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A Stepwise Approach to Managing Pediatric Post-Stroke Headache

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Abstract:

Background: Pediatric stroke survivorship is often challenged by a multitude of troublesome disabilities, including headache. Managing headaches in pediatric stroke survivors is complex, and no current guidelines exist. We present recommendations for managing post-stroke headache in the pediatric population, along with some illustrative cases.

Classification/Diagnosis: There is no pediatric definition for post-stroke headache. In our experience, the phenotype is similar to the definitions presented by the International Classification of Headache Disorders, 3rd Edition. Acute post-stroke headache is defined as developing in close temporal proximity to the stroke and resolving in three months. Persistent post-stroke headache continues past three months. It is critical to rule out secondary causes of headache in patients recovering from stroke through comprehensive assessment. A low threshold should be applied for repeating vascular and/or cortical imaging.

Key Management Principles: In the acute phase, analgesics such as acetaminophen, along with antiemetics, can often be used to treat headache pain post-stroke. A similar stepwise approach to treating migraine can be applied for persistent post-stroke headache, with important exceptions. Vasoactive headache medications must be avoided in stroke patients who are vascularly compromised. Headache interventions, such as injection therapies and non-invasive nerve stimulation, may minimize patients' reliance on oral medications. Opioid medications should be avoided, except as a last resort.

1. Introduction:

Stroke is not a common diagnosis for the pediatric age group. According to Pediatric Recommendations from the Canadian Heart and Stroke Foundation, stroke occurs in 2-5 per 100,000 children between the ages of 28 days to 18 years [1]. While rare, those children who experience a pediatric stroke may suffer from associated life-long morbidity and mortality, including chronic pain [2], cognitive and motor impairments [3], and of focus here, headache.

To our knowledge, only two studies have directly investigated post-stroke headaches in children. Mallick et al. [4] found that 20% of children (17 of 84) experienced headaches 1-year following their arterial ischemic stroke. Chelse et al. [5] found the prevalence of new headaches following arterial ischemic stroke in children was 36% (41 of 115) at 6-months follow-up. Compared to an average migraine prevalence of nearly 1 in 10 in the general pediatric population [6], more children recovering from arterial ischemic stroke report experiencing post-stroke headaches.

Understanding the underlying etiology of stroke may be important in determining the etiology of headache, thereby guiding management strategies. Most strokes in children are thought to be a result of 'rare' conditions such as cerebral arteriopathy, congenital heart disease, vascular malformations, vasculitis, and sickle cell disease among others [7, 8]. There are several neurovascular conditions where headache is often a prominent presenting feature for stroke such as craniocervical dissection, cerebral vasculitis, CADASIL and others, which are outlined in Table 1.

Thus, in certain neurovascular conditions the relationship between headache and stroke is postulated to be bidirectional. Adult data has demonstrated an increased risk of ischemic stroke in individuals who have migraine with aura [9]. Similarly in pediatrics, Gefland et al. [10] demonstrated in post-hoc analysis that the risk of ischemic stroke was significantly elevated in adolescents (ages 12-17 years) with migraine. While there remains a paucity of data in the literature, considering the pediatric patient's underlying cause for stroke, and whether headache was a significant compliant pre-stroke, may aid in clinical judgment to stratify a patient's risk for developing post-stroke headache and determine appropriate treatment options.

Post-stroke headache is complex, with management confounded by contraindications in stroke for many of the commonly prescribed vasoactive headache medications. The following text will review recommendations for managing pediatric post-stroke headaches based on clinical experience at the Stollery Children's Hospital in Edmonton, AB, Canada. Our aim is to provide a framework for care providers managing pediatric post-stroke headaches.

2. Defining Post-Stroke Headache

The International Classification of Headache Disorders, 3rd Edition (ICHD-3) defines acute post-stroke headache as *"developing in close temporal relation"* or "*significantly improving in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of stroke*" and resolving within 3 months [11]. Multiple studies have investigated the timeframe for "acute" onset of headache following stroke. Tentschert et al. [12] and Arboix et al. [13] found that headaches developed within the first 72 hours, meanwhile, Verdelho et al. [14] found that headaches usually started on the first day of the stroke but could occur up

to 5 days later. Regardless of the timing of headache onset, if the headache is ongoing past three months, then it surpasses the acute definition and moves to persistent.

The ICHD-3 definition of persistent post-stroke headache is continuing for 3 months following ischemic stroke, nontraumatic intracranial hemorrhage, cervical artery dissection, or reversible cerebral vasoconstriction syndrome [11]. Other stroke types are not included in the definition of persistent post-stroke headache. Importantly, the ICHD-3 definition also excludes patients whose headache is not attributed to stroke but instead to delayed onset of a new persistent headache. Features of the diagnostic criteria from the ICHD-3 for recognizing headache attributed to different stroke types is provided in Table 1.

3. Managing Post Stroke Headache:

3.1 Diagnosis:

The first step in managing post-stroke headache is to identify whether it is the emergence of a primary headache disorder in a post-stroke patient versus a different secondary cause for headache (i.e., due to an aneurysm or stroke recurrence). The SNOOP4 mnemonic is a helpful framework for identifying important secondary causes of headache (see Figure 1). A more extensive explanation of SNOOP4 can be found in Dodick, 2010 [15]. It is critical that secondary headaches are not missed in diagnosis to minimize the potential for recurrent brain injury on top of the patient's already existing injury. It is often under-recognized that stroke patients can continue to have secondary headaches. In accordance with the ICHD-3, which classifies post-stroke headache as a secondary headache attributed to a vascular disorder, we propose the following framework for pediatrics (Figure 2).

3.2 Imaging:

A low threshold for repeating both vascular and cortical imaging should be applied when a patient with stroke history presents with a new onset headache disorder. Even if the patient's headache seems to be more in keeping with a primary headache disorder (which we do not typically image – see Dao and Qubty [13], it is important to repeat imaging to rule out a secondary cause of headache.

4. Illustrative Patient Cases:

The following are examples of pediatric patients who may present with post-stroke headache at a Children's Hospital. The patient's details and demographics are fictional and illustrative.

4.1 Managing acute post stroke headache in an adolescent female

A.B. is a 16 y/o female who presented with a new onset throbbing headache in the bitemporal regions. She started on oral contraception (estrogen-based) 8 weeks prior to her presentation. Computed Tomography (CT) revealed an acute dural venous thrombosis. A.B. was given a migraine cocktail in the emergency room to treat her head pain (maxeran, ondansetron, and ketorolac).

Once admitted, A.B. was assessed by numerous teams including hematology who prescribed unfractionated heparin, eventually transitioning to enoxaparin. In regard to her headache, A.B. was started on morphine and acetaminophen. A repeat CT head and neck angiogram showed overall improvement in the venous sinus thrombosis, with the thrombi now appearing nonocclusive. MR imaging revealed abnormalities in diffusion confirming the presence of a venous infarction. There was a concern for optic disk edema, so A.B. was

switched to acetazolamide (specifically used to reduce increased intracranial pressure caused by venous congestion) and her headache greatly improved. At discharge, acetazolamide was only required at night.

4.2: Managing persistent post stroke headache in an adolescent male

C.D. was a previously healthy 13-year-old male who presented with headaches and confusion following a family fishing trip. His Dad reported that three days prior, he began to complain of headache pain. He was given two Advils and went to bed. Forty-five minutes later, he was found unable to get up and was crying. His Dad also noticed a left-sided mouth droop and drooling. The next day he was sleepy and confused and started to experience emesis. This emesis persisted to the third day, where he developed worsening confusion, a right-sided fine tremor of his arm, and an episode of fecal incontinence. At this point, he was brought to a rural emergency room and diagnosed with migraine, acute otitis media, and a sinus infection. He was given one dose of Toradol and an antibiotics prescription.

After the Toradol wore off, C.D.'s pain returned. He no longer had a fever or ear pain but a prominent droop on the left side of his mouth. Computed Tomography revealed a subacute right ischemic MCA stroke with abnormalities in the region of the right basal ganglia and caudate. C.D. was started on ASA 81 mg PO and was assessed by many in-patient teams. During his admission, C.D. struggled with headaches and photophobia. He was given Tylenol PRN and recommended to wear sunglasses or keep the lights dimmed.

