of the patients reported triptan usage and there was not a statistically significant increased risk of hemorrhage between patients taking triptans and patients not taking triptans. They identified that younger age at presentation and initial presentation with hemorrhage or brainstem hemorrhage increased risk of future hemorrhage. There is also a theory that because CMs do not contain smooth muscle, they are not subject to vasospasm and thus would not increase rates of hemorrhage[21].

Arteriovenous malformations

Another vascular malformation and the most common cause of pediatric brain hemorrhage are arteriovenous malformations (AVMs) with a prevalence rate of 0.02% (0.5-1% in adults)[22, 23]. AVMs are vascular networks that lack a capillary bed and subsequently result in high flow shunting of blood between an artery and a vein[24]. The prevalence of headaches in pediatric patients with AVMs is lacking, however, we do know that the headache prevalence (both non-hemorrhagic and

hemorrhagic) is highly variable in adult patients. Headache is present in 14-79% of adult patients with AVMs and is the presenting symptom 9-70% of the time. 61% of these patients had non-hemorrhagic headaches. According to ICHD-3 criteria this is a headache that developed in temporal relationship to the AVM and is localized to the site of AVM[25]. The most common headache phenotype in patients with AVMs is migraine with aura. Of note, patients with occipital AVMs are more likely to develop migraine with aura[21].

Management is resection, radiosurgery, or embolization[24]. Evidence on recurrence rates is conflicting. In the 2022 retrospective series by Hak et al, AVMs treated in the pediatric population recurred 15% of the time[22]. Conversely, a 2023 study by Oulasvirta et al. identified a 4.9% recurrence rate, in comparison to adult populations (~3%)[26]. Treatment of AVMs does not always result in improvement in headaches and an adult study showed that 8% of patients noted worsening and 54% had no change[22, 24, 27, 28]. There is very limited literature about triptan usage in adult patients with AVMs and none in pediatrics. Henkes et al. studied the effects of subcutaneous or middle meningeal intra-arterial sumatriptan in nine non-migraine patients with AVMs and two dural arteriovenous fistulas (dAVFs) noted that patients with the middle meningeal artery as a feeder artery resisted vasoconstriction[29]. The support for usage of triptans in this patient population is largely clinical observation of recently diagnosed patients that have been using triptans for years without adverse events. The theory behind the safety is the high flow nature of AVMs prevents any potential triptan induced vasoconstriction[3].

Intracranial aneurysms

The occurrence rate is 0.5-4.6% in pediatrics with a rupture rate of 0.6%[30, 31]. They are characterized as weakened dilatations in the vessel wall. Internal carotid and middle cerebral aneurysms happen at about the same frequency as adults, while anterior cerebral are less common, and posterior circulation are more common[30]. Of the different types of aneurysms, saccular aneurysms are more likely to rupture than fusiform or infectious due to the lack of elastin and smooth muscle[32]. Unruptured aneurysms can increase the prevalence of migraine without aura (42.2% vs 8.8%)[2].

In patients with aneurysms, the concern is rupture and subarachnoid hemorrhage (SAH) and this is the presenting symptom 20-72% of the time (89% in adults) with rebleeding happening half the time (16-29% in adults)[31]. The question is often posed how to differentiate between headache related to subarachnoid hemorrhage and that of migraine. SAH is associated with thunderclap headache, with sudden onset within 60 seconds and severity out of proportion to other headaches. Conversely, migraines develop over minutes to hours. Like migraine, SAH can be associated with nausea, vomiting, neck pain, visual field defects, and sensory changes. Photophobia is rarer in SAH than in migraine, and contrary to migraine without aura, patients with SAH can have focal neurologic deficits[33]. In a study of 63 patients with a sudden and severe onset of headache, 73% had SAH[34]. A 1999 prospective study by Quinn et al. of sumatriptan usage by 12,339 migraineurs ages 16-82 reported no associated intracranial hemorrhage including a subset of 41 patients with a prior history of stroke or TIA[35]. There was a case study of a 28-year-old patient who used daily rizatriptan for 15 years found to have three unruptured intracranial aneurysms, the largest being 18mm[36].

