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What is the Underlying Cause of Infantile Colic?

Tamar Itzkowitz

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Abstract

Infantile colic (IC) is an important area of current research due to the extreme distress it causes parents and their infants. It is vital that a cause is isolated so that treatment can be found because IC is a risk factor for child abuse. In this paper, two major theories were posed to elucidate the underlying cause of IC—the gastrointestinal model and the neurological model. The gastrointestinal model suggests that IC stems from issues such as an immature gut. The neurological model suggests that infantile migraines are the causative agents of IC. Both theories supply correlational evidence but are subject to scrutiny because they are incomplete. A third theory, the fourth trimester theory, is suggested to fill in the gaps found in the two major models. Due to the novelty of this area of research, additional studies, such as genetics studies are suggested for future IC research.

Introduction

Infantile colic (IC) is defined as recurrent periods of crying, fussing, or irritability, for a minimum of three hours per day, three days per week, for at least three weeks per month. This syndrome is unique to infants between approximately three weeks to three months of age. The symptoms persist even though the infants are well-fed and do not present with any other signs of illness (Levinsky, et al 2020). IC leaves parents feeling helpless and pediatricians lack success in treatment of the phenomenon.

Although there is insufficient supporting evidence, IC has long been assumed to have a gastrointestinal (GI) etiology. Attempts to treat IC have included GI drugs treatments such as simethicone, probiotics, dicyclomine hydrochloride, and proton pump inhibitors. In drug studies, it was determined that treatments did not cause better outcomes than placebo. Other treatments have included diet modification. Diet modification treatments have not been successful, and pediatricians do not believe that there is sufficient evidence to recommend this to parents (Gelfand..., et al 2016).

More recently, it has been hypothesized that the underlying problem in IC is neurologically based. Amy Gelfand, a pediatric resident, noticed that many infants in the NICU who presented with IC had mothers who suffered from migraines. This theory suggests that IC is a premature form of a migraine. Studies conducted have confirmed that the symptoms, such as cyclic vomiting, are consistent with those of an adult migraine.

If IC is indeed neurologically based, treatment with acetaminophen—which is known to be a safe treatment of other infantile illnesses—would be a potentially effective treatment. Acetaminophen is used in children as young as 4 years of age for migraine disorder treatment (with and without aura). Studies recommend against treatment with triptans, a class of medications commonly used to treat migraines, as there is no known evidence of its safety for infantile use (Gelfand..., et al 2016).

The aim of this meta-analysis is to review the existing literature to determine if there is a basis for IC being caused by neurological phenomenon.

Methods

To gather evidence-based research for this meta-analysis, scholarly search engines, such as EBSCO and ProQuest were used to sort and gather all relevant research and publications available on infantile colic. Google Scholar was utilized as well.

Discussion

The Gastrointestinal Basis of Infantile Colic

Gastrointestinal distress has long been considered the cause of infantile colic. Physicians have postulated that gas, an immature gut, and an unbalanced gastrointestinal microbiome serve as the culprit. IC typically subsides after three months of life and is benign in nature (Qubty et al..., 2016). Supporters of a gastrointestinal etiology suggest that since it is well known that newborns suffer from a sensitive and underdeveloped digestive system, it is the likely cause of IC. Problems, such as swallowing air during feedings can cause painful gas in newborns which can lead to the uncontrollable crying spells. In addition, reflux, a condition in which stomach acid or bile ascends from a baby's stomach, is often cited as a possible cause.

A study which fed the fecal matter of babies suffering from IC to mice led to the presentation of visceral hyperalgesia in the mice. Visceral hyperalgesia is a condition in which the nociceptors of the internal organs', specifically the intestines, are activated and amplified (Qubty et al..., 2016). The study suggests that perhaps infants suffering with IC experience pain related to digestive processes. This is credible because visceral hyperalgesia is present in other GI disorders, including irritable bowel syndrome (IBS).

