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Is Migraine a Risk Factor for Pediatric Stroke?

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Abstract

Importance—Our understanding of risk factors for childhood stroke is incomplete. In adults, migraine with aura is associated with a two-fold increase in ischemic stroke risk.

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Jacobson: Performed some of the statistical analyses, edited the manuscript for intellectual content.
Fullerton: Assisted with the conceptualization and design of the study and data interpretation, edited the manuscript for intellectual content.
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Objective—In this cohort study we examine the association between migraine and stroke among children in Kaiser Permanente Northern California (KPNC).

Design, Setting, and Participants—Children ages 2-17 years who were members of KPNC for ≥6 months between1997-2007 were included. Migraine cohort members had one or more of: an ICD-9 code for migraine, migraine listed as a significant health problem, or a prescription for a migraine-specific medication. The comparison group was children with no evidence of headache.

Main outcome measures—stroke incidence rates and incidence rate ratios (IR).

Results—Among the 1,566,952 children within KPNC during the study period, 88,164 had migraine, and 1,323,142 had no evidence of headache. Eight migraineurs had a stroke (3 [38%] hemorrhagic; 5 [63%]ischemic). Eighty strokes occurred in children without headache, (53 [66%]hemorrhagic;27 [34%] ischemic). The ischemic stroke incidence rate was 0.9/100,000 person-years in migraineurs vs. 0.4/100,000 person-years in those without headache; IR 2.0 (95% CI 0.8-5.2). A post-hoc analysis of adolescents (12-17 years) showed an increased risk of ischemic stroke among those with migraine; IR 3.4(95% CI 1.2-9.5). The hemorrhagic stroke incidence rate was 0.5/100,000 person-years in migraineurs and 0.9/100,000 person-years in those without headache; IR 0.6 (95% CI 0.2-2.0).

Conclusions—There was no statistically significant increase in hemorrhagic or ischemic stroke risk in pediatric migraineurs in this cohort study. A post-hoc analysis found that ischemic stroke risk was significantly elevated in adolescents with migraine. Future studies should focus on identifying risk factors for ischemic stroke among adolescent migraineurs. Based on adult data, we recommend that migraine aura status should be studied as a possible risk factor for ischemic stroke among adolescent migraineurs.

Keywords

migraine; childhood stroke; pediatric stroke; aura

Introduction

Childhood stroke is more common than previously thought, with an ischemic stroke incidence rate of 1.3 per 100,000 person-years at risk(1). Although children with congenital heart disease, sickle cell disease, prothrombotic conditions, and autoimmune diseases have an increased risk of ischemic stroke, most children with stroke are previously healthy(2-5). Recent studies (3, 6)suggests that minor infections and head or neck trauma are prevalent risk factors for childhood stroke; however, these are common disorders in childhood, whereas stroke is rare, suggesting that stroke in children is multifactorial. A better understanding of stroke risk factors is needed to guide primary and secondary stroke prevention strategies in children.

In adults, migraine with aura is associated with an approximately two-fold increased risk of ischemic stroke(7). Recent studies have also suggested an increased risk of hemorrhagic stroke in adults with migraine(8-10). Migraine is a common neurologic disorder characterized by episodes of headache accompanied by sensitivity symptoms such as photophobia, phonophobia, nausea and vomiting(11). Migraine is common among children

and the prevalence increases with age throughout adolescence; by age ten the one-year prevalence in the U.S. is approximately 5%(12). If migraine is as strongly associated with stroke in children as it is in adults, it would be the most common chronic condition associated with stroke in this age group.

This retrospective cohort study examines whether migraine is associated with an increased risk of ischemic or hemorrhagic stroke in a population of children enrolled in a large managed care organization, Kaiser Permanente Northern California (KPNC). Given that migraine has been associated with both ischemic and hemorrhagic stroke in adults, and that nearly half of all strokes in children are hemorrhagic(13), we examined for an association with each stroke type and for an association with the two types combined.

Methods

Ethical approvals—The study protocol was approved by the Committees for Human Research at University of California, San Francisco and KPNC. Procedures followed were in accordance with institutional guidelines.