Another case of 10 pre-coiled and 10 post coiled adult patients had no incidences reported[37]. In cases of triptan usage in the setting of aneurysms pre or post-repair, it is proposed that triptan vasoconstrictive action returns vascular tone to normal during a migraine, instead of constricting beyond baseline[2].

Dural arteriovenous fistulas

Dural arteriovenous fistulas (dAVF) are characterized by connections between the branches of the carotid and vertebral arteries and the dural venous sinuses, most commonly at the transverse-sigmoid junction[38,39]. In a retrospective study of 17 patients by Zaidi et al. 17.6% presented with headache[40]. In an adult study of 40 patients by Corbelli et al. the presenting symptom is migraine-like headache 45.2% of the time with 16.7% having a history of a migraine headache diagnosis[39]. Triptans have also been used with successful reduction in headache severity and intensity and no evidence of negative outcomes in a few adult case studies with a 47, 69, and 79-year-old female with cavernous sinus dural arteriovenous fistulas[41, 42, 43]. It is proposed that if triptans do cause extracranial, not intracranial vasoconstriction, then there would be a reduction of shunting through the dAVF resulting in improvement in headache[41].

Hemiplegic migraine and migraine with brainstem aura

It has been established that migraine with aura doubles the risk of ischemic stroke[3]. This was previously thought to be supported by the vascular theory of migraine, now replaced with the theory of cortical spreading depression. It was also previously proposed that hemiplegic migraine and migraine with brainstem aura had a higher likelihood of stroke and that triptan usage would further exacerbate this risk.

Hemiplegic migraine is a rare migraine with aura subtype. ICHD-3 criteria define it as migraine with aura, but the aura is described as fully reversible visual, sensory, speech/language symptoms as well as fully reversible motor weakness. This motor weakness can last days to weeks, but more commonly it is 20-60 minutes[25,44]. The onset of symptoms is around age 12-17. It is sporadic or familial, with three autosomal dominant subtypes being associated with the following genes: familial hemiplegic migraine (FHM) type 1: CACNA1A, FHM type 2: ATP1A2, and FHM type 3: SCN1A. These mutations are thought to increase cortical spreading depression. Patients with hemiplegic migraine have been excluded from triptan cases due to concern for increased risk of stroke compared to typical migraine with aura[44,45].

Migraine with brainstem aura is another subtype of migraine with aura with at least two of the following reversible brainstem symptoms: dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, or decreased level of consciousness as well as no motor or retinal symptoms[25]. The pathophysiology originally suggested was basilar artery vasoconstriction, although there is no evidence to suggest this[45].

To this day, triptan labeling maintains a contraindication for hemiplegic migraine and migraine with brainstem aura. In the 2016 study of adults by Mathew et al, 67 patients with migraine with

brainstem aura and 13 patients with hemiplegic migraine were successfully treated with sumatriptan or dihydroergotamine without any ischemic events[45]. In a 2020 paper by Yamanaka et al, two pediatric patients with brainstem aura, one with hemiplegic migraine, and one with retinal migraine were all treated with triptans without adverse events[46].

As we learn more about the pathophysiology of migraine, the consensus has moved away from the original vascular theory. This has led to widening the usage parameters of triptans to include patients with hemiplegic migraine, migraine with brainstem aura, and other secondary vascular related headaches with migraine phenotypes that were initially thought to have contraindications to triptan usage.

Table 2: Summary of data on triptan use in vascular patients

Reference	# of patients	Prospective bleeding risk (%)	Comments
Cavernous malformations			
Flemming et al.[21]	N=29	5.4%, p value =.18	No reports of triptans causing CM hemorrhage
Arteriovenous malformations			
Henkes et al.[29]	N=9	Not reported	Transient vasoconstriction did not result in bleeds in any patients
Aneurysm			
Quinn et al.[35]	N=12, 339	0%	Stroke N=6 TIA with recurrent TIA N= 1/41
Benndorf et al[36]	N=1	0%	Daily triptan usage without rupture of 3 intracranial aneurysms
Baron et al[37]	N=20	0%	Triptans used pre and post coil
Dural AV fistula			
Osaka et al[41]	N=1	0%	Triptans not required after transvenous embolization