C.D. was eventually discharged with an extensive follow-up plan. He developed persistent post-stroke headaches in the months to years following his stroke. C.D. used Greater Occipital Nerve Blocks (methylprednisolone 125 mg with lidocaine 40mg) with effect

every 8 weeks for one year. Importantly, triptans were contraindicated for C.D. given stroke history and risk for vasospasm. For acute headache treatment, he used diclofenac 50 mg.

After a year, C.D. started developing severe episodes of epistaxis, so he stopped these medications and was switched to a trial of non-NSAID medication (Tramacet 37.5mg-325mg). Unfortunately, Tramacet also stopped working well for this patient as he was experiencing more frequent headaches and was having fewer headache-free days. Compliance was also a challenge. C.D. started amitriptyline 50 mg as a daily preventative medication. He stopped amitriptyline after 3 months because he felt it did not work well and was subsequently lost to follow-up.

5. **Acute-Phase:**

During the acute phase of stroke recovery (<3 months), headache pain is not often a significant clinical complaint unless the patient has markedly increased intracranial pressure [17,18]. Usually, patients are more affected by hemiplegia and other symptoms resulting from the stroke episode, and that becomes the focus of their acute to chronic recovery.

In pediatric patients who do experience headaches during the acute phase, acetaminophen (Tylenol) can be used as an abortive therapy in stroke patients if their liver function is appropriate (Table 2). This recommendation is in keeping with guidelines for the treatment of headaches in adults, which suggest acetaminophen as a first-line agent due to its low risk and associated low cost [19, 20]. Along with being an analgesic, acetaminophen is an antipyretic. It is recommended that antipyretics are prescribed to treat elevated body temperature (>38 degrees °C) in stroke [11, 21]. A common cause of headaches in pediatrics is medication overuse, which most often occurs with simple analgesics like acetaminophen

or ibuprofen [16, 22]. Care providers should ensure that they are screening for medication overuse and counselling patients on proper administration regimens (subsection 8.2 ICHD-3) [11].

Additional medications that may be used acutely include metoclopramide, an antiemetic which acts as a dopamine antagonist in the chemoreceptor trigger zone [23], as well as a peripheral muscarinic agonist to enhance gastrointestinal motility and emptying [24]. A recent meta-analysis demonstrated the efficacy of Metoclopramide 10 mg IV for relieving pediatric migraine attacks, with minimal side effects compared to alternative treatment options [25]. Ondansetron, another antiemetic, also acts on the chemoreceptor trigger zone centrally and vagal nerve terminals peripherally to antagonize 5-HT_3 receptors [26]. A retrospective study investigating acute migraine management in the pediatric emergency department suggested that ondansetron might be comparable to antidopaminergic agents for efficacy in treating pediatric migraine [27]. These antiemetic agents are commonly used in the pediatric emergency department and may also be used to treat acute headaches in stroke patients (Table 3).

Importantly, the authors caution the use of NSAIDs acutely in stroke patients due to their actions of inhibiting platelet function, thereby increasing the tendency for systemic bleeding (as reviewed by Villa Zapata et al. [28]). This is especially relevant in stroke patients who have recently been administered large doses of antiplatelet agents (most often used is acetylsalicylic acid) or any other oral/intravenous anticoagulation. If the above first-line options for acute management of headache in stroke patients is ineffective, we suggest consulting the neurology service at your hospital for administration of greater and/or lesser

occipital nerve blocks or other cranial nerve blocks depending on the location of pain (supratrochlear, supraorbital, auriculotemporal). See Fernandes, Randell, & Idrova [29] for guidance on administering peripheral nerve blocks. Greater Occipital nerve blocks are further discussed in section 9.1.

6. **Chronic phase:**

To treat the chronic phase of post-stroke headache, healthcare providers should follow the same stepwise treatment strategy as with general headache management. This begins with lifestyle and non-pharmacological approaches.

6.1 Lifestyle management:

Lifestyle and non-pharmacological management of headache is critical for post-stroke patients because it avoids using medication in patients who are vascularly compromised. Migraine is very sensitive to homeostatic changes in the body. A resource for Primary Care Physicians on counselling patients on lifestyle modification for migraine management uses the acronym SEEDS for: 1) Sleep Hygiene, 2) Exercise 30 to 60 minutes 3-5 times a week, 3) Eat regular healthy meals, 4) keep a headache Diary, 5) Stress management through cognitive behavioral therapy, mindfulness, and relaxation [30]. Adequate hydration may be especially important in children with moyamoya or other vasculopathies, not only for maintaining vascular perfusion but also given that dehydration may precipitate headache symptoms.

Lifestyle management of chronic migraine also aligns with recommendations for preventing stroke in patients with a previous stroke or transient ischemic attack by the American Heart Association/ American Stroke Association [31]. These recommendations

include smoking cessation, regular aerobic activity, salt restriction, limiting alcohol consumption, and weight management. Adhering to post-stroke risk reduction guidelines will have beneficial effects on the management of post-stroke headaches.

6.2 Nutraceuticals:

Commonly discussed nutraceuticals for migraine include riboflavin, coenzyme Q10, and magnesium (reviewed by Hall, Brand, & Kedia [32]). Evidence for pediatric supplementation with nutraceuticals is more limited. The authors have had the most success using riboflavin supplementation for their chronic migraine patients. However, an important consideration of riboflavin is its associated cost, which must be considered when deciding the best treatments for your patients and their caregivers.

A systematic review of melatonin for migraine found that, while evidence is limited and highly heterogeneous, melatonin is very likely to act as a beneficial migraine prophylaxis [33]. Above and beyond headache pain, melatonin may also be beneficial for stroke recovery due to its neuroprotective effects (reviewed by Sadanandan et al. [34]) and the overall benefits of a more regulated sleep. For this reason, melatonin supplementation may be a good addition to the treatment plan for post-stroke headaches. Suggested pediatric dosing for nutraceuticals is provided in Table 4.

6.3 Mental Health

Common mental health conditions are experienced by both children and their families following recovery from a critical illness such as stroke. Lehman et al. [35] examined emotional outcomes in children (7-18 years) within two years of stroke occurrence, finding that 24% reported depression, 14% reported anxiety, and 6% reported post-traumatic stress

disorder. There are a multitude of challenges associated with stroke recovery in children which may include coping with cognitive and/or physical deficits, academic and social school difficulties, and activity restrictions. Anxiety and depression have been shown to influence the clinical course of migraine, including treatment response [36]. Screening for and treating comorbid mental health conditions is an important consideration in managing post-stroke headaches.

7. Abortive Therapies:

To treat acute headache attacks in stroke patients, we recommend following the American Academy of Neurology and the American Headache Society (AAN/AHS) Practice Guidelines, with a few modifications [37].

7.1 First line: Ibuprofen and Acetaminophen

In line with the AAN/AHS guidelines, the first-line treatment for headache attacks in stroke patients should remain ibuprofen and acetaminophen (Table 2

). It is essential to prescribe proper dosing for weight because underdosing will lead to a lack of response. Nonsteroidal anti-inflammatory drugs (NSAIDs), typically ibuprofen, are the standard first-line treatment for all patients with migraine [38]. The main consideration is that NSAIDS can exert an antiplatelet effect [39], so if the patient is already on anticoagulants, combining both medications may increase bleeding risk [40]. NSAIDs are also contraindicated for patients with upper gastrointestinal or renal disease and bleeding disorders [38]. If the patient has contraindications to NSAID use, acetaminophen is the next choice in stroke patients if their liver function is appropriate.

7.2 Second line: Diclofenac Powder

Diclofenac powder, a second-generation NSAID, may be used as a second-line treatment for post-stroke headache in pediatrics if a stronger analgesic is necessary (Table 5). There is limited data on the use of diclofenac powder in pediatrics. McVige et al. [41] conducted a clinical trial to assess the safety and tolerability of a single 50-mg dose of diclofenac potassium in pediatric patients aged 12-17 diagnosed with episodic migraine. They found that diclofenac was safe and well-tolerated among participants. In the author's experience, diclofenac powder has been a safe and rapidly effective option for patients with post-stroke migraines that have contraindications to triptan use.

7.3 What not to use:

7.31 Triptans/Ergots

Two vasoactive classes of medication that are often used for migraine treatment are triptans (Selective 5-HT1B/1D agonists) and ergots, including both dihydroergotamine (DHE) and ergotamine. These medications should be avoided when treating post-stroke headaches.

