RESEARCH

# Remote poststroke headache in children

## Characteristics and association with stroke recurrence

Ana B. Chelse, MD, MS*, Jonathan E. Kurz, MD, PhD*, Kathleen M. Gorman, MD, Leon G. Epstein, MD, Lauren C. Balmert, PhD, Jody D. Ciolino, PhD, and Mark S. Wainwright, MD, PhD

**Correspondence**
Dr. Wainwright
mark.wainwright@seattlechildrens.org

*Neurology: Clinical Practice* June 2019 vol. 9 no. 3 194-200 doi:10.1212/CPJ.0000000000000652

## Abstract

### Background

New-onset headache after stroke is common among adult stroke survivors. However, pediatric data are limited. The primary aim of this study was to investigate the prevalence of new-headache after pediatric ischemic stroke. Secondary outcomes were to describe the characteristics of patients experiencing poststroke headache and the association between poststroke headache and stroke recurrence.

### Methods

We conducted a single-center retrospective study on children aged 30 days to 18 years with a confirmed radiographic diagnosis of arterial ischemic stroke (AIS) from January 1, 2008, to December 31, 2016. Patients were identified from an internal database, with additional data abstracted from the electronic medical record. Poststroke headache (occurring >30 days after stroke) was identified through electronic searches of the medical record and confirmed by chart review.

### Results

Of 115 patients with confirmed AIS, 41 (36%) experienced poststroke headache, with headache developing a median of 6 months after stroke. Fifty-one percent of patients with poststroke headache presented to the emergency department for headache evaluation; 81% of the patients had an inpatient admission for headache. Older age at stroke (odds ratio [OR] 21.5; $p = 0.0001$) and arteriopathy (OR 8.65; $p = 0.0029$) were associated with development of poststroke headache in a multivariable analysis. Seventeen patients (15%) had a recurrent stroke during the study period. Poststroke headache was associated with greater risk for stroke recurrence ($p = 0.049$).

### Conclusions

Remote poststroke headache is a common morbidity among pediatric stroke survivors, particularly in older children. Headaches may increase health care utilization, including neuroimaging and hospital admissions. We identified a possible association between poststroke headache and stroke recurrence.