Saiki et al[42]	N=1	0%	
Yamada et al[43]	N=1	0%	Three triptans used
Hemiplegic migraine/migraine with brainstem aura			
Mathew et al[45]	N=45	0%	N=70 had no adverse cerebrovascular events with triptans or DHE
Yamanaka et al[46]	N=7	0%	Pediatric study

Recommendation

Effective abortive treatments like triptan medications are an essential component of migraine management. Clinician triptan usage has been limited in vascular malformations and subtypes of migraine with aura due to concern for increasing the risk of ischemic stroke and hemorrhage. Our knowledge of these potential outcomes is limited to case reports and retrospective studies but has been overall positive with directly related adverse outcomes debatable and exceedingly rare. Considering this, we suggest that these medications may be used safely and effectively, but with caution. If a patient has a headache that is different from their normal headaches either in severity or with associated focal neurologic deficits, a triptan should not be used. If a triptan has been used and the headache continues to progress, then further evaluation is warranted. After the initial hemorrhage of a CM, there is a clustering phenomenon of hemorrhage for two to three years afterwards, and it is reasonable to wait to use triptans until after this period. Our opinion is that triptans are likely safe for usage in pediatric patients with CMs and do not increase the risk of hemorrhage. However, caution is recommended in younger patients, if there is hemorrhage at initial presentation, or the presence of brain stem CM. We also postulate that triptans can be used safely in patients with other vascular findings including secured AVMs, aneurysms, and dAVF with stable imaging, however evidence is limited in adults and scarce in pediatrics. Further studies in pediatric patients would be beneficial and the focus should be on establishing an effective headache prevention medication to reduce the need for usage of triptans.

References

1. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study [published correction appears in Headache. 2007 Oct;47(9):1365]. *Headache*. 2007;47(3):355-363. doi:10.1111/j.1526-4610.2006.00631.x

2. Baron EP. Headache, cerebral aneurysms, and the use of triptans and ergot derivatives. *Headache*. 2015;55(5):739-747. doi:10.1111/head.12562

3 Leroux E, Rothrock J. Triptans for Migraine Patients With Vascular Risks: New Insights, New Options. *Headache*. 2019;59(9):1589-1596. doi:10.1111/head.13656

4. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol*. 2018;17(2):174-182. doi:10.1016/S1474-4422(17)30435-0

5. Khan J, Asoom LIA, Sunni AA, et al. Genetics, pathophysiology, diagnosis, treatment, management, and prevention of migraine. Biomed Pharmacother. 2021;139:111557. doi:10.1016/j.biopha.2021.111557

6. Ahn AH, Basbaum AI. Where do triptans act in the treatment of migraine?. *Pain*. 2005;115(1-2):1-4. doi:10.1016/j.pain.2005.03.008

7. Greene K, Irwin SL, Gelfand AA. Pediatric Migraine: An Update. *Neurol Clin*. 2019;37(4):815-833. doi:10.1016/j.ncl.2019.07.009

8. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. *Ann Neurol*. 1981;9(4):344-352. doi:10.1002/ana.410090406

9. Friberg L, Olesen J, Iversen HK, Sperling B. Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. Lancet. 1991;338(8758):13-17. doi:10.1016/0140-6736(91)90005-a

10. Thomaides T, Karagounakis D, Spantideas A, Katelanis S. Transcranial Doppler in migraine attacks before and after treatment with oral zolmitriptan or sumatriptan. Headache. 2003;43(1):54-58. doi:10.1046/j.1526-4610.2003.03009.x

11. Benemei S, Cortese F, Labastida-Ramírez A, et al. Triptans and CGRP blockade - impact on the cranial vasculature. *J Headache Pain*. 2017;18(1):103. Published 2017 Oct 10. doi:10.1186/s10194-017-0811-5