Study setting—KPNC is a large integrated healthcare delivery system that provides care to approximately 30% of the population of northern California. The members of KPNC are demographically similar to the overall population of California, except that the very wealthy and very poor are underrepresented(14). KPNC maintains extensive electronic databases that include demographics, all inpatient and outpatient diagnoses, pharmacy records, and radiology records.

Study population—The study cohort consisted of KPNC members ages 2-17 years with at least one continuous membership period of ≥6 months during the study period (1997-2007). Pediatric stroke is most common in the neonatal period, followed by the period from age 29 days to two years(1), however diagnosis of migraine typically is not given to children in this age range. Therefore children younger than age 2 years were excluded. Those children who had a gap in membership during the study period were allowed to re-enter the cohort and contribute more person time to the analysis as long as they returned for a minimum of 6 contiguous months while they were still age <18 years.

Determination of stroke outcomes—Stroke outcomes were ascertained previously as part of the Kaiser Pediatric Stroke Study (KPSS) and the methods for stroke determination have been described previously(1). The methods to identify pediatric stroke cases in KPSS were more comprehensive than in previous pediatric stroke research, and accuracy was assured via independent case confirmation by a child neurologist board-certified in vascular neurology (HJF). In brief, KPSS used two search strategies to identify potential cases of pediatric ischemic stroke: (1) diagnostic (ICD-9) code searches for inpatient and outpatient diagnoses suggestive of hemorrhagic or ischemic stroke; and (2) radiology text string searches of all pediatric head imaging reports for terms suggestive of ischemic stroke. The full imaging reports were then reviewed by a pediatric stroke expert (HJF) to exclude those not consistent with stroke. For hemorrhagic stroke, cases were ascertained through ICD-9 search as it was not feasible to review all imaging reports given the large number that

comment on presence or absence of blood. Traumatic hemorrhagic stroke cases were included given that changes in concentration or vision during a migraine attack could put a child at higher risk for a traumatic hemorrhagic stroke. All stroke cases were confirmed through chart review by two independent neurologists using predefined clinical and radiographic criteria; disagreements were resolved through adjudication by a third neurologist.

Determination of migraine status

To be included in the migraine group, a child had to have one or more of the following: 1) an ICD-9 code for migraine (i.e., any 346.XX code) from any encounter, 2) migraine listed on their significant health problem list, or 3) pharmacy records showing a prescription of a migraine-specific medication. The migraine-specific medications included in the search were: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, dihydroergotamine, and ergotamine. Almotriptan and rizatriptan are now approved by the Federal Drug Administration for use in children (almotriptan for ages 12-17, rizatriptan for ages 6-17 years); the remainder of the listed medications have been studied for migraine in pediatrics and/or are used clinically off label(15-31). To qualify via pharmacy records there also had to be no ICD-9 code for cluster headache, as this is the only other diagnosis these medications could be used to treat.

Previous research within KPNC has shown that the coding error rate for migraine ICD-9 codes is very low, however the sub-type of migraine (i.e., with or without aura) is not accurate(32), therefore it is not possible to reliably subdivide those migraineurs with aura from those without based on ICD-9 code.

Because there is a high potential for ascertainment bias following a stroke diagnosis, as all children with stroke are evaluated by a neurologist, it was required that a child be seen clinically for headache *prior* to the stroke date in order to be included in the migraine group. Charts were also reviewed for those children, whose medical encounter for *headache* occurred prior to their stroke date, and who ultimately went on to be diagnosed with migraine. This was to ensure there was no identifiable cause of the headaches (other than migraine) prior to the stroke date; specifically, head trauma and infection were ruled out. Previous research indicates that 94% of adult patients who come to the primary care doctor for recurrent headaches have migraine or probable migraine(33), therefore it was assumed that these children who had headache severe enough to report to a doctor, who ultimately received a diagnosis of migraine were experiencing migraine attacks prior to their stroke date—they simply had a delay in diagnosis.

Comparison group

It is estimated that only 48% of adult migraineurs in the U.S. have ever been diagnosed by a physician(34), and the likelihood that the rate of under-diagnosis is even higher in children(35). Therefore, the primary comparison group consisted of children with no evidence of headache in order to minimize contamination by undiagnosed migraineurs. To be included in the no-headache comparison group, children had to have no evidence of any

ICD-9 code for headache of any type, and could not have headache listed as a significant health problem.