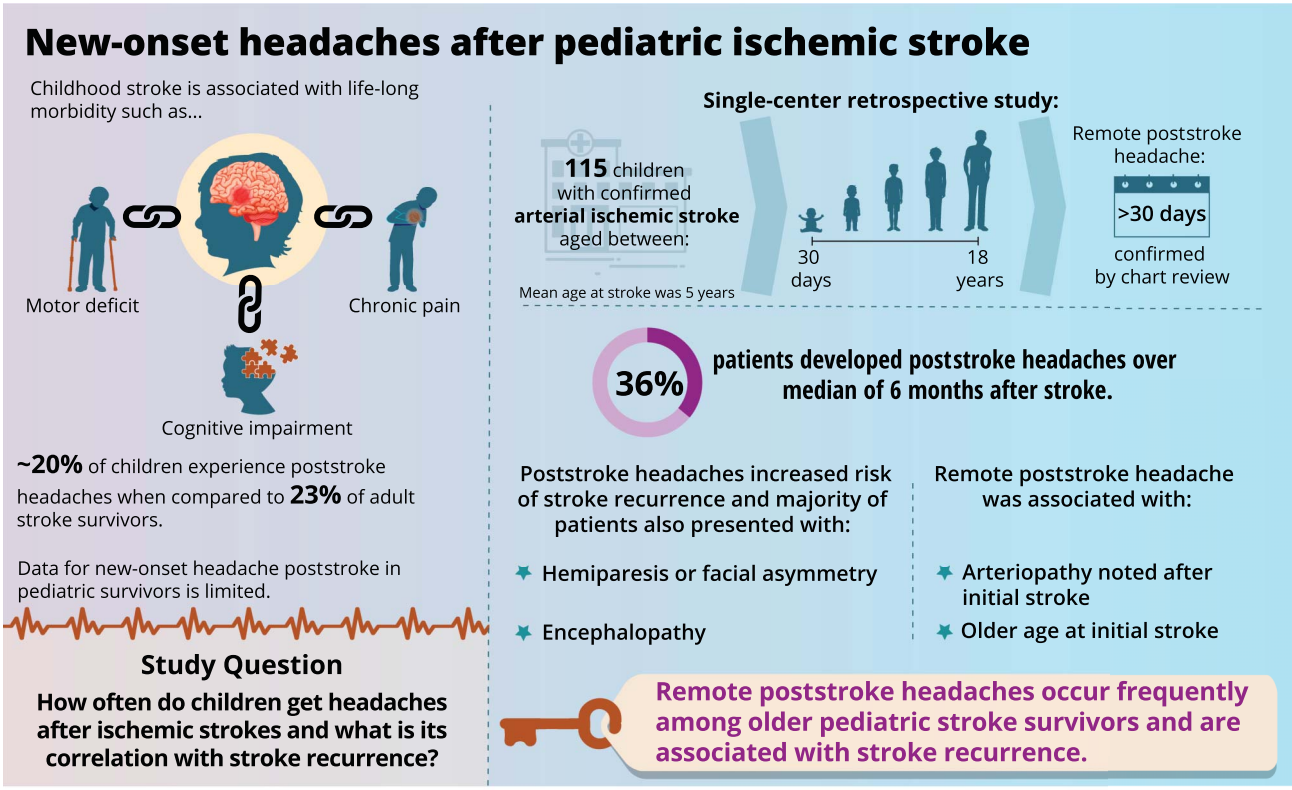
Childhood stroke is associated with life-long morbidity, including motor deficits, cognitive impairment, and chronic pain.[1,2] At 1-year follow-up after stroke, approximately 20% of children experience headaches.[3] Poststroke headaches also affect up to 23% of adults[1,4] and are associated with fatigue and increased mortality.[1] Whether poststroke headaches are associated

*These authors contributed equally to the manuscript.

From the Department of Pediatrics (ABC, JEK, LGE), Division of Neurology, Northwestern University Feinberg School of Medicine; Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program (JEK, KMG), Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine; Department of Preventive Medicine (LCB, JDC), Northwestern University Feinberg School of Medicine, Chicago, IL; and Division of Pediatric Neurology (MSW), University of Washington Medical School, Seattle.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.




doi:10.1212/CPJ.0000000000000652

Neurology Clinical Practice

with stroke recurrence or increased morbidity in children is not known. The primary aim of this retrospective study was to estimate the prevalence of new-onset headache after pediatric ischemic stroke. Secondary aims included time to headache development, age and gender distribution, and contribution to the risk for stroke recurrence.

# Methods

## Study design

We conducted a retrospective study on children (aged 30 days to 18 years at the time of initial stroke) identified from a database of patients seen by the neurocritical care service with radiographically confirmed arterial ischemic stroke (AIS) at Lurie Children's Hospital of Chicago between January 2008 and December 2016.

## Standard protocol approvals, registrations, and patient consents

The local Institutional Review Board approved this study.

## Data sources, demographic and clinical data

Among 183 patients identified from the neurocritical care database, 68 patients were excluded from analysis for the following reasons: 36 because of age, specifically, patients who had a stroke but died before the age of 3 years (n = 29) or who were younger than 3 years at the time of data abstraction (n = 7); 32 patients were excluded because of other diagnoses that were identified upon chart review (cerebral venous sinus thrombosis, primary hemorrhagic injury, CNS infection, brain neoplasm, traumatic brain injury, and diffuse global ischemic injury). AIS was defined as acute neurologic symptoms in the setting of acute cerebral ischemia in a corresponding arterial distribution. AIS with secondary hemorrhage was included, whereas primary intracerebral hemorrhage and ischemic venous infarcts were not.