Researchers have investigated the association between triptan use and stroke after case reports linked the two [42,43]. In a cohort study of 63,575 migraine patients by Hall and colleagues [44], 13,664 were prescribed a triptan; they found no association between triptan use and stroke. Still, due to limited data, it is recommended that in stroke patients who are already vascularly compromised, triptans be avoided [45].

DHE and ergotamine (nonselective 5-HT1 agonists) are generally contraindicated for use in stroke due to limited efficacy and side effects. DHE has been reported to be associated with cerebrovascular events, such as cerebral ischemia [46], especially when combined with potent CYP3A4 inhibitors such as the macrolide class of antibiotics [47].

Ergotamine has also been associated with an increased risk of cerebrovascular, cardiovascular, and peripheral ischemia, especially in those using cardiovascular medications [48].

In summary, while triptans and ergots may be effective treatments for non-stroke patients suffering from migraine, in stroke patients, the risk of adverse events increases, and therefore other alternatives should be exhausted before resorting to their use.

7.32 Opioids:

Many studies have found that non-opioid, nonbarbiturate analgesics are the most effective migraine treatments [49, 50]. Furthermore, opioids are associated with significantly greater adverse effects, including dependence, addiction, and overdose [51]. Due to ineffective evidence for the use of opioids, combined with the rise of the opioid epidemic in teens [52] we recommend that opioids not be used for pediatric post-stroke headaches, except as a last resort.

8. Prophylaxis:

8.1 When is a good time to provide prophylaxis to a patient?

There are no guidelines for prophylaxis management of post-stroke headache. Follow the same indications for general pediatric migraine prophylaxis, which include 1) when a patient has one headache per week or more, 2) or when headaches are less frequent but very disabling [38,53,54]. Other indications for prophylaxis also include if acute treatments are ineffective, contraindicated, intolerable, or overused. We will present some common preventative medications used in clinical practice and their dosing (Table 6). Clinicians

should refer to resources such as Kacperski et al. [38]; Jacobs and Gladstein [53]; Teleanu et al. [54] for more pharmacological options.

8.2 Topiramate & Valproate– Anti Seizure medication

Topiramate is the only preventive medication for migraine that is approved by the US Food and Drug Administration (FDA) for use in children ages 12 to 17 years [55,56]. Based on evidence from four Class I studies, the 2019 AAN/AHS suggests that topiramate is probably more effective than placebo for reducing migraine frequency [57]. In the author's experience, this medication is preferred in patients with obesity due to appetite suppression effects [58]. It should be used with caution in patients with language and learning disabilities because it can cause cognitive slowing and concentration difficulties [59]. Lastly, it should be avoided in patients with eating disorders, again due to its appetite-restricting effects [58].

Valproate is another anticonvulsant medication used for preventative migraine treatment. A recent trial of 158 children found that 66% of those who received sodium valproate (at 15 mg/kg/dose divided twice per day) achieved more than 50% reduction in headache frequency [60]. Five adverse events were reported among patients, including sedation, nausea or vomiting, anorexia, or dizziness. Other side effects observed with valproate include weight gain, alopecia, and tremor. Importantly, it should be avoided in females with pregnancy potential due to teratogenic effects and children with MELAS due to its action of inhibiting the biosynthesis of carnitine [61]. For this reason, it may be an option particularly considered in adolescent males without weight concerns.

8.3 Amitriptyline – Tricyclic Antidepressant

Amitriptyline is a first-line medication for migraine, preferred by some clinicians for its once-a-day dosing [59]. That said, a 24-week CHAMP trial conducted in 2017 found that amitriptyline was no better than placebo or Topiramate for headache prevention in adolescents aged 8 to 17 years of age [62]. Support for the use of amitriptyline mainly comes from adult data [63]. This medication also has the added benefit of improving bladder control to reduce enuresis [64] and reducing sleep latency, so amitriptyline may be especially relevant for stroke patients who develop post-stroke insomnia in addition to post-stroke headaches [65].

8.4 Propranolol – Beta blockers

Based on the few pediatric studies available, the 2019 AAN/AHS Guidelines conclude that propranolol is possibly more effective than placebo at achieving a >50% reduction in headache frequency [37]. As with other beta-blockers, the adverse effects of propranolol include drowsiness and sleep disturbances [66]. It is also not to be used in patients with asthma due to the risk of bronchospasm [67].

Importantly, in the context of treating pediatric post-stroke headache, for patients who have infantile hemangioma, extra precaution must be taken while prescribing propranolol. Bradycardia or hypotension may worsen and should be monitored and discontinued if severe (<80 bpm) or symptomatic. Decreases in blood pressure caused by propranolol may also increase the risk for stroke in PHACES (posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies) patients. Therefore patients with large facial infantile hemangiomas should be screened for PHACES followed by careful consideration and neuroimaging to assess for intracranial stenosis ahead of

treatment with propranolol, which should be titrated slowly with close monitoring for hypotension [68].

8.5 Flunarizine & Verapamil – Calcium channel blockers

Calcium channel blockers, including cinnarizine, verapamil, and flunarizine, have also been investigated for treating pediatric migraine. The largest and historic placebo-controlled RCT included 63 children treated with 5mg/day of flunarizine, finding that it significantly reduced headache frequency and duration compared to placebo [69]. However, the 2019 AAN/AHS guideline found that there was insufficient evidence that flunarizine is an effective treatment for pediatric migraine beyond placebo [37]. Also in 2019 Stubberud et al. [70] conducted a systematic review to investigate flunarizine finding it to be moderately effective in children. Adverse effects of flunarizine noted in these studies were weight gain and sedation.

Data from small case studies in pediatric patients suggest verapamil may be considered as a first-line agent for hemiplegic migraine [71, 72]. Another systematic review of case reports on cluster headache in children were supportive of verapamil and hypothesized that it may stabilize vascular tone, however there was insufficient evidence [73]. More broadly, neurosurgical literature suggests benefit of intra-arterial administration of verapamil for treatment of cerebral angiospasm following intracranial hemorrhage after aneurysm rupture [74]. Due to the consideration of verapamil in alleviating vasospasm, it may be useful particularly in patients with Reverse Cerebral Vasoconstriction Syndromes (RCVS).

Summary: A variety of medications can be used for post-stroke headache prophylaxis in pediatric patients. In the author's clinical experience, topiramate or amitriptyline are

preferred having the greatest efficacy in migraine patients. In patients with underlying vasculopathies, avoid antihypertensive medications which may decrease blood pressure briskly.

9. Interventional:

Besides pharmacological treatment, there are also many interventional strategies that can be employed to treat chronic migraine. These strategies may also be used in patients with post-stroke headaches, although, as with post-stroke headaches in general, data is limited. Interventional strategies such as Botox and nerve blocks are more invasive and therefore are generally reserved for patients who have been unresponsive to other conservative treatments.

9.1 Greater Occipital Nerve Block

A headache intervention that pediatric neurologists commonly perform is peripheral nerve blocks of the scalp, usually greater occipital nerve blocks (GONBs; Figure 3). The medications in the nerve blocks are usually local anesthetic (1-2% lidocaine) with concomitant steroids (ex. methylprednisolone). A survey by Szperka et al. [75] found that in 82 members of the Pediatric and Adolescent Section of the American Headache Society, over half (63%) performed nerve blocks themselves, while another 17% referred to another provider.

A study by Gelfand et al. [76] found that over half of a pediatric cohort who received greater occipital nerve block for primary headache disorders experienced benefit, with 28% experiencing significant benefit. A more recent study by Puledda et al. [77] found that in 159

patients with disabling migraine, improvement was seen in 66% of patients and lasted an average of 9 weeks.

While there is no literature on nerve blocks in post-stroke patients for head pain, peripheral and diagnostic nerve blocks have been used. As an example, Picelli et al. [78] used a suprascapular nerve block (containing methylprednisolone with bupivacaine hydrochloride) for hemiplegic shoulder pain in adult stroke patients. They found that there were significant improvements in pain and functional shoulder rotation following the nerve block. Fitterer et al. [79] used lidocaine-containing nerve blocks to differentiate spasticity from other immobility issues following stroke, helping to guide rehabilitation and treatment.