Statistical analysis

Pediatric ischemic and hemorrhagic stroke incidence rates per 100,000 person-years were calculated for the migraine group and the no-headache comparison group. Incidence rate ratios (IR) and 95% confidence intervals were then calculated as a measure of relative risk.

The primary analysis was the ischemic stroke incidence rate ratio between the migraine group and the no-headache comparison as the association between migraine and ischemic stroke is most clearly elucidated in adults. Secondary analyses included: 1) stroke (overall) incidence rate ratio between the migraine group and the no-headache group, and 2) the hemorrhagic stroke incidence rate ratio between the migraine group and the no-headache group. When our primary analysis demonstrated that children in the migraine group who had ischemic strokes were older than those in the no-headache comparison group, we performed a post-hoc stratified analysis considering ischemic stroke incidence rates and rate ratios among those 12-17 years old (with person-time only contributed between ages12-17). Statistical analyses were performed using SAS 9.3 (Cary, North Carolina)and Stata v. 12.0 (College Station, Texas). A *p*-value of <0.05 was considered significant, and two-sided tests were used.

Results

There were 1,566,952 children in the study cohort. Of these, 88,164(6%) had migraine. Another 155,646 had some evidence of headache in their chart, and so were removed from the analysis given the possibility they might have undiagnosed migraine. The other 1,323,142 had no evidence of headache and constituted the no-headache comparison group. The patient characteristics of the cohort are shown in Table 1. The mean age of the migraine group was older (9.2 years (SD 4.6) compared to 7.5 years (SD 4.9), p<0.0001).

The children experienced 88 strokes during the study period (32 ischemic, and 56 hemorrhagic). The characteristics of the children who had strokes are shown in Table 2. Children who had ischemic stroke in the migraine group were older than those who had ischemic stroke in the no-headache group.

Stroke location, etiology, hospital course details, and stroke outcome data are also shown in Table 2. There were no statistically significant differences between groups in terms of proportion requiring ICU admission, hospital length of stay, proportion with a persistent neurologic deficit, or mortality.

The number of children who suffered a stroke in each group is shown in Table 3, along with the number who had hemorrhagic and ischemic strokes in each group and stroke incidence rates and rate ratios. While the rate of ischemic stroke was higher in the migraine group compared with the no-headache group, the 95% confidence interval for the incidence rate ratio overlapped the null (IR 2.0, 95% CI 0.8-5.2). However, when this analysis was

restricted to 12-17 year olds, the ischemic stroke incidence rate was higher in the migraine group (IR 3.4 (1.2-9.5)).

Discussion

Results of our large retrospective study of KPNC children show that there is no statistically significant elevation in combined ischemic and hemorrhagic stroke risk among children with migraine. Migraine was also not associated with increased risk of hemorrhagic stroke in this study.

The incidence rate ratio for the risk of ischemic stroke among children with migraine compared to a comparison group of children without headache was 2.0 (95% CI 0.8-5.2). Given the small number of ischemic strokes in the study, the confidence interval was too wide to exclude the possibility of no effect.

However, a *post-hoc* analysis showed that the ischemic stroke incidence rate ratio was elevated in adolescents (ages 12-17 years) with migraine compared to those without headache (IR 3.4 (1.2-9.5)). Of note, all five of the ischemic strokes in the migraine group occurred in adolescents. While this was a post-hoc analysis, it leads us to hypothesize that an elevated risk of ischemic stroke exists in adolescents with migraine but not in pre-pubertal children with migraine. This suggests there may be a hormonal effect mediating the relationship between adolescent migraine and stroke risk, and in fact evidence of such a hormonal effect is seen in adult migraineurs wherein reproductive age women with migraine with aura have an increased risk for ischemic stroke. In adults, migraine with aura is associated with an approximately two-fold increased risk of ischemic stroke, with results from two meta-analyses reporting odds ratios of 2.51 (95% CI 1.52-4.14)(36) and 2.16 (95% CI 1.53-3.03)(7). This risk appears to be greatest among women under age forty-five (i.e. young women), particularly if they smoke (OR 9.03, 95% CI 4.22-19.34) or use estrogen-containing contraceptives (OR 7.02; 95% CI 1.51-32.68)(7). Based on Women's Health Study data, migraine with aura is thought to account for an additional four ischemic strokes per 10,000 woman-years(37). Fortunately, these women are more likely to have non-disabling strokes(38).