We defined poststroke headache as a headache occurring >30 days after stroke. Poststroke headache patients reported headache during a clinic visit or sought medical care for acute headache, including children who presented to the emergency room or had an inpatient neurologic consultation for headache. Headache during a febrile illness, CNS infection, or with an underlying brain neoplasm was not classified as poststroke headache.

Stroke recurrence was identified as an acute neurologic symptom with evidence of a new radiographically confirmed AIS. Demographic characteristics, infarct location, headache history, emergency department (ED) visits, neuroimaging, hospital admissions, and headache treatment were obtained from the medical record. Stroke etiologies were categorized using the CASCADE criteria as previously described.[5] Etiologies were collapsed as arteriopathy, cardioembolic, and other/multifactorial because of small sample sizes in individual subcategories.

Statistical analysis was performed using SAS (v 9.4). Descriptive statistics summarized all variables overall, by poststroke headache status and by stroke recurrence status. Chi-squared tests and

**Table 1** Characteristics of patients with and without poststroke headache

| | Poststroke headache (n = 41) | No poststroke headache (n = 74) | *p* Value[a] |
|---|---|---|---|
| **Age at first stroke** | | | <0.0001 |
| **0–3** | 5 (12) | 47 (64) | |
| **4–11** | 16 (39) | 17 (23) | |
| **12+** | 20 (49) | 10 (13) | |
| **Sex** | | | 0.3924 |
| **Male** | 25 (61) | 39 (53) | |
| **Female** | 16 (39) | 35 (47) | |
| **Family history of headache** | | | 0.0255 |
| **Yes** | 15 (36) | 9 (12) | |
| **No** | 10 (24) | 21 (28) | |
| **Not provided** | 16 (38) | 44 (59) | |
| **Etiology[b].** | | | 0.0005 |
| **Arteriopathy** | 25 (61) | 18 (25) | |
| **Small vessel** | 1 (2) | 6 (8) | |
| **Unilateral focal** | 10 (24) | 3 (4) | |
| **Bilateral** | 9 (22) | 4 (6) | |
| **Aortic/cervical** | 5 (12) | 5 (7) | |
| **Cardioembolic** | 8 (20) | 29 (41) | |
| **Other** | 7 (17) | 25 (35) | |
| **Multifactorial** | 1 (2) | 2 (3) | |
| **Stroke subtype** | | | 0.1844 |
| **Hemorrhagic (secondary)** | 4 (10) | 2 (3) | |
| **Ischemic** | 37 (90) | 72 (97) | |
| **No. of infarcts** | | | 0.6662 |
| **Single** | 20 (49) | 33 (45) | |
| **Multiple** | 21 (51) | 41 (55) | |
| **Laterality of initial infarct** | | | 0.0224 |
| **Bilateral** | 9 (22) | 32 (43) | |
| **Unilateral** | 32 (78) | 42 (57) | |
| **Lesion distribution** | | | 0.4139 |
| **Anterior circulation** | 23 (56) | 48 (65) | |
| **Both anterior and posterior** | 8 (20) | 8 (11) | |
| **Posterior circulation** | 10 (24) | 18 (24) | |
| **Anticoagulation/aspirin** | | | 0.0442 |
| **Yes** | 30 (73) | 40 (54) | |
| **No** | 11 (27) | 34 (46) | |

[a] *p* values from $\chi^2$ tests or Fisher exact tests where appropriate. Values are reported as n (%).
[b] Etiology collapsed into arteriopathy, cardioembolic, and other/multifactorial in $\chi^2$ test.

