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Infant Colic

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Abstract

This article reviews the evidence for an association between infant colic and migraine. Infant colic, or excessive crying in an otherwise healthy and well-fed infant, affects approximately 5–19% of infants. Multiple case-control studies, a cross-sectional study, and a prospective cohort study have all found an association between infant colic and migraine. While infant colic is often assumed to have a gastrointestinal cause, several treatment trials aimed at gastrointestinal etiologies have been negative. Teaching parents how best to respond to inconsolable crying may be helpful and important for preventing shaken baby syndrome. Given accumulating evidence for a connection between infant colic and pediatric migraine, future studies should examine migraine-oriented treatments for infant colic. Infant colic should be moved into the main body of International Classification of Headache Disorders (ICHD-III beta) as one of the "Episodic syndromes that may be associated with migraine".

Introduction

A lay definition of infant colic is excessive crying in an otherwise healthy and well-fed infant. Given mounting evidence for an association between infant colic and migraine, infantile colic is now included in the appendix section of the most recent iteration of the International Headache Society's Classification system, ICHD-III beta, in the section on "Episodic syndromes that may be associated with migraine".[1] This paper will review the epidemiology of infant colic, what is known about its cause, the evidence for a connection to migraine, and a proposed approach to management of infant colic from a migraine perspective.

Normal Infant Crying and how Infant Colic Differs

While all babies cry, what distinguishes colicky babies is that they cry more, and they often cry inconsolably. There is typically a predictable diurnal pattern to colicky crying with more crying occurring in the evening hours. Normal infant crying peaks at five to six weeks of life (corrected for gestational age at birth) and declines by three to four months of age.[2,3] Colic is an amplified version of this developmental crying pattern. The prevalence of colic is thought to be 5–19% of infants.[4,5] Definitions of infant colic vary, but one of the most

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commonly used is Wessel's criteria crying for at least 3 hours a day, at least 3 days a week, for at least 3 weeks.[6]

What Causes Infant Colic?

While Wessel first described infant colic in 1954,[6] we still don't know what causes it, or whether there is one cause or multiple. While the term "colic" implies an abdominal etiology, there is little direct evidence for this localization. All that seems certain is that the babies are in distress. Wessel in fact seemed to recognize the uncertainty of colic's underlying etiology and titled his manuscript, "Paroxysmal Fussing in Infancy, Sometimes Called Colic"[6]

It is important that we ultimately determine the cause of infant colic in order to manage these infants appropriately. Excessive and inconsolable crying can lead to caregiver frustration and can be a trigger for shaken baby syndrome, a form of child abuse with potential for significant neurologic morbidity and mortality.[2,7–9] An estimate 1% of parents of 1-month-old babies admit to having shaken their child at least once to try to stop crying, and 2.2% admit to having shaken, slapped, or smothered the baby at least once in an attempt to stop crying. By age 6-months, the percentage of parents who have performed one of these dangerous physical maneuvers is a frightening 5.6%.[10]

Part of the reason many have assumed the etiology of infant colic is gastrointestinal is that the infants often pull up their legs and pass gas during the crying. Naturally this has led to concern that something in the infants' formula is at fault or that something in the maternal diet is getting into the breast milk and causing the baby abdominal distress. However, research has generally not lent support to this hypothesis. A randomized placebo-controlled trial of simethicone for infant colic, a treatment aimed at easing intestinal gas, showed no efficacy.[11]

While cow's milk protein allergy may play a causative role in a proportion of formula-fed colicky infants,[12] their symptomatology may distinguish them from those with idiopathic infant colic.[13] Indicators of dietary protein hypersensitivity and intestinal damage, such as alpha-1 antitrypsin and fecal hemoglobin, are not elevated in babies with infant colic.[14] Counseling parents about how to respond best to their infant's crying leads to a greater decrease in crying than eliminating dietary cow or soy protein, and reintroduction of these proteins does not aggravate crying.[15] There does not seem to be evidence that colicky babies are suffering from lactose intolerance.[5,16] While supplementation with probiotics appeared promising in one group's experience,[17,18] their benefits have not been reproduced.[19,20] In fact, in one study in the formula-fed subgroup the probiotic treated infants suffered significantly more fussing than the placebo group, indicative of potential harm.[19]

In addition to the research summarized above, the temporal pattern of colicky crying is difficult to explain from a feeding or gastrointestinal perspective. Colicky infants typically cry most in the late afternoon and evening hours,[2,3] while feeding in young infants occurs around the clock.