The bowels of infants' lack a diverse microbiome. Specifically, species of bifidobacteria and lactobacilli, which act as anti-inflammatory agents in the gut, are missing. On the other hand, species such as proteobacteria, which produce gas and inflammation are present in higher numbers than adults. Therefore, scientists can infer that infants have a higher propensity of GI inflammatory syndromes that do adults. Based on this evidence, it would be reasonable to infer that IC can have a gastrointestinal basis.

The GI basis of IC falls short in a few areas. Firstly, while babies suffering from reflux should exhibit crying as a symptom, it is unlikely that crying should be the only

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manifestation of the dysfunction. Therefore, reflux as an isolated cause is unlikely. Secondly, if IC is a disorder of the digestive tract, it would be reasonable to assume that breastfed and formula fed babies would be affected differently. However, this is not the case. Both types of feeding options have similar rates of IC. Additionally, altering maternal diet in breastfed babies does not pose significant improvement in crying spells (Qubty et al., 2016). Changes to partially hydrolyzed formula for formula fed babies, a transition known to help reflux, does not relieve IC either. This further indicates that diet and reflux are perhaps not the causative agents. Lastly, drugs that reduce GI distress, such as probiotics, simethicone (a drug that reduces surface tension and breaks down gas bubbles), dicyclomine hydrochloride (an anti-spasmodic agent), and proton pump inhibitors (PPI) which aim to reduce the crying spells, do not reduce the symptoms of IC. This poses the obvious question—if IC is caused by a gastrointestinal cause alone, then why do drugs known to help with those issues not help?

The Neurological Basis of Infantile Colic

Alternatively, physicians have wondered if perhaps there is something else entirely that is causing the distress. Based on Dr. Gelfand's observations of the relationship of maternal migraines and IC, a longitudinal study was initiated and replicated by other researchers and physicians, to unveil the potential relationship between migraine disorder and IC.

Efforts to reduce the symptoms of IC using methods such as shaking and shushing babies in brightly lit rooms have only exacerbated symptoms. Using the migraine-based approach this would make sense, as methods such as shushing and shaking would only worsen the headache. However, treating the colic in a way that migraine sufferers prefer, such as being placed in a cool, dark room and being put to sleep, have reduced IC significantly (Gelfand, et al 2016).

A study was published in 2015 that related IC with migraines. In this study, 1267 infants were assessed for IC and 13% were IC candidates. Of the infants participating, 787 of the infants were followed to the age of 18 years and reassessed for migraine disorder. Of the infants studied, 16% had developed a diagnosable migraine disorder, and 22% of those had a history of IC. Interestingly, IC was the only statistically significant predictor of migraine disorder in these adults. Moreover, migraine sufferers only developed migraine without aura (aura is described as visual sensations, such as flashing light, that precede neurological events.) There was no statistical correlation between IC and migraine with aura (Sillanpaa, 2015). This

is important because migraine with aura and migraine without aura are correlated with different genetic mutations. Therefore, perhaps there are migraine genetics that are significant in IC. This would be an excellent hypothesis to study in future research of IC.

An earlier cross-sectional survey was done in 2012. This survey followed 154 mother-infant pairs of which 14% of the infants were determined to have IC. To allow for more accuracy in the self-reporting process, the infants were re-screened at two months when IC is at its worse. Maternal migraine disorder conferred a 2.6-fold likelihood of having a baby with IC (Gelfand et al., 2012).

Another study conducted in 2013 compared 208 children with migraine disorder to 471 controls. The study found that 72.6% of children with migraine had a history of IC compared to the 26.5% likelihood of IC history of the control group (Romanello et al., 2013).

In a study conducted, children ages 6-18 who were admitted for migraine disorders were screened for a history of IC. The positive correlation was significant ($p=.001$). Such a correlation was not found for other types of tension-type headaches ($p=.10$) (J. G. M., et al 2013). This is important because it isolates migraine headaches as the only type of headache related to IC. As mentioned previously, there is plenty of genetic research available for migraine disorders which can provide more insight on potential genetic mutations related to IC.