**Table 2** Multivariable logistic regression model for poststroke headache[a]

| Variable | OR[b] | 95% CI | *p* Value |
|---|---|---|---|
| **Age group** | | | |
| **0–3 (reference)** | | | |
| **4–11** | 5.86 | 1.73, 19.88 | <0.0001 |
| **12+** | 21.50 | 5.46, 84.70 | |
| **Laterality** | | | 0.0698 |
| **Unilateral (reference)** | | | |
| **Bilateral** | | | |
| **Anticoagulation/aspirin** | 0.37 | 0.13, 1.08 | 0.4425 |
| **No (reference)** | | | |
| **Yes** | 1.53 | 0.52, 4.50 | |
| **Etiology** | | | |
| **Cardioembolic** | | | 0.0029 |
| **Arteriopathy** | 8.65 | 2.42, 30.92 | |
| **Other/multifactorial** | 2.37 | 0.60, 9.31 | |

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Model stability in question due to small cell counts.
[b] Odds ratio represents the odds of poststroke headache for each level of categorical variables compared with the reference category.

Fisher's exact tests, where appropriate, were used to assess associations between categorical variables of interest and presence of poststroke headache. Similar methods were employed for associations with stroke recurrence. Exploratory multiple logistic regression models included predictors deemed significant in univariable analyses. All statistical tests assumed a 2-sided type one error rate of 0.05, and no adjustments were made for multiple hypothesis tests. Given the exploratory nature of this study, a statistical correction for multiple testing was not performed.

## Data availability

Data not provided in this report will be shared at the request of other investigators for purposes of replicating procedures and results.

# Results

## Factors associated with poststroke headache

The analysis cohort included 115 patients, with a mean age of 5 years at the time of initial stroke. Forty-one (36%) patients experienced poststroke headache (table 1). The age distribution was significantly different between children with and without poststroke headache ($p < 0.0001$) (table 2). Those without remote poststroke headache were generally younger at the time of index stroke (0–3 years old), whereas the majority (n = 36, 87%) of children who developed headache after stroke were more than 3 years of age at the time of sentinel stroke. A family history of headache was only recorded for 55 of the entire cohort, and was present in 26 (48%) of these children (table 1). Those with poststroke headache were more likely to have a family history of headache, a specific stroke etiology of arteriopathy, unilateral stroke location, or to have been treated with anticoagulant/antiplatelet agents. In a multiple logistic regression model, older age ($p = 0.0001$) was associated with an increased odds of poststroke headache, after adjusting for laterality, anticoagulant/antiplatelet agents, and etiology. The odds of poststroke headache were higher ($p = 0.0029$) for arteriopathic stroke etiologies relative to children with cardioembolic stroke (odds ratio 8.65; 95% confidence interval, 2.42–30.92). Although significant in univariable associations, family history was not included in the multivariable logistic regression model because of large percentage with missing data (56%).

## Disease course and treatment of poststroke headache

Thirty-seven patients developed new poststroke headache, with a median time to onset of 6 months (Interquartile Range: 1.0–24) (table 3). An additional 4 patients experienced poststroke exacerbation of preexisting headaches. A majority (51%) visited the ED at least once for poststroke

**Table 3** Descriptive summary of patients who developed poststroke headache

| Variable | N (%)/median (IQR) |
|---|---|
| **Preexisting headache** | |
| **No** | 37 (90) |
| **Yes** | 4 (10) |
| **Time to headache onset (mo) (n = 37)** | 6 (1, 24) |
| **ED presentation for poststroke headache** | |
| **Yes** | 21 (51) |
| **No** | 20 (49) |
| **CNS imaging in ER for poststroke headache** | |
| **Yes** | 20/21 (95) |
| **No** | 1/21 (5) |
| **Inpatient admission for poststroke headache** | |
| **Yes** | 17/21 (81) |
| **No** | 4/21 (19) |
| **Headache prophylaxis** | |
| **Gabapentin** | 4 (10) |
| **Lifestyle** | 8 (20) |
| **Topiramate** | 1 (2) |
| **None** | 28 (68) |

Abbreviation: ED = emergency department.