9.2 Botulinum Toxin

Injections with onabotulinumtoxinA are generally administered every three months via intramuscular injections to the forehead and neck (Figure 4). Evidence for this therapy is mainly derived from adult data as pediatric cases are limited. In adults, data from two 24-week multicenter randomized controlled trials, referred to as PREEMPT 1 and PREEMPT 2, together enrolled 1384 adults finding that onabotulinumtoxinA seemed to decrease the frequency of headache days and most secondary outcomes (frequency of migraine days, frequency of moderate/severe headache days, monthly headache hours, etc.) [80,81]. Other pediatric data, however, has been less clear. A systematic review on onabotulinumtoxinA for pediatric migraine was conducted recently by Marcelo and Freund [82] . Here, the authors included seven studies (2 retrospective, 3 case series, 1 case report, and 1 RCT) that involved between 1 and 125 patients each. In these studies, onabotulinumtoxinA injections were

administered between 1 and 11 times. They found that results may generally favor a decrease in headache frequency, although due lack of standardization in methods across trials, the quality of evidence was low and hard to compare.

9.3 Monoclonal Antibodies

Another novel treatment option being developed for headache treatment is monoclonal antibodies. The FDA has approved the use of many different Calcitonin gene-related peptide (CGRP) monoclonal antibody antagonists for migraine prevention in adults, after investigations have demonstrated efficacy [83–92]. There are currently ongoing trials to test the safety and efficacy of CGRP for migraine in special populations such as children, but the outcomes from this data will likely not be available for several years.

Given the emerging interest in this novel therapy by care providers, a 2018 manuscript was released by the Pediatric & Adolescent Headache special interest group of the American Headache Society to act as an expert opinion helping to guide treatment decisions [93]. Due to the effects of CGRP on both the neurological and cardiovascular systems, they recommend against using CGRP monoclonal antibodies in children and adolescents who have a history of stroke and a potentially compromised blood-brain barrier until more data is available (see Szperka et al. [93]).

9.4 Neurostimulation

Neurostimulation is a non-invasive technique which utilizes electrical currents and magnetic fields to modulate brain activity. There are many different types of neurostimulation that have been investigated for use in headache, including but not limited to transcutaneous electrical nerve stimulation (TENS) [94], non-invasive vagus nerve stimulation (nVNS) [95],

and transcranial magnetic stimulation (TMS) [96]. Most studies on the safety and tolerability of these neurostimulation techniques have been conducted in adults, and clinical trials for pediatric patients are outstanding. Expert opinion on the potential of neurostimulation for pediatric migraine treatment is optimistic and presented by Börner et al. [97] and Brighina et al. [98].

Neurostimulation has also been investigated for stroke recovery and rehabilitation. As reviewed by Ting et al. [99], it is thought that neurostimulation might help strengthen synaptic connections and improve neuronal activation post-stroke according to the principles of stimulation-driven plasticity. Authors of an ongoing clinical trial on nVNS, the NOVIS study, also hypothesize that acute neurostimulation might result in a smaller final infarct volume, therefore minimizing disability from stroke [100]. While investigations on neurostimulation for post-stroke headache are yet to be conducted, it is hypothesized that neurostimulation may be beneficial for stroke patients above and beyond head pain cessation and might be a good alternative treatment for persistent post-stroke headache.

10. Conclusion

Here we reviewed case studies and provided management suggestions for pediatric post-stroke headache based on the author's clinical experience and adapted pediatric migraine management guidelines. Further research is required to better understand persistent post-stroke headaches and develop evidence-based management strategies. As discussed throughout, only two studies could be identified that investigated post-stroke headaches in pediatric patients to date [4,5]. Literature on comorbidities, including

headache, following different stroke types, is lacking. As Lai et al. [101] proposed, standardization of the "acute" and "delayed" periods of headache onset following stroke is necessary for clinical management and reporting for future database studies.

Taken together, managing post-stroke headache in pediatric populations is complex, especially since there are no current guidelines. The stepwise approach to managing pediatric migraine can often be applied to treating persistent post-stroke headache, with lifestyle, pharmacologic, and interventional (e.g., nerve block) options existing that can adequately treat headache while ensuring that vasoactive medications are avoided in patients who are vascularly compromised.

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12. Declaration of conflicting interest

The authors have no competing interests to declare that are relevant to the content of this article.

13. **Authors' contributions**

J.C. is a medical student who wrote the main manuscript. J.M. is a pediatric neurologist with expertise in pediatric stroke and neurocritical care. T.R. is a pediatric neurologist with a fellowship in headache and facial pain. T.R. is the research supervisor of J.C., who directed

and oversaw all aspects of manuscript preparation. All authors reviewed the manuscript and approved of its publication.

14. References

1. Heart and Stroke Foundation. Summary of Pediatric Recommendations Across Modules. Canadian Stroke Best Practice Recommendations 5th Edition. 2016; 1-12.
2. Naess H, Lunde L, Brogger J, Waje-Andreassen U. Post-stroke pain on long-term follow-up: the Bergen stroke study. J Neurol. 2010 Sep;257(9):1446–52.
3. deVeber GA, Kirton A, Booth FA, Yager JY, Wirrell EC, Wood E, et al. Epidemiology and Outcomes of Arterial Ischemic Stroke in Children: The Canadian Pediatric Ischemic Stroke Registry. Pediatr Neurol. 2017 Apr; 69:58–70.
4. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, et al. Outcome and recurrence 1 year after pediatric arterial ischemic stroke in a population-based cohort: Outcome after Pediatric AIS. Ann Neurol. 2016 May;79(5):784–93.
5. Chelse AB, Kurz JE, Gorman KM, Epstein LG, Balmert LC, Ciolino JD, et al. Remote post stroke headache in children: Characteristics and association with stroke recurrence. Neurol Clin Pract. 2019 Jun;9(3):194–200.
6. Ishaq Abu-Arafeh, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies: Review. Dev Med Child Neurol. 2010 Dec;52(12):1088–97.

7. Sporns PB, Fullerton HJ, Lee S, Kim H, Lo WD, Mackay MT, et al. Childhood stroke. Nature Reviews Disease Primers. 2022 Feb; *8*, 12.
8. Fraser S, Pabst L, Smith F. Stroke in the young. *Current opinion in neurology*. 2023 Apr; *36*(2): 131–139.
9. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ (Clinical research ed.)*. 2009 Oct; *339*, b3914.
10. Gelfand AA, Fullerton HJ, Jacobson A, Sidney S, Goadsby PJ, Kurth T, Pressman A. Is migraine a risk factor for pediatric stroke?. *Cephalalgia. 2015 Mar; 35*(14): 1252–1260.
11. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1–211.
12. Tentschert S, Wimmer R, Greisenegger S, Lang W, Lalouschek W. Headache at stroke onset in 2196 patients with ischemic stroke or transient ischemic attack. Stroke. 2005 Dec;36(2): e1–e3.
13. Arboix A, Grau-Olivares M, Garcia-Eroles L, Massons J, Comes E, Targa C. Clinical Implications of Headache in Lacunar Stroke: Relevance of Site of Infarct.: CME. Headache J Head Face Pain. 2006 Jul;46(7):1172–80.
14. Verdelho A, Ferro J, Melo T, Canhão P, Falcão F. Headache in Acute Stroke. A Prospective Study in the First 8 Days. Cephalalgia. 2008 Apr;28(4):346–54.
15. Dodick DW. Pearls: Headache. Semin Neurol. 2010 Feb; 30(1):74–81.

16. Dao JM, Qubty W. Headache Diagnosis in Children and Adolescents. Curr Pain Headache Rep. 2018 Mar;22(3):17.

17. Ahmadi Aghangar A, Bazoyar B, Mortazavi R, Jalali M. Prevalence of headache at the initial stage of stroke and its relation with site of vascular involvement: A clinical study. Casp J Intern Med. 2015;6(3):156–60.

18. Ferro JM, Melo TP, Oliveira V, Salgado AV, Crespo M, Canhao P, et al. A Multivariate Study of Headache Associated With Ischemic Stroke. Headache J Head Face Pain. 1995 Jun;35(6):315–9.

19. MacGregor EA. In the Clinic. Migraine. Ann Intern Med. 2013 Nov 5;159(9):ITC5-1.

20. Becker WJ. Acute Migraine Treatment in Adults. Headache J Head Face Pain. 2015 Jun;55(6):778–93.

21. Correction to: Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12).

22. Gelfand AA, Goadsby PJ. Medication Overuse in Children and Adolescents. Curr Pain Headache Rep. 2014 Jul;18(7):428.

23. Desmond PV, Watson KJR. Metoclopramide — a review. Med J Aust. 1986 Mar;144(7):366–9.

24. Valenzuela JE, Dooley CP. Dopamine antagonists in the upper gastrointestinal tract. Scand J Gastroenterol Suppl. 1984; 96:127–36.

