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Before the headache

Infant colic as an early life expression of migraine



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ABSTRACT

Objective: Childhood periodic syndromes are thought to be early life expressions of the genetic tendency for migraine. The objective of this study was to determine whether maternal migraine is associated with an increased risk of infant colic, because this may indicate that colic is a childhood periodic syndrome.

Methods: This was a cross-sectional study performed in general pediatric clinics. To minimize recall bias, mothers were surveyed at their infants' 2-month-old well-child visit, the age when colic is most prevalent. Colic was ascertained via parental report using modified Wessel criteria. Migraine history was obtained by having a physician diagnosis or a positive screen on ID Migraine. The primary outcome measure was difference in colic prevalence in infants with and without a maternal history of migraine.

Results: Data from 154 infant-mother pairs were analyzed. Infants with a maternal history of migraine were 2.6 times as likely to have colic as infants without a maternal history of migraine (29% vs 11%, prevalence ratio 2.6 (95% confidence interval 1.2–5.5), $p = 0.02$). There was no difference in the accuracy with which migraineur mothers perceived their infants' colic status compared with that of nonmigraineur mothers. Data on paternal history of migraine were available for 93 infants. Infants with a paternal history of migraine may have a higher prevalence of colic (22% vs 10%), although the prevalence ratio 2.3 (0.6–9.4, $p = 0.24$) had wide confidence intervals.

Conclusions: Maternal migraine is associated with increased risk of infant colic. Because migraine has a strong genetic underpinning, this association suggests that colic may be an early life manifestation of migraine. **Neurology® 2012;79:1392-1396**

GLOSSARY

CI = confidence interval.

Migraine is a complex disorder of the brain with strong genetic underpinnings.^{1–3} A family history of migraine is the single strongest risk factor for developing the condition.⁴ Despite this marked genetic tendency, only in the case of the relatively rare migraine subtype of familial hemiplegic migraine have the genetics been well dissected.⁵

Childhood periodic syndromes, such as benign paroxysmal vertigo of childhood or benign paroxysmal torticollis, are thought to be early life expressions of those genes that later in life will be expressed as migraine.^{6,7} There is some evidence to suggest that infant colic may also be an early life expression of migrainous tendencies.^{8–10} If true, this would push our understanding of when migraine genetics can first be expressed back into the first weeks of infancy and have major implications for the treatment of this common and often distressing disorder of infancy.

The research to date linking infant colic to migraine is primarily retrospective in nature,^{9,10} making it subject to recall bias. The goal of this study was to assess whether a maternal history of migraine predicts colic in young infants.

METHODS In this cross-sectional study, the population consisted of mothers who were bringing their infants in for 2-month well-child visits to the University of California San Francisco–affiliated general pediatric clinics. The study period ran from July 2010

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to September 2011. Consecutive mothers attending the pediatric clinics were invited to complete a short survey about colic and migraine in the waiting room.

The primary outcome measure was whether a maternal history of migraine was associated with infant colic. We chose maternal history of migraine, given the higher prevalence of migraine in women¹¹ and the experience of local pediatricians that mothers were more likely to attend the 2-month well-child visits.

A maternal history of migraine was defined as either a positive maternal response to the question, “Has a physician ever diagnosed you with migraines?” or a positive maternal screen on ID Migraine. ID Migraine is a validated 3-question survey instrument with high sensitivity and specificity for a migraine diagnosis (sensitivity 0.81, specificity 0.75, and positive predictive value 0.93).¹² A positive screen is defined as answering yes to 2 or more of the questions.

Infant colic peaks between 6 and 8 weeks of life.^{13,14} Therefore, infants within 4 weeks of this window when their mothers completed the survey, i.e., 2–12 weeks of age, based on corrected gestation age to adjust for premature birth, were included.

Because there is no validated parental survey instrument for identifying infants with colic, in previous studies colicky infants were identified by parental report or by pediatricians’ documentation.^{13,15} After discussion with our pediatricians revealed that in local practice colic is rarely coded for or systematically documented in infants’ charts, we chose to identify infant colic via parental report. Colic was defined using modified Wessel criteria, and mothers were asked, “Has your baby cried for at least 3 hours a day, at least 3 days a week, for at least a week?”