**Table 4** Characteristics of patients with stroke recurrence and patients without stroke recurrence

| | Stroke recurrence (n = 17) | No stroke recurrence (n = 98) | *p* Value[a] |
|---|---|---|---|
| **Presence of poststroke headache** | | | 0.0067 |
| **Yes** | 11 (65) | 30 (31) | |
| **No** | 6 (35) | 68 (69) | |
| **Age at first stroke** | | | 0.3115 |
| **0–3** | 5 (29) | 47 (48) | |
| **4–11** | 7 (41) | 26 (27) | |
| **12+** | 5 (29) | 25 (26) | |
| **Sex** | | | 0.8074 |
| **Male** | 9 (53) | 55 (56) | |
| **Female** | 8 (47) | 43 (44) | |
| **Family history of headache** | | | 0.8763 |
| **Yes** | 5 (29) | 19 (19) | |
| **No** | 7 (41) | 24 (24) | |
| **Missing** | 5 (29) | 55 (56) | |
| **Etiology[b]** | | | 0.2998 |
| **Arteriopathy** | 9 (53) | 34 (35) | |
| **Small vessel** | 0 (2) | 7 (7) | |
| **Unilateral focal** | 1 (24) | 12 (4) | |
| **Bilateral** | 7 (22) | 6 (6) | |
| **Aortic/cervical** | 1 (12) | 9 (9) | |
| **Cardioembolic** | 5 (29) | 32 (32) | |
| **Other** | 3 (18) | 29 (30) | |
| **Multifactorial** | 0 (0) | 3 (3) | |
| **Stroke subtype** | | | 0.5897 |
| **Hemorrhagic (secondary)** | 0 (0) | 6 (6) | |
| **Ischemic** | 17 (100) | 92 (94) | |
| **Infarcts** | | | 0.1351 |
| **Single** | 5 (29) | 48 (49) | |
| **Multiple** | 12 (71) | 50 (51) | |
| **Laterality** | | | 0.9734 |
| **Bilateral** | 6 (35) | 35 (36) | |
| **Unilateral** | 11 (65) | 63 (64) | |
| **Lesion distribution** | | | 0.1313 |
| **Anterior circulation** | 13 (76) | 58 (59) | |
| **Both anterior and posterior** | 3 (18) | 13 (13) | |
| **Posterior circulation** | 1 (6) | 27 (28) | |

[a] *p* value from $\chi^2$ tests or Fisher exact tests.
[b] Etiology collapsed into arteriopathy, cardioembolic, and other/multifactorial in $\chi^2$ test.

Earlier recognition of pediatric stroke survivors at increased risk for remote headaches and treatment of poststroke headache may improve poststroke recovery and quality of life.

headache; almost all of these children (20/21, 95%) received neuroimaging during that visit. Eighty-one percent of children who presented to the ED for poststroke headache had at least 1 hospital admission related to this complaint. Headache prophylaxis included gabapentin (10%), topiramate (2%), or lifestyle modifications (20%) (increased fluid intake, improved sleep hygiene, dietary modifications, trigger avoidance). A majority (68%) did not have any pharmacologic or behavioral intervention documented.

### Stroke recurrence

Recurrent stroke occurred in 17 patients (15%), typically seen in the first 6–12 months after the sentinel stroke (table 4). Poststroke headache was more common in these patients (11/17; 65%) compared with patients who did not have recurrent stroke (30/98; 31%) ($p = 0.0067$). Other factors including age, sex, and initial stroke etiology were not associated with stroke recurrence in univariable analyses. Thus, no multivariable modeling was considered. Importantly, children who experienced headache during stroke recurrence also had other associated neurologic symptoms. Of the 17 subjects with stroke recurrence, most children also presented with hemiparesis or facial asymmetry and encephalopathy.

**TAKE-HOME POINTS**

- Of 115 children aged 30 days to 18 years with confirmed arterial ischemic stroke, 41 (36%) experienced poststroke headache, with headache developing a median of 6 months after stroke.
- Remote (>30 day after stroke onset) poststroke headache was associated with arteriopathy and older age at stroke.
- Poststroke headache was also associated with greater risk for stroke recurrence. These children also presented with hemiparesis or facial asymmetry and encephalopathy.
- Counseling childhood stroke survivors about risk for remote headache after stroke is reasonable.
- Treatment strategies to reduce the risk for remote headache are not known.