The Case for Infant Colic as a Migrainous Phenomenon

As migraine is a highly genetic disorder,[21,22] it is possible that children with migrainous genetics may express migrainous genes in one manner early in brain development and then as migraine headache later in childhood or adolescence.

An association between infant colic and childhood migraine has been reported in several retrospective case-control studies.[23–25] In a cross-sectional study, mothers with migraine were more than twice as likely to have an infant with colic.[26] In a meta-analysis study, odds of migraine were increased five to six-fold if there was a history of infant colic (OR 5.6 (95% CI 3.3–9.5)).[27] In a prospective cohort study, “hyperreactivity” in early infancy, with crying being one of the factors incorporated into this concept, was a predictor of migraine in childhood.[28] Most convincingly, in a recent population-based prospective cohort study, infant colic was associated with increased risk of developing migraine without aura by age eighteen (RR 2.7 (95% CI 1.5–4.7)), but not migraine with aura,[29] suggesting that certain migraine genes might lead to specific clinical migraine phenotypes.

If infant colic is in fact a migrainous disorder, it is still not understood exactly why the babies cry. Do they have headache? Do they have abdominal pain like what is seen in abdominal migraine? Or are they excessively sensitive to stimuli, as migraineurs often are, and express that sensitivity through excessive crying at the end of the day? With rapid brain growth and development, infants’ visual perceptual abilities increase markedly during the first few weeks of life.[30] This could help explain why colicky crying generally does not begin until about two weeks of life, even though babies feed and interact with the world from birth onwards. Circadian biology may also play a role in colic as it does in migraine. Three months of age is when infants’ endogenous melatonin secretion takes on a diurnal rhythm, facilitating nocturnal sleep consolidation.[31–33] A circadian rhythm to melatonin secretion, either in itself or mediated through the ability to sleep through the night, could explain why infant colic resolves around age three months.[34]

Treatment of Infant Colic from a Migraine Perspective

Educating parents about the association between infant colic and migraine may help parents understand why their baby is crying so much, hopefully alleviating maternal guilt or concern about diet and breast milk related causes. Educating parents about the developmental pattern of infant crying, and how it will generally improve by age three months,[3] may also help them to cope with it in the interim.

While the prognosis of infant colic is generally good, it is important to educate the baby’s caregivers about the importance of never shaking the baby[7] It is better for a parent to place the baby safely on his or her back in a crib or bassinet and leave the room to take a break rather than to continue holding the baby when they are becoming frustrated and at risk of losing control. Parent educational materials about infant crying have been developed and studied in multiple countries.[35,36] It may also be helpful to provide a resource such as a 24/7 parenting hotline, where the caregiver can gain support during times of frustration.

Given the young age of these infants, non-pharmacologic colic treatment strategies are generally preferable. It would make sense to use what we know about how young children behave when they are having a migraine to hopefully help soothe babies with colic. Young children with migraine who are experiencing photophobia or phonophobia might go to their rooms, crawl into bed and pull the covers up over their eyes.[1] Notably a small study suggests that decreasing stimulation may also be helpful for infant colic.[37] Concrete suggestions for how to decrease stimulation include:

- Turn down loud music and avoid rattling or musical toys
- Dim the lights in the room
- Have young siblings or pets go to another room, if possible
- Avoid strong smells from cooking, perfume, cologne etc.
- Rock the baby gently, rather than jiggling or vigorously bouncing

Providing parents with a crying diary can help track response to interventions. The Baby's Day Diary[38] has been used in infant colic studies[19] and is relatively intuitive.