Furthermore, there is reason to believe that IC is maternally inherited. A survey conducted in 2019 asked parents if their infant has cried for at least three hours a day for a minimum of three weeks. A follow up question asked if the parent had a known migraine disorder. Of the respondents, 827 mothers responded yes to the initial question. Of those respondents, 33.5% had a migraine problem. Of these mothers, a frequency of 15 or more migraines a month corresponded to a higher likelihood of IC. In the same study, 592 fathers responded yes to the initial question. However, paternal history of migraine disorder was not correlated to higher probability of IC. This was especially true if the infant was a female, suggesting that being female was protective (Gelfand, et al 2019). This information strongly suggests that the relation between IC and migraine disorder is potentially maternally inherited. This study is important because while it is commonly known that migraines are genetically inherited, it was not known that it is specifically inherited maternally.

A recent cross-sectional historical study looked to compare pediatric headache types to a history of IC. The study included 219 patients between the ages of 3-18 years. Prevalence of a positive history of IC was compared for children with migraine and other types of primary

headaches. The results showed an association of IC to pediatric migraine but not to other types of pediatric headaches. The study included 132 females and 87 males. The mean age was 12.8 ± 3.48 years. Migraine headaches were diagnosed for 170 patients (77.6%). Other types of primary headaches were diagnosed in 49 of the patients (22.3%). There were 51 patients with a history of IC. Of these patients, 45 were in the migraine group. The statistical significance in the rate of colic for the migraine group was extraordinarily strong ($p=.0196$), building on the hypothesis that migraines and IC are related (Levinsky et al., 2020).

In a study conducted in 2013, IC was determined based on parental responses and physician diagnosis. The study included 208 children—66 with aura, 120 with tension headache—and compared them to 471 controls. The prevalence of IC was 72% in children with migraine—70% with aura and 74% without aura. The results showed a 33% prevalence of IC for those with tension type headaches, and 27% for the controls. Interestingly, a pulsating quality of headache pain was significantly more common for those with colic than those without. This study confirmed the association on between childhood migraine headache and IC (F. B. S et al., 2013).

A meta-analysis conducted in 2019 included seven large studies looking at the relationship between IC and migraine headaches. The study found an increased incidence of infantile colic history for migraine groups ($p=.05$) than for those with tension type headaches ($p=.51$) (Zhang et al., 2019).

Conclusion

The causative agent of IC is yet to be fully elucidated. However, there is promise in the neurologically based theory of IC. The main critique of the studies on the neurological basis of IC is that many of them include too few patients. Additionally, many of the results are based on surveys which are subject to inaccuracy due to self-reporting. Lastly, the neurological basis of IC fails to include tangible and measurable elements that the gastrointestinal basis of infantile colic addresses, such as bacterial imbalance in the gut.

The gastrointestinal basis of IC has many components which make it a reasonable causative agent of IC, but it is similarly incomplete. Many of the studies are based on trials performed on mice. The results of such trials cannot be simply assumed to be identical in human infants. Additionally, the fact that drugs aimed to reduce gastrointestinal distress are ineffective poses a suspicion regarding its accuracy. This can be because gastrointestinal distress is not the only cause of IC.

Many physicians suggest that perhaps it is a combination if the two theories. There may even be more causes that we are currently unaware of. More research on the topic of IC is warranted to make definitive statements. However, based on the studies cited it can be said with certainty that there is a correlation relationship between IC and migraine disorder.

Another theory has been posed by a group of pediatricians consulted on this meta-analysis. This theory suggests that the “4th trimester”, or the first 3 months of life, is a sensitive time for the newborn. The infant is familiar only with the quiet, warmth, and darkness of the amnion. These conditions are comfortable for the baby. The harsh transition from womb to the bright and often noisy external world is the suggested causative agent of IC. Perhaps the reason that colic subsides while swaddled in a quiet and dark room is due to the infants’ comfort and recognition of a familiar and safe space. This theory perhaps serves as the missing part to the gaps found in the gastrointestinal and neurological basis of infantile colic.

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