To account for the possibility that mothers with migraine might be more sensitive to the sound of their baby crying due to sound sensitivity (phonophobia) and therefore more likely to think their baby was colicky, we asked the mothers an additional question about whether they perceived their baby as colicky. We compared the mothers’ responses to this perception question with their responses to the question that used modified Wessel criteria for colic. If the mother’s response to the perception question agreed with her response to the Wessel criteria–based question, the mother’s response was considered accurate.

As an exploratory secondary analysis, there was a section of the survey that fathers could complete if they were present at the visit. Questions in this section focused on paternal history of migraine and paternal perception of whether their infant was colicky; these questions were identical to those used for the mothers.

To ensure that survey responses were provided directly by the mother, and, if present, directly by the father, it was clearly indicated on the survey that the questions specific to each parent were to be completed only by that parent.

Analysis. Data were analyzed using STATA (version 12; Stata-Corp, College Station, TX). χ^2 analysis was performed for the primary outcome analysis of whether maternal migraine is associated with infant colic. Logistic regression was used to assess for an effect of infant sex or age on this outcome. Student *t* test was used to compare the age of infants with colic with those without colic, and χ^2 analysis was used to compare the sex proportions between these 2 groups and the proportion of maternal accuracy in assessing colic. For the smaller exploratory analysis involving paternal migraine history, the Fisher exact test was used. A *p* value of 0.05 was considered significant.

Standard protocol approvals, registrations, and patient consents. The Committee for Human Research at the University of California, San Francisco approved this study (study

number 10-01640). Because this was an observational study, it was not entered into a trial registry.

RESULTS A total of 165 surveys were collected. Three were excluded for missing data on colic. Eight were excluded for having a corrected age either less than 2 weeks or greater than 12 weeks. Data from the remaining 154 surveys were analyzed. We have no data on how many parents refused the survey, and no identifying data to check differences.

Colic. Twenty-two infants had colic (14%). The mean age (corrected) of the colicky infants was 8.0 weeks (SD 1.4 weeks) and for the noncolicky infants was 8.3 weeks (SD 2.1 weeks) (*p* = 0.56). Of the colic group, 55% were girls, whereas 47% were girls in the noncolic group (*p* = 0.51). Twenty-eight (18%) of the mothers had migraine.

Maternal migraine status. Infants with a maternal history of migraine were 2.6 times more likely to have colic than infants without a maternal history of migraine (29% vs 11%, prevalence ratio 2.6, 95% confidence interval [CI] 1.2–5.5, *p* = 0.02). Infant age and sex had no effect on this outcome.

There was no difference in the accuracy with which migraineur mothers perceived their infants’ colic status compared with that of nonmigraineur mothers. Migraineur mothers’ accuracy was 86%, compared with nonmigraineur mothers’ accuracy of 87% (*p* = 0.91).

Paternal migraine status. Data on paternal history of migraine was available in 93 of the 154 surveys (60%). Nine of the fathers had migraine (10%). There were 10 colicky infants in this group. Infants with a paternal history of migraine may have a higher prevalence of colic (22% vs 10%, prevalence ratio 2.3, 95% CI 0.6–9.4, *p* = 0.24); however, the confidence intervals were too wide to exclude the possibility of no effect. Fathers with migraine were as likely to perceive their infant’s colic status accurately as were nonmigraineur fathers (78% vs 90%, *p* = 0.3).