Unlike in the adult population, (8-10) we found no association between pediatric migraine and increased risk of hemorrhagic stroke in this study population. Of note, the stroke incidence rates for both ischemic and hemorrhagic stroke in all groups in this study were lower than the 1.3/100,000 person-years childhood stroke incidence rate observed in the Kaiser Pediatric Stroke study. This is likely due to the fact that we excluded the twenty-nine day to age two years age group in this study, and that age bracket has the highest childhood stroke incidence rate(1).

Our study results are generalizable as the Kaiser Permanente Northern California membership is representative of the general population of children in California(14). While an even larger study population would have been optimal, our cohort of nearly 1.6 million children within one medical system with integrated electronic medical records, pharmacy records, and radiology records provided an excellent opportunity to examine this research

question. While this was a retrospective study, our stroke outcomes were carefully defined and adjudicated.

One limitation of this study was the small number of stroke events in the migraine group. As such we did not have power to adjust for potential confounding or mediating factors that could influence the association between migraine and ischemic stroke in children and adolescents, such as smoking or use of oral contraceptives. Furthermore as the medical record did not include aura status we were not able to examine how aura might mediate the relationship between migraine and stroke, as it appears to do in adult women. Future prospective studies on stroke risk in adolescent migraineurs should aim to measure migraine aura status in adolescent migraineurs.

Lastly, we cannot be certain that we identified all migraineurs within the overall pediatric cohort. Only about half of all adults with migraine ever receive a diagnosis(34), and the proportion of migraineurs diagnosed is probably even lower among children. Therefore it is possible that even after we removed children with evidence of headache that our comparison group may still have been contaminated with children with undiagnosed migraine.

Because childhood stroke is still a rather rare event and migraine in children and adolescents is common, care must be taken in counseling parents so as not to create unnecessary anxiety. Parents can be reassured that even if there is an association between pediatric migraine and ischemic stroke, the likelihood that their child with migraine will have an ischemic stroke remains extremely low at 0.9/100,000 person-years. Furthermore, in adults with migraine, their strokes tend to result in better functional outcomes(38). There is some suggestion this may also be the case with pediatric stroke associated with migraine, as the hospital length of stay for the migraineurs in this study in both the ischemic and hemorrhagic strokes were shorter (though not statistically significantly). In addition there is no evidence to suggest that increased ischemic stroke risk extends to migraineurs without aura, and only about a quarter of migraineurs have aura(39-41). It would however remain prudent to counsel children and adolescents against smoking, given its overall detrimental health effects and the increased stroke risk among adult migraineurs with aura who smoke. It is more complicated to decide whether estrogen-containing contraceptives should be considered contra-indicated in an adolescent girl with migraine with aura. As the data stand there is no evidence for admonishing the estrogenic oral contraceptives, therefore each clinical case must be individualized. While their use is associated with increased stroke risk in adult women with migraine with aura(7), pregnancy and the post-partum state are also associated with an increased risk of stroke(42, 43), and a history of migraine is associated with an increased risk of stroke in pregnancy (OR 8.5, 1.5-62.1)(44).

The status of the relationship between adolescent migraine, particularly with aura, and ischemic stroke needs further evaluation and will require clinicians' careful assignment of diagnoses, or a biomarker for aura, to support further studies.

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Abbreviations

ICHD	International classification of Headache Disorders
KPNC	Kaiser Permanente Northern California
IR	incidence rate ratio
CI	confidence interval

Bullet Points

- There does not appear to be an increased risk of hemorrhagic stroke among children or adolescents with migraine
- There may be an increased risk of ischemic stroke among adolescents with migraine, though further study is needed as this was a post-hoc analysis.