As sleep seems to be useful in terminating a migraine attack, particularly in young children,[39] anything that can be done to encourage the young baby to sleep may be helpful. If the mother is breastfeeding, she may wish to remain in a dark or dimly lit environment in the evening in order to optimize melatonin in the breast milk. Melatonin levels are generally higher at night and a higher melatonin level in the milk could potentially help the infant sleep.[40]

If the above behavioral treatment strategies fail, pharmacologic treatment with acetaminophen could be considered. Acetaminophen has been widely used in neonates for procedural pain and has a known dosing and safety profile in this age group.[41–43] It has been studied for acute migraine down to age four and found to be superior to placebo.[44] While infant colic generally improves within a matter of weeks, it is at least theoretically possible that frequent use of acetaminophen (or other acute medications) during this period could lead to something analogous to medication overuse headache, or "medication overuse crying". While by ICHD criteria overuse of acute migraine medications must occur for several months before headache is attributed to treatment overused, the duration of frequent acute medication use it might take to cause this phenomenon in the young developing brain is unknown. Generally limiting the number of days of exposure as much as possible would be prudent. While ibuprofen appears to be superior to acetaminophen for acute migraine treatment in young children,[44] its use in general pediatrics is typically limited to infants at least six months of age.

Similarly, triptans are unstudied in this age group and the pharmacokinetics of triptan metabolism in the neonatal liver is not well known. Triptans act as agonists predominantly at $5HT_{1B}$ and $_{1D}$ receptors. Given that neonates whose mothers were on SSRI's during pregnancy can present with irritability and tremors after birth, the serotonin system is likely active in the neonate.[45,46] However, it does not necessarily follow that agonist activity at serotonin receptors would be helpful in treating a neonatal migrainous phenomenon, as

activation of certain receptors in the neonatal brain can have paradoxical actions compared to their effects in older brains. For example while GABA is generally an inhibitory neurotransmitter in the adult brain, it can actually be neuroexcitatory in the neonatal period.[47]

There are no controlled studies of migraine preventive treatments in this age group. There is a case report of using cyproheptadine for infant colic where it appeared to be useful.[48] Cyproheptadine is recommended by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition for treatment of cyclic vomiting syndrome in children under age five.[49] Propranolol has been used to treat infantile hemangioma at a dose of 3mg/kg daily in infants one to five months of age for a duration of 24 weeks without significant increase in adverse events compared to placebo.[50]

It is intriguing to consider exogenous melatonin supplementation for infant colic, given the evening crying pattern and how colic improves around the age when developmentally the brain acquires the capacity for sleep consolidation and circadian melatonin secretion.[31–34] There are human data to suggest that the antioxidant properties of melatonin may be helpful in the treatment of sick neonates[51–54] and animal data to suggest that melatonin might even be neuroprotective after hypoxic ischemic perinatal injury.[55,56] However, there may be developmental reasons why sleep consolidation does not occur until several months of age, such as ensuring frequent feeds at night to allow for adequate weight gain and avoiding deep sleep as a safeguard against SIDS in the immature cardiorespiratory system. Certainly, there is much to be learned about what pharmacologic treatments might be both safe and effective for migrainous infant colic.

Conclusion

Given the totality of the evidence, infant colic was introduced into the appendix section of ICHD-III beta under “Episodic syndromes that may be associated with migraine”.[1] As further evidence of an association has emerged in the interim, it would seem sensible that infant colic be moved into the main body of the document in the final version of ICHD-III. Additional prospective cohort studies are needed to determine the natural history of children with infant colic, specifically whether they are more likely to go on to develop other childhood periodic syndromes such as benign paroxysmal torticollis or abdominal migraine, and whether they are more likely to have earlier onset of migraine headaches or more severe migraine headaches. Treatment studies of infant colic are also necesssary to see whether principles of managing migraine in children can be used to soothe colicky babies.

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