## Discussion

The principal finding of this report is the frequency of remote poststroke headache in children, occurring in 36% of survivors, with onset within the first year of recovery. Survivors with poststroke headache were more likely to be older at first stroke and have stroke due to arteriopathy. An association between stroke recurrence and poststroke headache was also identified but must be interpreted with caution, given the limitations of this retrospective study. Earlier recognition of pediatric stroke survivors at increased risk for remote headaches and treatment of poststroke headache may improve poststroke recovery and quality of life.

The effect of headache on quality of life in children following stroke is not known. Pain is common among adult stroke survivors and is associated with fatigue and decreased quality of life[1,6] and impedes rehabilitation.[7] The frequency of poststroke headache in our study (36%, 32% with new headache) is consistent with a previous report of recurrent headaches at 1-year recovery in children after stroke.[3] The results of our study do not permit conclusions about optimal treatment strategies for poststroke headache in the pediatric population, or whether such treatment alters overall recovery and rehabilitation.

In our cohort, remote headache after stroke was associated with an increased number of ER visits, urgent neuroimaging, and hospital admissions. Our finding, that urgent imaging was obtained in almost all children who presented to the ED with remote poststroke headache has not previously been reported. Despite unchanged neurologic examinations and imaging, 81% of these patients were admitted to the hospital for observation. These findings suggest that a careful history and examination may help guide decisions about urgent diagnostic testing and may be sufficient to avoid hospitalization. Our data highlight the importance of early recognition of patients at risk for poststroke headache to guide early treatment and limit the cost burden to the patient, family, and healthcare system.

The pathophysiology of poststroke headache is not fully understood. Stroke-induced excitotoxic and inflammatory changes may increase neuronal excitability and produce central pain sensitization, or structural injury to brainstem nuclei may disinhibit pain pathways.[8] Vessel injury or inflammation may contribute to headache pathophysiology, potentially explaining the association between arteriopathy and poststroke headache in our study. Genetic risk factors or other preexisting headache tendencies likely also play a role in the development of poststroke headache. Family history of headache was documented in a higher proportion of patients with poststroke headache than those without in

our study; however, this history was questioned less frequently in headache-free patients, biasing these results. These data suggest that specific documentation of headache risk factors in the medical record for children recovering from a stroke may help in later urgent assessment of and evaluation of children who present with new-onset headache after stroke.

Children with poststroke headache had a higher rate of stroke recurrence than headache-free children in our study. Previous studies have shown an association between preexisting migraine and stroke risk,[9] including in adolescents with migraine.[10] These findings suggest a relationship between the mechanisms underlying stroke and some headaches. Migraine is associated with cortical spreading depression, as well as endothelial dysfunction and pathologic vascular reactivity, which may contribute to stroke risk.[11] The retrospective nature of our dataset limits our ability to report individual headache characteristics including with migraine with aura, migraine without aura, or tension-type headache in this group. If the occurrence of remote headache after stroke were a risk factor for recurrence, this would require prospective studies to test the hypothesis and it remains unclear whether effective headache treatment would lower this risk or whether these children warrant closer observation or different secondary stroke prevention than children without headache.

This study has a number of limitations. Lifestyle variables, medication overuse, psychosocial stressors, and socioeconomic status were not systematically recorded, and we cannot exclude the possibility that children who developed poststroke headache may have developed headaches due to other concomitant triggers. In addition, the complaint of headache was retrospectively abstracted from the medical record and may be affected by reporting and ascertainment bias. Given the retrospective nature of our study, headache characteristics were not recorded according to the International Classification of Headache Disorders and could have implications for treatment and preventive measures. The spectrum of headache types affecting stroke survivors and the chronicity and overall headache burden remain open questions.