Table 1
Patient Characteristics of Migraine vs. No Headache Groups

	Migraine (n=88,164)	No Headache (n=1,323,142)
Age at entry (mean(SD)), in years*	9.2(4.6)	7.5(4.9)
Age at midpoint of follow-up (mean(SD), range), in years*	12.4 (3.7) 2-17	9.8 (4.8) 2-17
Follow-up time (mean(SD)), in years*	6.4(3.2)	4.7(3.3)
Percent female*	66%	47%
Race (percent)	White 47% Afr-American 10% Asian 7% Other 7% Unknown 29%	White 30% Afr-American 7% Asian 11% Other 3% Unknown 49%
Percent Hispanic (Percent unknown)	22% (40%)	16% (61%)
Number of ischemic strokes	5	27
Number of hemorrhagic strokes	3	53

* $p<0.0001$

Table 2

Comparison of Stroke Features Between the Migraine and No Headache Groups (*n*=88 total)

	Migraine	**No Headache**
Ischemic Stroke:		
Number of ischemic strokes	5	27
Age at stroke occurrence (mean(SD), range), in years	16.4 (0.9) 15-17	10.4 (5.1)* 2-17
Percent female	40%	30%ns
Race	1 African American 1 Hispanic 3 Caucasian	5 African American 9 Caucasian 4 Asian 5 Hispanic 1 Native American 3 Unknown
Vascular territory infarcted:	3 MCA 1 PICA 1 Not recorded—but left parietal location	18 MCA 2 ACA 3 PCA 1 PICA 5 Other vascular territory
Required ICU admission, *n*(%)	3/5 (60%)	17/26 (65%)ns
Hospital length of stay, mean(SD); range, in days	8(6.1); 2-16	18.2 (24.2); 1-117ns
Persistent neurologic deficit	4/5 (80%)	22/26 (85%)ns
Stroke etiology	1 Autoimmune 1 Cardiac, (atrial myxoma) 1 Idiopathic 2 Vasculopathy	6 Idiopathic 1 Cardiac 10 Vasculopathy 3 Hypercoagulability 5 Infection 2 Other
Mortality n(%)	0/5 (%)	1/27(4%)ns
Hemorrhagic Stroke:		
Number of hemorrhagic strokes	3	53
Age at stroke occurrence (mean(SD), range), in years	13.3 (3.5) 10-17	10.4 (4.7)ns 2-17
Percent female	67%	32%ns
Race	1 Asian 1 Hispanic 1 Unknown	3 African-American 17 Caucasian 12 Asian 13 Hispanic 8 Unknown
Etiology	2 Structrual (1 aneurysmal, 1 AVM) 1 traumatic	26 Structural 13 Trauma 7 Idiopathic 7 Other
Required ICU admission	2/3 (66%)	40/50 (80%)ns
Hospital length of stay, mean(SD); range, in days	6.3 (6.5); 0-13	14 (15.2); 0-49ns
Persistent neurologic deficit, n (%)	0/3, (0%)	26/51 (51%)ns
Mortality, n (%)	0/3, (0%)	5/53 (9%)ns

* p-value <0.0001

[ns]not significant

MCA=middle cerebral artery
PICA=posterior inferior cerebellar artery
ACA=anterior cerebral artery
PCA=posterior cerebral artery
ICU=intensive care unit
AVM=ateriovenous malformation
SD=standard deviation

Table 3

Stroke incidence rates and incidence rate ratios in children (2-17 years of age) enrolled in Kaiser Permanente Northern California (1997-2007), stratified by presence or absence of migraine.

		Migraine vs. No Headache
All stroke:		
Number of strokes in migraine group vs. comparison group		8 vs. 80
Incidence rate/100,000 person-years		1.4 vs. 1.3
Incidence rate ratio (95% CI)		1.1(0.5-2.3)
ISCHEMIC STROKE:		
Number of strokes in migraine group vs. comparison group	Overall Cohort	5 vs. 27
	Ages 12-17 only	5 vs. 12
Incidence rate/100,000 person-years	Overall Cohort	0.9 vs. 0.4
	Ages 12-17 only	1.7 vs. 0.5
Incidence rate ratio (95% CI)	Overall Cohort	2.0(0.8-5.2)
	Ages 12-17 only	3.4(1.2-9.5)
HEMORRHAGIC STROKE:		
Number of strokes in migraine group vs. comparison group		3 vs. 53
Incidence rate/100,000 person-years		0.5 vs. 0.9
Incidence rate ratio (95% CI)		0.6 (0.2-2.0)