25. Abdelmonem H, Abdelhay HM, Abdelwadoud GT, Alhosini ANM, Ahmed AE, Mohamed SW, et al. The efficacy and safety of metoclopramide in relieving acute migraine attacks compared with other anti-migraine drugs: a systematic review and network meta-analysis of randomized controlled trials. BMC Neurol. 2023 Jun 8;23(1):221.
26. Ye JH, Ponnudurai R, Schaefer R. Ondansetron: A Selective 5-HT3 Receptor Antagonist and Its Applications in CNS-Related Disorders. CNS Drug Rev. 2006 Jun 7;7(2):199–213.
27. Talai A, Heilbrunn B. Ondansetron for Acute Migraine in the Pediatric Emergency Department. Pediatr Neurol. 2020 Feb; 103:52–6.
28. Villa Zapata L, Hansten PD, Panic J, Horn JR, Boyce RD, Gephart S, et al. Risk of Bleeding with Exposure to Warfarin and Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review and Meta-Analysis. Thromb Haemost. 2020 Jul;120(07):1066–74.
29. Fernandes L, Randall M, Idrovo L. Peripheral nerve blocks for headache disorders. Pract Neurol. 2020 Oct 23;practneurol-2020-002612.
30. Robblee J, Starling AJ. SEEDS for success: Lifestyle management in migraine. Cleve Clin J Med. 2019 Nov;86(11):741–9.
31. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021 Jul;52(7).
32. Hall A, Brand A, Kedia S. Nonpharmaceutical options for pediatric headache: Nutraceuticals, manual therapies, and acupuncture. In: Pediatric headache. Elsevier; 2022. p. 223–66.

33. Long R, Zhu Y, Zhou S. Therapeutic role of melatonin in migraine prophylaxis: A systematic review. Medicine (Baltimore). 2019 Jan;98(3):e14099.

34. Sadanandan N, Cozene B, Cho J, Park YJ, Saft M, Gonzales-Portillo B, et al. Melatonin—A Potent Therapeutic for Stroke and Stroke-Related Dementia. Antioxidants. 2020 Jul 28;9(8):672.

35. Lehman LL, Maletsky K, Beaute J, Rakesh K, Kapur K, Rivkin MJ, Mrakotsky C. Prevalence of Symptoms of Anxiety, Depression, and Post-traumatic Stress Disorder in Parents and Children Following Pediatric Stroke. Journal of child neurology. 2020 Mar; 35(7): 472–479.

36. Peres MFP, Mercante JPP, Tobo PR, Kamei H, Bigal ME. Anxiety and depression symptoms and migraine: a symptom-based approach research. The journal of headache and pain. 2017 Mar; 18(1): 37.

37. Oskoui M, Pringsheim T, Holler-Managan Y, Potrebic S, Billinghurst L, Gloss D, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2019 Sep 10;93(11):487–99.

38. Kacperski J, Kabbouche MA, O'Brien HL, Weberding JL. The optimal management of headaches in children and adolescents. Ther Adv Neurol Disord. 2016 Jan;9(1):53–68.

39. Wood AJJ, Patrono C. Aspirin as an Antiplatelet Drug. N Engl J Med. 1994 May 5;330(18):1287–94.

40. Davidson BL, Verheijen S, Lensing AWA, Gebel M, Brighton TA, Lyons RM, et al. Bleeding Risk of Patients With Acute Venous Thromboembolism Taking Nonsteroidal Anti-Inflammatory Drugs or Aspirin. JAMA Intern Med. 2014 Jun 1;174(6):947.
41. McVige JW, Hogan RM, Shanahan CM, Amend DL, Ferger SM. An Open-Label Study Evaluating the Pharmacokinetics and Safety of Diclofenac Potassium for Oral Solution for the Acute Treatment of MWA or MWoA in Pediatric Participants. Headache J Head Face Pain. 2020 Oct;60(9):1939–46.
42. Cavazos JoseE, Caress JamesB, Chilukuri VaniR, Devlin T, Gray L, Hurwitz BarrieJ. Sumatriptan-induced stroke in sagittal sinus thrombosis. The Lancet. 1994 Apr;343(8905):1105–6.
43. Jayamaha JEL, Street MK. Fatal cerebellar infarction in a migraine sufferer whilst receiving sumatriptan. Intensive Care Med. 1995 Jan;21(1):82–3.
44. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: The risks of stroke, cardiovascular disease, and death in practice. Neurology. 2004 Feb 24;62(4):563–8.
45. Jamieson DG. The safety of triptans in the treatment of patients with migraine. Am J Med. 2002 Feb;112(2):135–40.
46. Farooq MU, Naravetla B, Bhatt A, Masih A, MacFalda B, Kassab MY. Possible iatrogenic bilateral cerebral ischemic infarcts in a woman with vasculitis. J Headache Pain. 2008 Jun;9(3):189–90.
47. Delaforge M, Rivière R, Sartori E, Doignon JL, Grognet JM. Metabolism of dihydroergotamine by a cytochrome P-450 similar to that involved in the metabolism of macrolide antibiotics. Xenobiotica. 1989 Jan;19(11):1285–95.

48. Wammes-van der Heijden EA, Rahimtoola H, Leufkens HGM, Tijssen CC, Egberts ACG. Risk of ischemic complications related to the intensity of triptan and ergotamine use. Neurology. 2006 Oct 10;67(7):1128–34.

49. Evers S, Áfra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968–81.

50. Kelley NE, Tepper DE. Rescue Therapy for Acute Migraine, Part 3: Opioids, NSAIDs, Steroids, and Post-Discharge Medications: March 2012. Headache J Head Face Pain. 2012 Mar;52(3):467–82.

51. VanderPluym JH, Halker Singh RB, Urtecho M, Morrow AS, Nayfeh T, Torres Roldan VD, et al. Acute Treatments for Episodic Migraine in Adults: A Systematic Review and Meta-analysis. JAMA. 2021 Jun 15;325(23):2357.

52. Substance Abuse and Mental Health Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. 2019.

53. Jacobs H, Gladstein J. Pediatric Headache: A Clinical Review. Headache J Head Face Pain. 2012 Feb;52(2):333–9.

54. Teleanu RI, Vladacenco O, Teleanu DM, Epure DA. Treatment of Pediatric Migraine: a Review. Maedica. 2016 Jun;11(2):136–43.

55. Sakulchit T, Meckler GD, Goldman RD. Topiramate for pediatric migraine prevention. Can Fam Physician Med Fam Can. 2017 Jul;63(7):529–31.

56. FDA approves Topamax for migraine prevention in adolescents. Silver Spring, MD: US Food and Drug Administration. 2014 [Internet]. Available from: https://wayback.archive-it.org/7993/20170112222908/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391026.htm
57. Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, et al. Meta-Analysis: Pharmacologic Treatment of Obesity. Ann Intern Med. 2005 Apr 5;142(7):532.
58. Janssen Pharmaceuticals (per FDA). TOPAMAX(R) SPRINKLE CAPSULES oral capsules, topiramate oral capsules [Internet]. Titusville, NJ; 2014. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020844s041lbl.pdf
59. O'Brien HL, Kabbouche MA, Kacperski J, Hershey AD. Treatment of Pediatric Migraine. Curr Treat Options Neurol. 2015 Jan;17(1):1.
60. Amanat M, Togha M, Agah E, Ramezani M, Tavasoli AR, Azizi Malamiri R, et al. Cinnarizine and sodium valproate as the preventive agents of pediatric migraine: A randomized double-blind placebo-controlled trial. Cephalalgia. 2020 Jun; 40(7): 665–674.
61. Chaudhry N, Patidar Y, Puri V. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes unveiled by valproate. Journal of pediatric neurosciences. 2013 May; 8(2):135–137.
62. Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, et al. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. N Engl J Med. 2017 Jan 12;376(2):115–24.
63. Pringsheim T, Davenport WJ, Becker WJ. Prophylaxis of migraine headache. Can Med Assoc J. 2010 Apr 20;182(7):E269–76.