This study represents a detailed description of poststroke headache in a pediatric population. Improved identification of children at risk for headache, early treatment and lifestyle modifications, may reduce morbidity and improve quality of life for survivors of childhood stroke.


## Study funding

Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program.


## Disclosure

The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.


## Publication history

Received by *Neurology: Clinical Practice* September 10, 2018. Accepted in final form March 28, 2019.


## Appendix Authors

| Name | Location | Role | Contribution |
|---|---|---|---|
| **Ana B. Chelse, MD, MS** | Northwestern University Feinberg School of Medicine, Chicago | Author | Involved in study design, data collection, analysis, and writing the manuscript |
| **Jonathan E. Kurz MD, PhD** | Northwestern University Feinberg School of Medicine, Chicago | Author | Involved in study design, analysis, and writing the manuscript |
| **Kathleen M. Gorman, MD** | Northwestern University Feinberg School of Medicine, Chicago | Author | Involved in study design, data collection, analysis, and writing the manuscript |
| **Leon G. Epstein, MD** | Northwestern University Feinberg School of Medicine, Chicago | Author | Involved in study design, analysis, and writing the manuscript |
| **Lauran C. Balmert, PhD** | Northwestern University Feinberg School of Medicine, Chicago | Author | Developed the statistical analysis plan, reviewed analyses and results for soundness in interpretation, and reviewed the manuscript |
| **Jody D. Ciolino, PhD** | Northwestern University Feinberg School of Medicine, Chicago | Author | Developed the statistical analysis plan, reviewed analyses and results for soundness in interpretation, and reviewed the manuscript |
| **Mark S. Wainwright, MD, PhD** | University of Washington Medical School, Seattle | Author | Supervised the study and was involved in study design, data collection, analysis, and writing the manuscript |

## References


1. Naess H, Lunde L, Brogger J, Waje-Andreassen U. Post-stroke pain on long-term follow-up: the Bergen stroke study. J Neurol 2010;257:1446–1452.
2. deVeber GA, Kirton A, Booth FA, et al. Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian pediatric ischemic stroke registry. Pediatr Neurol 2017;69:58–70.
3. Mallick AA, Ganesan V, Kirkham FJ, et al. Outcome and recurrence 1 year after pediatric arterial ischemic stroke in a population-based cohort. Ann Neurol 2016;79:784–793.
4. Hansen AP, Marcussen NS, Klit H, Andersen G, Finnerup NB, Jensen TS. Pain following stroke: a prospective study. Eur J Pain 2012;16:1128–1136.
5. Bernard TJ, Manco-Johnson MJ, Lo W, et al. Towards a consensus-based classification of childhood arterial ischemic stroke. Stroke 2012;43:371–377.
6. Jönsson AC, Lindgren I, Hallström B, Norrving B, Lindgren A. Prevalence and intensity of pain after stroke: a population based study focusing on patients' perspectives. J Neurol Neurosurg Psychiatry 2006;77:590–595.
7. Aprile I, Briani C, Pazzaglia C, Cecchi F, Negrini S, Padua L. Pain in stroke patients: characteristics and impact on the rehabilitation treatment. A multicenter cross-sectional study. Eur J Phys Rehabil Med 2015;51:725–736.
8. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. Lancet Neurol 2009;8:857–868.
9. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914.
10. Gelfand AA, Fullerton HJ, Jacobson A, et al. Is migraine a risk factor for pediatric stroke? Cephalalgia 2015;35:1252–1260.
11. Gryglas A, Smigiel R. Migraine and stroke: What's the link? What to do? Curr Neurol Neurosci Rep 2017;17:22.

Neurology® Clinical Practice

# Remote poststroke headache in children: Characteristics and association with stroke recurrence

Ana B. Chelse, Jonathan E. Kurz, Kathleen M. Gorman, et al.

*Neurol Clin Pract* 2019;9;194-200 Published Online before print May 17, 2019
DOI 10.1212/CPJ.0000000000000652