12. Eiland LS, Hunt MO. The use of triptans for pediatric migraines. Paediatr Drugs. 2010;12(6):379-389. doi:10.2165/11532860-000000000-00000

13. Imitrex (sumatriptan) package insert; GlaxoSmithKline; 2020.

14. Onofri, A., Pensato, U., Rosignoli, C. *et al.* Primary headache epidemiology in children and adolescents: a systematic review and meta-analysis. *J Headache Pain* **24**, 8 (2023). https://doi.org/10.1186/s10194-023-01541-0

15. Al-Holou WN, O'Lynnger TM, Pandey AS, et al. Natural history and imaging prevalence of cavernous malformations in children and young adults. *J Neurosurg Pediatr*. 2012;9(2):198-205. doi:10.3171/2011.11.PEDS11390

16. Paddock M, Lanham S, Gill K, Sinha S, Connolly DJA. Pediatric Cerebral Cavernous Malformations. *Pediatr Neurol*. 2021;116:74-83. doi:10.1016/j.pediatrneurol.2020.11.004

17. Tasiou A, Brotis AG, Kalogeras A, et al. Cavernous malformations of the central nervous system: An international consensus statement. *Brain Spine*. 2023;3:102707. Published 2023 Nov 10. doi:10.1016/j.bas.2023.102707

18. Ghali MG, Srinivasan VM, Mohan AC, Jones JY, Kan PT, Lam S. Pediatric cerebral cavernous malformations: Genetics, pathogenesis, and management. Surg Neurol Int. 2016;7(Suppl 44):S1127-S1134. Published 2016 Dec 28. doi:10.4103/2152-7806.196921

19. Zyck S, Gould GC. Cavernous Venous Malformation. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; March 27, 2023.

20. Lee JW, Kim DS, Shim KW, et al. Management of intracranial cavernous malformation in pediatric patients. *Childs Nerv Syst*. 2008;24(3):321-327. doi:10.1007/s00381-007-0465-8

21. Flemming KD, Chiang C-C, Brown RD, Lanzino G. Safety of select headache medications in patients with cerebral and spinal cavernous malformations. Cephalalgia Reports. 2021;4. doi:10.1177/25158163211062254

22. Hak JF, Boulouis G, Kerleroux B, et al. Pediatric brain arteriovenous malformation recurrence: a cohort study, systematic review and meta-analysis. *J Neurointerv Surg*. 2022;14(6):611-617. doi:10.1136/neurintsurg-2021-017777

23. Rani, D., Kumar, M., Jain, M., & Kochhar, A. Cerebral Arteriovenous Malformation in a Pediatric Patient with Severe Systemic Hypertension. *Journal of Neuroanaesthesiology and Critical Care*. 2024.

24. Ellis JA, Mejia Munne JC, Lavine SD, Meyers PM, Connolly ES Jr, Solomon RA. Arteriovenous malformations and headache. *J Clin Neurosci*. 2016;23:38-43. doi:10.1016/j.jocn.2015.08.003

25. International Headache Society. IHS Classification ICHD-3. Part I: The Primary Headaches, https://ichd-3.org/. 2021.

26. Oulasvirta E, Koroknay-Pál P, Numminen J, et al. Recurrence of brain arteriovenous malformations in pediatric patients: a long-term follow-up study. *Acta Neurochir (Wien)*. 2023;165(6):1565-1573. doi:10.1007/s00701-023-05612-8

27. Dehdashti AR, Thines L, Willinsky RA, et al. Multidisciplinary care of occipital arteriovenous malformations: effect on nonhemorrhagic headache, vision, and outcome in a series of 135 patients. Clinical article. *J Neurosurg*. 2010;113(4):742-748. doi:10.3171/2009.11.JNS09884

28. Lv X, Jiang C, Wang J. Pediatric intracranial arteriovenous shunts: Advances in diagnosis and treatment. *Eur J Paediatr Neurol*. 2020;25:29-39. doi:10.1016/j.ejpn.2019.12.025