64. Caldwell PH, Sureshkumar P, Wong WC. Tricyclic and related drugs for nocturnal enuresis in children. The Cochrane database of systematic reviews. 2016 Jan; (1):CD002117.

65. Glozier N, Moullaali TJ, Sivertsen B, Kim D, Mead G, Jan S, et al. The Course and Impact of Poststroke Insomnia in Stroke Survivors Aged 18 to 65 Years: Results from the Psychosocial Outcomes In StrokE (POISE) Study. Cerebrovasc Dis Extra. 2017 Feb 3;7(1):9–20.

66. Dahlöf C, Dimenäs E. Side Effects of β-Blocker Treatments as Related to the Central Nervous System. Am J Med Sci. 1990 Apr;299(4):236–44.

67. Covar RA, Macomber BA, Szefler SJ. Medications as asthma triggers. Immunol Allergy Clin North Am. 2005 Feb;25(1):169–90.

68. Metry D, Frieden IJ, Hess C, Siegel D, Maheshwari M, Baselga E, et al. Propranolol Use in PHACE Syndrome with Cervical and Intracranial Arterial Anomalies: Collective Experience in 32 Infants. Pediatr Dermatol. 2013 Jan;30(1):71–89.

69. Sorge F, Simone RD, Marano E, Nolano M, Orefice G, Carrieri P. Flunarizine in Prophylaxis of Childhood Migraine: A Double-Blind, Placebo-Controlled, Crossover Study. Cephalalgia. 1988 Mar;8(1):1–6.

70. Stubberud A, Flaaen NM, McCrory DC, Pedersen SA, Linde M. Flunarizine as prophylaxis for episodic migraine: a systematic review with meta-analysis. Pain. 2019 Apr;160(4):762–72.

71. Asghar SJ, Milesi-Hallé A, Kaushik C, Glasier C, Sharp GB. Variable manifestations of familial hemiplegic migraine associated with reversible cerebral edema in children. Pediatric neurology. 2012 Sep; 47(3):201–204.

72. Kumar G, Topper L, Maytal J. Familial hemiplegic migraine with prolonged aura and multimodality imaging: a case report. Headache. 2009 Jan; 49(1): 139–142.

73. Bastos SNMAN, Barbosa BLF, Silva SF, Krymchantowski AG, Jevoux C, Krymchantowski A, et al. Cluster headache in children and adolescents: a systematic review of case reports. Developmental medicine and child neurology. 2021 Oct; 63(10):1155–1160.

74. Mikeladze KG, Okishev DN, Belousova OB, Konovalov AN, Pilipenko YV, Ageev IS, et al. Intra-arterial Administration of Verapamil for the Prevention and Treatment of Cerebral Angiospasm. Acta neurochirurgica. 2020 Jan; 127: 179–183.

75. Szperka CL, Gelfand AA, Hershey AD. Patterns of Use of Peripheral Nerve Blocks and Trigger Point Injections for Pediatric Headache: Results of a Survey of the American Headache Society Pediatric and Adolescent Section. Headache J Head Face Pain. 2016 Nov;56(10):1597–607.

76. Gelfand AA, Reider AC, Goadsby PJ. Outcomes of Greater Occipital Nerve Injections in Pediatric Patients With Chronic Primary Headache Disorders. Pediatr Neurol. 2014 Feb;50(2):135–9.

77. Puledda F, Goadsby PJ, Prabhakar P. Treatment of disabling headache with greater occipital nerve injections in a large population of childhood and adolescent patients: a service evaluation. J Headache Pain. 2018 Dec;19(1):5.

78. Picelli A, Bonazza S, Lobba D, Parolini M, Martini A, Chemello E, et al. Suprascapular nerve block for the treatment of hemiplegic shoulder pain in patients with long-term chronic stroke: a pilot study. Neurol Sci. 2017 Sep;38(9):1697–701.

79. Fitterer JW, Picelli A, Winston P. A Novel Approach to New-Onset Hemiplegic Shoulder Pain With Decreased Range of Motion Using Targeted Diagnostic Nerve Blocks: The ViVe Algorithm. Front Neurol. 2021 May 28; 12:668370.

80. Aurora S, Dodick D, Turkel C, DeGryse R, Silberstein S, Lipton R, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010 Jul;30(7):793–803.

81. Diener H, Dodick D, Aurora S, Turkel C, DeGryse R, Lipton R, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010 Jul;30(7):804–14.

82. Marcelo R, Freund B. The Efficacy of Botulinum Toxin in Pediatric Chronic Migraine: A Literature Review. J Child Neurol. 2020 Oct;35(12):844–51.

83. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia. 2018 May;38(6):1026–37.

84. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017 Nov 30;377(22):2123–32.

85. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018 Sep 1;75(9):1080.

86. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018 May 15;319(19):1999.

87. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia. 2018 Jul;38(8):1442–54.

88. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017 Nov 30;377(22):2113–22.

89. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017 Jun;16(6):425–34.

90. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings ELH, Diener HC, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015 Nov;14(11):1091–100.

91. Ashina M, Goadsby PJ, Reuter U, Silberstein S, Dodick DW, Xue F, et al. Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial. Eur J Neurol. 2021 May;28(5):1716–25.

92. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four

migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet. 2019 Sep;394(10203):1030–40.

93. Szperka CL, VanderPluym J, Orr SL, Oakley CB, Qubty W, Patniyot I, et al. Recommendations on the Use of Anti-CGRP Monoclonal Antibodies in Children and Adolescents: Headache. Headache J Head Face Pain. 2018 Nov;58(10):1658–69.
94. Tao H, Wang T, Dong X, Guo Q, Xu H, Wan Q. Effectiveness of transcutaneous electrical nerve stimulation for the treatment of migraine: a meta-analysis of randomized controlled trials. J Headache Pain. 2018 Dec;19(1):42.
95. Tassorelli C, Grazzi L, de Tommaso M, Pierangeli G, Martelletti P, Rainero I, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study. Neurology. 2018 Jul 24;91(4):e364–73.
96. Starling AJ, Tepper SJ, Marmura MJ, Shamim EA, Robbins MS, Hindiyeh N, et al. A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE Study). Cephalalgia. 2018 May;38(6):1038–48.
97. Börner C, Urban G, Beaulieu LD, Sollmann N, Krieg SM, Straube A, et al. The bottom-up approach: Non-invasive peripheral neurostimulation methods to treat migraine: A scoping review from the child neurologist's perspective. Eur J Paediatr Neurol. 2021 May;32:16–28.
98. Brighina F, Raieli V, Messina LM, Santangelo G, Puma D, Drago F, et al. Non-invasive Brain Stimulation in Pediatric Migraine: A Perspective from Evidence in Adult Migraine. Front Neurol. 2019 Apr 12; 10:364.

99. Ting WKC, Fadul FAR, Fecteau S, Ethier C. Neurostimulation for Stroke Rehabilitation. Front Neurosci. 2021 May 14; 15:649459.

100. van der Meij A, van Walderveen MAA, Kruyt ND, van Zwet EW, Liebler EJ, Ferrari MD, et al. Non-invasive Vagus nerve stimulation in acute Ischemic Stroke (NOVIS): a study protocol for a randomized clinical trial. Trials. 2020 Dec;21(1):878.

101. Lai J, Harrison RA, Plecash A, Field TS. A Narrative Review of Persistent Post-Stroke Headache - A New Entry in the International Classification of Headache Disorders, 3rd Edition. Headache J Head Face Pain. 2018 Oct;58(9):1442–53.

102. Ghosh A, Silva E, Burish MJ. Pediatric-onset trigeminal autonomic cephalalgias: A systematic review and meta-analysis. Cephalalgia. 2021 Nov;41(13):1382–95.

103. Ashkenazi A, Levin M. Greater occipital nerve block for migraine and other headaches: Is it useful? Curr Pain Headache Rep. 2007 Jul;11(3):231–5.

104. Blumenfeld A, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, Binder WJ. Method of Injection of OnabotulinumtoxinA for Chronic Migraine: A Safe, Well-Tolerated, and Effective Treatment Paradigm Based on the PREEMPT Clinical Program: October 2010. Headache J Head Face Pain. 2010 Oct;50(9):1406–18.

15. Figures

Figure 1. SNOOP4 mnemonic for eliciting common causes of secondary headache disorders (Adapted from: Dodick [15].