DISCUSSION The current study was a hypothesis-generating study designed to investigate whether infant colic may be related to migraine. The data show a significantly higher prevalence of colic in children of mothers with migraine, suggesting that infantile colic may be a childhood periodic syndrome that is a migraine precursor. Infant colic (excessive crying in an otherwise healthy infant) has an incidence of 5%–19% in prospective studies.^{13,16} Normal infant crying increases in the first weeks of life, peaks at 6–8 weeks of age, and tapers off by age 3 months.^{14,17} Infant colic is a highly intensified ver-

sion of this same temporal pattern, often with bouts of prolonged, inconsolable crying.^{13,17} Colic is classically defined as at least 3 hours of crying, at least 3 days a week, for 3 weeks (Wessel criteria).¹⁸ Practically applied, the more succinct modified Wessel criteria of crying for at least 3 hours a day, at least 3 days a week, for the past week, are often used in practice and in research.^{19,20}

The underlying pathogenesis of colic is not well understood, despite much research.^{9,13} The term “colic” implies an abdominal derivation for the infants’ distress, although no clear evidence for that localization exists. Some have implicated excessive intestinal gas²¹ or a problem with the infant’s milk. However, a randomized placebo-controlled trial of simethicone, a medication that speeds the transit of intestinal gas, showed no benefit over placebo.²² In addition, type of infant feeding, be it breast milk or formula, does not affect the rate of colic.²³ There is no evidence for lactose intolerance in colicky infants^{21,24} and although supplementation with probiotics appeared promising in a small study,²⁵ the effect could not be reproduced in a larger study.²⁶ Cow’s milk protein allergy may cause excessive crying in a subset of infants²⁷; however, these infants’ symptomatology may distinguish them from those with idiopathic colic.²⁸ Markers of dietary protein hypersensitivity and intestinal damage, such as fecal α_1 -antitrypsin concentrations and fecal hemoglobin, are not elevated in infants with colic.²³ Moreover, counseling parents about how best to respond to their infants’ colicky crying is more effective in treating colic than eliminating cow or soy protein, and reintroducing cow or soy protein does not worsen crying.²⁹ Whereas colicky infants cry more in the late afternoon and evening hours,^{14,17} young infants feed every few hours throughout the day and night, and it is challenging to identify a gastrointestinal etiology that would have this temporal pattern.

Two previous retrospective studies reported a link between childhood migraine and infant colic,^{9,10} and young infants with cerebral injuries are prone to excessive crying, suggesting a potential neurologic etiology to colic.³⁰ It is important that we ultimately determine the underlying pathophysiology of colic so that these infants can be treated appropriately. Excessive infant crying is frustrating for caregivers³¹ and is a risk factor for shaken baby syndrome.^{14,32,33} The peak in hospitalizations for shaken baby syndrome falls temporally right after the peak in infant crying.¹⁴

In the current study, maternal migraine was associated with a more than 2-fold increase in the prevalence of infant colic in this study. Overall, 14% of the infants in this study had colic, which is in keeping with previously reported colic prevalence estimates of 5%–19%.^{13,16} Similarly, the migraine

prevalence of 18% in the mothers is highly in keeping with the 18% 1-year migraine prevalence estimate among women in North America.¹¹

The method for determining maternal migraine in this study was either a positive screen on ID Migraine or maternal report of a physician diagnosis of migraine. Physician diagnosis of migraine is almost always correct, with 98% accuracy.³⁴ However, only 48% of adult migraineurs in the United States have ever received a physician diagnosis of migraine,³⁵ so relying on physician diagnosis alone is inadequate, and it is a strength of this study to have also identified maternal migraineurs via a validated survey instrument.

Previous studies on the relationship between migraine and infant colic were retrospective and therefore subject to recall bias.^{9,10} This study minimized recall bias by collecting data on colic prevalence during the period of infancy when colic occurs. The magnitude of the association between colic and maternal migraine in this study is consistent with what has been described previously. In a small retrospective study by Jan and Al-Buhairi,⁹ 52% of the children with migraine had a history of colic vs 20% of control children. Because our study uses maternal history of migraine as a means for inferring possible familial migraine tendency in the infants, it is notable that in the study of Jan and Al-Buhairi,⁹ a history of infant colic in a first-degree relative was more likely in the migraineur children, and those children with a history of colic were more likely to have a family history of migraine.⁹ In the second study, a history of colic was also more likely in children with migraine than in headache-free control children (38.4% vs 26.9%) or in children with tension-type headache (38.4% vs 25.2%).¹⁰