29. Henkes H, May A, Kühne D, Berg-Dammer E, Diener HC. Sumatriptan: vasoactive effect on human dural vessels, demonstrated by subselective angiography. *Cephalalgia*. 1996;16(4):224-230. doi:10.1046/j.1468-2982.1996.1604224.x

30. Jian BJ, Hetts SW, Lawton MT, Gupta N. Pediatric intracranial aneurysms. *Neurosurg Clin N Am*. 2010;21(3):491-501. doi:10.1016/j.nec.2010.03.005

31. Sorteberg A, Dahlberg D. Intracranial Non-traumatic Aneurysms in Children and Adolescents. *Curr Pediatr Rev*. 2013;9(4):343-352. doi:10.2174/221155281120100005

32. Levy ML, Levy DM, Manna B. Pediatric Cerebral Aneurysm. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537085/

33. Ostergaard JR. Headache as a warning symptom of impending aneurysmal subarachnoid haemorrhage. *Cephalalgia*. 1991;11(1):53-55. doi:10.1046/j.1468-2982.1991.1101053.x

34. Duffy GP. The "warning leak" in spontaneous subarachnoid haemorrhage. *Med J Aust*. 1983;1(11):514-516. doi:10.5694/j.1326-5377.1983.tb136193.x

35. O'Quinn S, Davis RL, Gutterman DL, Pait GD, Fox AW. Prospective large-scale study of the tolerability of subcutaneous sumatriptan injection for acute treatment of migraine. *Cephalalgia*. 1999;19(4):223-200. doi:10.1046/j.1468-2982.1999.019004223.x

36. Benndorf G, Naeini RM, Lehmann TN. Triple carotid aneurysms in a patient with migraine attacks. *J Neurol Neurosurg Psychiatry*. 2004;75(7):993. doi:10.1136/jnnp.2004.037168

37. Baron EP, Moskowitz SI, Tepper SJ, et al. Headache following intracranial neuroendovascular procedures. *Headache*. 2012;52(5):739-748. doi:10.1111/j.1526-4610.2011.02059.x

38. Zyck S, De Jesus O, Gould GC. Dural Arteriovenous Fistula. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; August 23, 2023.

39. Corbelli I, De Maria F, Eusebi P, et al. Dural arteriovenous fistulas and headache features: an observational study. *J Headache Pain*. 2020;21(1):6. Published 2020 Jan 16. doi:10.1186/s10194-020-1073-1

40. Zaidi HA, Kalani MY, Spetzler RF, McDougall CG, Albuquerque FC. Multimodal treatment strategies for complex pediatric cerebral arteriovenous fistulas: contemporary case series at Barrow Neurological Institute. *J Neurosurg Pediatr*. 2015;15(6):615-624. doi:10.3171/2014.11.PEDS14468

41. Osaka M, Shibata M, Oki K, et al. Clinical utility of triptans in the management of headache attributed to dural arteriovenous fistula involving the cavernous sinus. *J Neurol Sci*. 2015;349(1-2):260-261. doi:10.1016/j.jns.2015.01.011

42. Saiki M, Suzuki K, Takekawa H, et al. *Rinsho Shinkeigaku*. 2018;58(3):188-192. doi:10.5692/clinicalneurol.cn-001118

43. Yamada SM, Masahira N, Shimizu K. A migraine-like headache induced by carotid-cavernous fistula. *Headache*. 2007;47(2):289-293. doi:10.1111/j.1526-4610.2006.00698.x

44. Nandyala A, Shah T, Ailani J. Hemiplegic Migraine. *Curr Neurol Neurosci Rep*. 2023;23(7):381-387. doi:10.1007/s11910-023-01277-z

45. Mathew PG, Krel R, Buddhdev B, et al. A retrospective analysis of triptan and dhe use for basilar and hemiplegic migraine. *Headache*. 2016;56(5):841-848. doi:10.1111/head.12804

46. Yamanaka G, Go S, Morichi S, et al. Clinical Features and Burden Scores in Japanese Pediatric Migraines With Brainstem Aura, Hemiplegic Migraine, and Retinal Migraine. *J Child Neurol*. 2020;35(10):667-673. doi:10.1177/0883073820927840