Figure 2. Pediatric Headache Classification. The International Classification of Headache Disorders, 3rd Edition outlines headaches as either primary or secondary in etiology [11]. Primary headaches are divided into migrainous, tension-type, or trigeminal autonomic cephalgia, which are rare in pediatrics [102]. A subset of disorders associated with migraine with and without aura are childhood periodic syndromes [11]. Secondary headaches result from a variety of etiologies including due to vascular events, infection or inflammation, trauma to the head or neck, structural changes such as neoplasms or increased cerebral spinal fluid, and many more less common causes. The ICHD-3 outlines headache attributed to a vascular disorder as either acute (resolving within 3 months post-stroke) or persistent (extending beyond 3 months post-stroke). We propose that a similar definition should be used to classify pediatric post-stroke headache. Further, in the author's clinical experience, post-stroke headache in pediatrics can often times present with migrainous features (severity of pain, location, and associated symptoms e.g., nausea, vomiting, photophobia). For this reason, the stepwise approach to managing migraine headache, with exceptions, can often be applied to managing post-stroke headaches.

Figure 3. Injection Location for Greater Occipital Nerve Blocks of the Scalp (Based on: Ashkenazi & Levin [103]).

Figure 4. Injection sites of OnabotulinumtoxinA for Chronic Migraine according to the PREEMPT study protocol [104].

16. Tables

Table 1. Pediatric stroke etiologies associated with headache and corresponding International Classification of Headache Disorders, 3rd edition (ICHD-3) diagnostic criteria [11].

Condition:	**Pathophysiology:**	**Features of Headache Outlined in the ICHD-3 Diagnostic Criteria[1]:**
Cerebral Ischemic Event	Impaired blood flow to an area of the brain, caused by a thrombotic or embolic event.	New and usually acute-onset headache associated with focal neurological signs of the stroke. Headache is very rarely the presenting or a prominent feature of ischemic stroke. It usually has a self-limiting course.
Non-traumatic intracranial hemorrhage	Spontaneous intracranial hemorrhage, occurring outside the context of trauma. There are numerous etiologies including aneurysms, vascular malformations, neoplasms, and bleeding disorders.	Headache generally occurs with sudden (even thunderclap) onset. May be isolated or associated with focal neurologic deficits. Headache has <u>at least one</u> of the following three characteristics: 1) sudden or thunderclap onset 2) maximal on the day of its onset 3) localized in accordance with the site of the hemorrhage
Headache attributed to unruptured vascular malformation:		
Unruptured saccular aneurysm[2]	Abnormal dilatation (i.e., a berry-like outpouching) which often occurs at arterial bifurcation points. Unruptured saccular aneurysms may present symptomatically, with headache, seizures, cranial nerve palsies, and focal deficits.	Headache often has a thunderclap onset and/or is associated with a painful IIIrd nerve palsy with retro-orbital pain and a dilated pupil.
Arterial Venous Malformations (AVM)[3]	Congenital cerebrovascular malformations which usually present between the ages of 10 and 40 years. May be	Headache has significantly worsened in parallel with the growth of the AVM and/or improved in parallel with effective treatment. Migraine

	asymptomatic and discovered on incidental imaging, or present with intracranial hemorrhage, headache, seizure, or focal deficits.	with aura is commonly reported. Headache may be localized to the site of the AVM.
Dural Arteriovenous Fistula (DAVF)[4]	Vascular malformation where there is a pathologic connection between branches of dural arteries and veins or a venous sinus. Clinical courses vary widely, ranging from benign to fatal as a result of cerebral hemorrhage.	Headache may be accompanied by painful pulsatile tinnitus, ophthalmoplegia, and/or is progressive and worse in the morning, during coughing, and/or bending over. Headache may be localized to the site of the DAVF.
Cavernous Malformations (CM)[5]	Developmental abnormality of blood vessels, resulting in adjacent dilated capillaries forming “caverns”, which have a characteristic mulberry appearance on gross examination. May occur sporadically or in a familial pattern. The presentation of symptomatic CMs is specific to their location, often occurring in the supratentorial region.	Headache has significantly worsened in parallel with the growth of the CM and/or improved in parallel with effective treatment. Headache may be localized to the site of the CM.
Encephalotrigeminal Angiomatosis (Sturge-Weber)[6]	Neurocutaneous disorder caused by somatic mosaic mutation in the GNAQ gene. It is characterized by angiomas involving the face (port-wine stain), choroid, and leptomeninges. Headaches secondary to vascular disease commonly occur.	Headache is migraine-like, either bilateral or localized to the site of the angioma, and associated with aura contralateral to the site of the angioma.
Headache attributed to arteritis:		
Cerebral Vasculitis[7]	Heterogenous group of vascular disorders resulting in vessel wall inflammation, and a common cause for pediatric stroke. Other clinical symptoms include	Headache resulting from symptomatic inflammation of cervical, cranial, and/or cerebral arteries. Headache may be the sole symptom.

	headache, seizure, fever, and encephalopathy.	
Headache attributed to cervical carotid or vertebral artery disorder:		
Craniocervical arterial dissection[8]	Most common reported cerebral arteriopathy associated with arterial ischemic stroke in children. Half of the pediatric cases are caused by head and neck trauma; the remaining are classified as spontaneous. Hemiparesis and headache are the most common clinical presentations.	Headache and/or pain in the face and/or neck caused by dissection of a cervical carotid or vertebral artery. The pain is usually ipsilateral to the dissected vessel and generally has a sudden (even thunderclap) onset. It often has the following features: 1) pain is severe and continuous for days or longer 2) pain precedes signs of acute retinal and/or cerebral ischemia 3) pain is unilateral and ipsilateral to the affected cervical artery
Headache attributed to cranial venous disorder:		
Cerebral Venous Sinus Thrombosis (CVST)[9]	Increasingly recognized cause of childhood and neonatal stroke. Thrombosis in the venous system results in outflow obstruction and venous congestion, which may lead to cerebral edema, infarction, and hemorrhage. Clinical manifestations are nonspecific and may be subtle, including well documented cases of isolated headache. Many children also suffer from chronic sequelae including persistent headache.	Headache has no specific characteristics. It is often diffuse and severe but can also be unilateral and sudden, or mild, and sometimes migraine-like. Headache can be the only manifestation of CVST but is often associated with focal signs and/or intracranial hypertension, subacute encephalopathy, or cavernous sinus syndrome.
Headache attributed to genetic vasculopathy:		
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and	Autosomal dominant inherited angiopathy, caused by pathogenic variants in NOTCH3 gene on chromosome 19. Clinically CADASIL presents with one or more of: migraine with aura,	Recurrent attacks of migraine with typical, hemiplegic or prolonged aura. Attacks of migraine with aura may improve when other manifestations of CADASIL appear or worsen.

Leukoencephalopathy (CADASIL)[10]	acute reversible encephalopathy, ischemic episodes, cognitive impairment and dementia, and/or psychiatric disturbance. Onset of CADASIL typically occurs in adulthood, however there are emerging case-reports of children with confirmed CADASIL.	
Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS)[11]	Rare maternally inherited disorder caused by mutations of mitochondrial DNA. Clinical features include stroke-like episodes resulting in hemiparesis, hemianopia, or cortical blindness. In older-children, onset commonly involves recurrent episodes of migraine-like headache, seizures, vomiting, encephalopathy, and focal neurological deficits.	Headache is either recurrent migraine attacks with or without aura, or a presenting symptom of stroke-like episodes associated with focal neuro deficits and/or seizures.
Moyamoya Angiopathy (MMA)[12]	Cerebrovascular condition of progressive narrowing of larger intracranial arteries, and secondary development of small-vessel collaterals. Spectrum of symptoms may range from headaches to repetitive strokes.	Headache has developed in close temporal relation to MMA and has worsened in parallel or improved after revascularization. Outside of acute vascular events, chronic headaches are common and phenotypically resemble migraine-like headaches.
Headache attributed to other intracranial arterial disorders:		
Reverse Cerebral Vasoconstriction Syndrome (RCVS)[13]	Transient vasculopathy associated with severe and recurrent thunderclap headaches and stroke, caused by underlying reversible cerebral arterial vasoconstriction which can persist for days or weeks.	Headache is typically thunderclap and recurring over 1-2 weeks. Headache can remain the sole symptom of RCVS or be a warning symptom preceding hemorrhagic or ischemic stroke. Headache has one or more of the following characteristics and/or is

		diagnosed on angiography with a "string of beads" appearance: a. thunderclap onset b. triggered by sexual activity, exertion, Valsalva maneuvers, emotion, bathing and/or showering c. present or recurrent during ≤1 month after onset, with no new significant headache after >1 month