One previous study attempted to look at a similar question prospectively.⁸ Infants were evaluated for evidence of hyperreactivity, which included parental report of frequent spontaneous crying; The Wessel criteria for infant colic were not used. Infants’ responses to stimuli, as well as their soothability, were also assessed. At follow-up 10.8 years (on average) later, 52.9% of the infants in the hyperactive group had migraine compared with an 11% prevalence of migraine in the control infants ($p < 0.01$). Childhood periodic syndromes were also more likely in the hyperactive group (64.5% vs 12.5%, $p < 0.001$).⁸

Why infants with migrainous genetics may be more likely to have colic is unclear, although an increased sensitivity to stimuli is one possible explanation. Increased sensitivity to stimuli is a hallmark of migraine; migraineurs describe heightened sensitivity to sound and light during attacks⁶ and are more likely to be sensitive to motion and cold-induced headache even between at-

tacks.^{6,36,37} Transitioning from in utero life to extrauterine life brings a flood of new and intensified stimuli. It is possible that babies with migrainous genetics are the ones who are the most sensitive to this transition and express this sensitivity through excessive crying. In one study, counseling parents to decrease infant stimulation improved colic.³⁸

Although new stimuli are present at birth, infants' ability to perceive these stimuli increases rapidly in the first weeks of life, given their rapid neurodevelopment. For example, between birth and 2 months of life an infant's visual acuity more than doubles, going from an estimated 20/200 to 20/80.³⁹ This marked increase in perceptual ability could explain why colic peaks at 6–8 weeks of life rather than immediately in the neonatal period.

This study has several limitations. For one, it is possible that a phonophobic, migrainous mother may be more likely to overestimate the length of her baby's crying and to assess her infant as colicky. However, the accuracy of migrainous mothers in perceiving whether their infants had colic was no different from that of nonmigrainous mothers. In future studies, prospective crying diaries would be a more reliable means to assess infants' crying duration.

Because this study was preliminary and targeted the parents of very young infants, the survey was kept short. We did not collect data on other epidemiologic variables that could interact with migraine in the relationship with colic, such as history of mood disorders in the parents or stress within the family.^{15,20} Our data on family history were limited in that to evaluate truly for a genetic association between migraine and colic a 3-generation family tree would have been optimal, however impractical in a well-baby visit setting. Future studies would also benefit from a means of comparing demographic characteristics of survey responders with those of survey nonresponders.

The main limitation of this study was that the marker of migraine genetics used for the infants was maternal history of migraine rather than development of migraine in the children themselves. Long-term follow-up studies are needed to confirm whether infants with colic are indeed more likely to go on to develop migraine and other childhood periodic syndromes, such as abdominal migraine, as they grow through childhood.

In the meantime, because we do not yet know the reason for distress in colicky babies, perhaps the name of the diagnosis should more closely mirror our limited knowledge of the organ systems involved. "Paroxysmal fussing of early infancy," a modification of the term originally used in the 1954 article of Wessel et al.¹⁸ may be more accurate than "colic."

Assuming that the infants' distress is abdominal in localization due to the infants' movements is analogous to watching a toddler have a tantrum and interpreting his or her flailing limbs as indicative of diffuse extremity pain. Even if the localization is abdominal, the etiology may still be migrainous and analogous to abdominal migraine. If colic is indeed migrainous rather than gastrointestinal in etiology, one wonders what the number needed to treat with age-appropriate migraine therapy would be to prevent a case of shaken baby syndrome.

AUTHOR CONTRIBUTIONS

All authors had full access to all of the data in the study, including the statistical reports. Amy A. Gelfand is the guarantor for the study, designed the study, did the data analysis and interpretation of results, drafted the majority of the first draft, and critically revised the manuscript. Katherine C. Thomas contributed to study design, performed data collection and entry, drafted portions of the manuscript, critically revised the manuscript, and provided administrative support. Peter J. Goadsby contributed to study design, assisted in interpreting the results, critically revised the manuscript, and provided supervision.

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