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1–211.
2. Hammed A, Mahfoud M, & Hammed, S. Symptomatic unruptured pediatric intracranial aneurysm poses a diagnostic and management dilemma. Interdisciplinary Neurosurgery. 2022 Sep; 30: 101657.
3. El-Ghanem M, Kass-Hout T, Kass-Hout O, et al. Arteriovenous Malformations in the Pediatric Population: Review of the Existing Literature. *Interv Neurol*. 2016;5(3-4):218-225.
4. Yadav V, Bhatt S, Athaullah, Dangwal S. Rare occurrence of dural arteriovenous fistula in a child: Multi-modality imaging and literature review. Radiol Case Rep. 2021 Jan 30;16(4):879-883.
5. Ghali MG, Srinivasan VM, Mohan AC, Jones JY, Kan PT, Lam S. Pediatric cerebral cavernous malformations: Genetics, pathogenesis, and management. Surg Neurol Int. 2016 Dec;7(44):S1127-S1134.
6. Balkuv E, Isik N, Canturk IA, Isik N, Basaran R. Sturge-weber syndrome: a case report with persistent headache. Pan Afr Med J. 2014 May;18:87.
7. Gupta N, Hiremath SB, Aviv RI, Wilson N. Childhood Cerebral Vasculitis: A Multidisciplinary Approach. Clinical neuroradiology. 2022 June; 33(1), 5–20.
8. Nash M, Rafay MF. Craniocervical Arterial Dissection in Children: Pathophysiology and Management. Pediatric neurology. 2019 June; *95:* 9–18.
9. Dlamini N, Billinghurst L, Kirkham FJ. Cerebral venous sinus (sinovenous) thrombosis in children. Neurosurg Clin N Am. 2010 Jul;21(3):511-27.
10. Torres M, Hamby T, Tilley J, Schenk A, Acosta F, Kurjee N, et al. Three Pediatric Siblings With CADASIL. Pediatric neurology, 2022 April; *129*, 31–36.
11. El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. Molecular genetics and metabolism. 2015 Oct; *116*(1-2), 4–12.
12. Hackenberg A, Battilana B, Hebeisen M, Steinfeld R, Khan N. Preoperative clinical symptomatology and stroke burden in pediatric moyamoya angiopathy: Defining

associated risk variables. European Journal of paediatric neurology. 2021 Nov; 35, 130–136.
13. Coffino SW, Fryer RH. Reversible Cerebral Vasoconstriction Syndrome in Pediatrics: A Case Series and Review. J Child Neurol. 2017 Jun;32(7):614-623.

Table 2. Pediatric Dosing for Acetaminophen and Ibuprofen.

	Pediatric Weight	**Dosing (IV)**
Acetaminophen	Infant and Children < 2 years	Limited data. 7.5 to 15 mg/kg/day every 6 hours
	Children ≥2 years <50 kg	15 mg/kg/dose every 6 hours or 12.5 mg/kg/dose every 4 hours
	Children ≥2 years ≥50 kg	15 mg/kg/dose every 6 hours or 12.5 mg/kg/dose every 4 hours
	Adolescents ≤17 years <50 kg	15 mg/kg/dose every 6 hours or 12.5 mg/kg/dose every 4 hours
	Adolescents ≤17 years ≥50 kg	1,000 mg every 6 hours or 650 mg every 4 hours
Ibuprofen	Infants ≥6 months and Children <12 years	10.0 mg/kg/dose every 4-6 hours
	Children ≥12 years and Adolescents ≤17 years	400 mg every 4-6 hours

Ibuprofen and Acetaminophen. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 27 Jul 2023; cited 27 Jul 2023]. Available from: http://online.lexi.com. Subscription required to view.

Table 3. Pediatric Dosing for Antiemetics*

	Pediatric Weight	**Dosing (IV)**
Metoclopramide	Children and Adolescents	0.25 mg/kg/dose as a single dose; maximum 10 mg/dose. Every 6 hours as needed
Ondansetron	Children <12 years	0.15 mg/kg every 8 hours as

		needed
	Adolescents	4-8 mg every 4 to 8 hours as needed

*Limited data in headache on the dosing of antiemetics for pediatric headache

Metoclopramide. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 25 Sep 2023; cited 1 Oct 2023]. Available from: http://online.lexi.com. Subscription required to view.

Ondansetron. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 30 Sep 2023; cited 1 Oct 2023]. Available from: http://online.lexi.com. Subscription required to view.

Table 4. Pediatric Dosing for Nutraceuticals.

	Pediatric Weight	**Dosing (oral)**
Riboflavin	Children < 12 years	200-400 mg once per day
	Adults	400mg daily
Coenzyme Q10	Children < 12 years	1-3mg/kg/day 100mg/day
	Adults	100-400 mg/day
Magnesium Salt	Children < 12 years	9mg/kg/day divided into 2 doses
	Adults	102-800 mg divided into 1-3 doses
Melatonin	Children < 12 years	0.3mg/kg (up to 6mg) at bedtime
	Adults	3-10 mg at bedtime
Hall A, Brand A, Kedia S. Non Pharmaceutical options for pediatric headache: Nutraceuticals, manual therapies, and acupuncture. In: Pediatric headache. Elsevier; 2022. p. 223–66.		

Table 5. Pediatric Dosing for Diclofenac

	Pediatric Weight	**Dosing (oral)**
Diclofenac (Powder for oral solution)	Children ≥ 12 years and Adolescents	50 mg (1 packet) as a single dose at head pain onset
Diclofenac. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 22 Jul 2023; cited 27 Jul 2023]. Available from: http://online.lexi.com. Subscription required to view.		

Table 6. Pediatric Dosing for Prophylaxis Medications

	Pediatric Weight	**Dosing (oral)**
Topiramate	Children 6 to <12 years ≥20kg	Start with 15 mg once daily for 1 week; then increase to 15 mg twice daily for 1 week; then increase to 25 mg twice daily for 7 days. Gradually titrate to effect up to target dose of 2 to 3 mg/kg/day divided twice daily.
	Children ≥ 12 years and Adolescents	Start with 25 mg/day once daily at night for 1 week; increase at weekly intervals in 25 mg/day increments as tolerated and indicated to the recommended dose of 50 mg twice daily.

Divalproex sodium	Children 6 to ≤16 years	Limited data available. Start with 10 to 15 mg/kg/day in 2 divided doses; maximum initial dose: 250 mg/dose. Titrate as needed over 4 to 6 weeks to 40 to 45 mg/kg/day in 2 divided doses; maximum daily dose: 1,000 mg/day.
	Adolescents ≥ 17 years	250 mg twice daily; titrate as needed; maximum daily dose: 1,000 mg/day.
Amitriptyline	Older Children and Adolescents	Limited data available. Start with 0.25mg/kg/day given at bedtime; increase dose by 0.25 mg/kg/day every 2 weeks to 1 mg/kg/day.
Propranolol	Children ≥ 7 years and Adolescents	Limited data available. Start with 10 mg daily; increase at weekly intervals in 10 mg increments; usual dose range: 10 to 20 mg 3 times daily
Verapamil	Children ≥ 12 years and Adolescents	Off-label use. 2 to 8 mg/kg/day in 3 divided doses. Maximum daily dose: 480 mg/day.

Topiramate. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 26 Jul 2023; cited 27 Jul 2023]. Available from: http://online.lexi.com. Subscription required to view.

Valproate (valproic acid). In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 9 Apr 2024; cited 3 Sep 2024]. Available from: http://online.lexi.com. Subscription required to view.

Amitriptyline. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 22 Jul 2023; cited 27 Jul 2023]. Available from: http://online.lexi.com. Subscription required to view.

Propranolol. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 24 Jul 2023; cited 27 Jul 2023]. Available from: http://online.lexi.com. Subscription required to view.

Verapamil. In: Pediatric and Neonatal Lexi-Drugs [database on the Internet]. Waltham, MA: Lexicomp, Inc.; 2021 [updated 26 Jul 2024; cited 12 Aug 2024]. Available from: http://online.lexi.com. Subscription required to view.

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