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Is Infant Colic An Allergic Response to Cow's Milk? What Is The Evidence?

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ABSTRACT

Background: Despite enormous effort spent in determining a cause for infant colic, the source of the problem still eludes researchers. **Objective:** To review the published evidence to establish whether infant colic is due to an allergic reaction to cow's milk. **Method:** A literature search was completed using Medline, Cochrane Clinical Review and a hand search from 1980 to March 2013. Publications were included if they were systematic reviews, RCTs with a control group, or specifically related to dietary interventions. **Results:** The majority of studies had faults due to non-randomization, non-blinding, too few participants, skewed populations and inadequate follow-ups. There appeared to be some relief of crying with change in diet in several studies, but crying time was still considered longer than normal. **Conclusion:** There is no clear evidence that infant colic is a form of cow's milk protein allergy (CMPA). Research trials have been contaminated with a subgroup of infants who have been diagnosed with colic who actually have CMPA. Future studies need to subgroup the irritable infant to better understand the etiology of colic.

Keywords: infant colic, allergy, soy, dairy and dietary interventionstic, probiotics, pediatric, infant, formula.

Introduction

Infant colic is the leading cause of patient visits to clinicians in the first six months of life with one in six families consulting from one to seven physicians in the first 16 weeks of life.[1,2] Infant colic is defined as excessive crying in an otherwise healthy infant, commonly linked to paroxysmal abdominal pains.[3] The classic Wessel definition is an infant crying more than three hours a day more than three days a week for more than three weeks.[1,2] No link to the specific source of infant nutrition, either breast milk or formula milks has been found.[4] However, several studies have given conflicting evidence as to the relationship between diet and infant colic. Three systematic reviews disagree as to the evidence-based role for hypoallergenic diet.[5-7] Other studies disagree as to whether or not the prevalence of colic is higher in infants with a family history of atopy or allergies.[8,9] However, recent management strategies have stated that crying may reduce with the elimination of cow's milk protein (CMP) in the infant who is afflicted with infant colic.[10] Considering the conflicting advice to clinicians and parents, this review aims to examine the evidence in order to answer the clinical question, "Is infant colic an allergic response to cow's milk protein?"

Cow's milk protein allergy (CMPA) is the most common food allergic disease of infancy.[11] Symptoms of CMPA are shown in 5-15% of infants,[12] with a range of prevalence between 2 and 7.5%.[12] Infant colic is said to afflict 5-40% of infants with the most common prevalence of 21%.[1-7] Soy protein is the most common substitute for milk protein. It is not only another common infant allergen,[13] but it has been found to be a cross allergen with milk protein.[14] The ESPGHAN Committee has recommended that soy protein be withheld from infants showing signs of allergy/intolerance.[13]

Methods

A literature search using the key words infant colic, allergy and dietary interventions was completed using Medline, Cochrane Clinical Review and a hand search from 1980 to March 2013. Publications were included if they were systematic reviews, RCTs with a control group, or specifically related to dietary interventions. Those

which showed any positive results were included. In all, 142 articles were sourced with 14 meeting the criteria of the search. Other general articles were used to supply background to the study.

Results

Characteristics and results of included trials are found in Table 1. Pertinent features of infant colic and pertinent features of CMPA are shown in Table 2. The NICE guidelines for infant colic are presented in Table 3.[24] A study into whether cow's milk allergy was the etiology of infant colic was undertaken by Campbell in 1989. This study followed 19 formula-fed subjects out of 41 who were referred for severe colic[15] and randomised to soy formula (SF) or cow's milk formula (CMF). If crying did not decrease, the infant was given a highly hydrolyzed formula (HF). This was a small sample in a region which produced 650 newborns annually and there would logically have been a potential sample of at least 175 infants who might have had colic during the time frame of the study. The small sample

Authors	Type of Study/Number Subjects/Intervention	Results/commentary
Campbell[15]	RCT/ 41 infants referred for study; 19 of 3-14 weeks of age (11 from atopic families) accepted; ½ given Soya Milk (Cow and Gate Formula S) and ½ given C&G Premium. Those not improving on either were given milk free of whole protein (Cow and Gate Peptalac) on unblinded basis	Crying decreased to 9 hours per week or less with soya formula/problems of study were non-random selection process (over ½ from atopic families), no blinding of CMP-free formula, age of entry into trial too old and admits bias of natural history reduction in crying; poor quality RCT which did not give method of randomisation
Estep and Kulczycki[16,17]	2 studies substituting Neocate, amino acid based infant formula v standard milk formula and breast milk, N=6 in each study	Reduction in total cry/fuss time 45% = 148 mins/sample size of 6 is too small to apply to a general population; non-blinding
Evans, et. al.[19]	RCT, infants 3-18 weeks of age, Elimination of cow's milk in breast feeding mother in cross-over trial	Elimination of cow's milk had no significant effect on colic, wide range of ages of infants may have biased natural history
Forsythe[20]	RCT/17 infants <8 weeks/4 days on CMF alternating twice with 4 days extensively hydrolysed formula	Resulted in increased crying on CMF and reduced crying on HIF, but this attenuated on second round. This is a small sample with reducing effect even within the trial time of 16 days; no known effect in longer term.
Hill, et.al.[21]	Comparison trial of effects of 2 maternal diet programs, i.e. a low-allergen diet that excluded major food allergens v control diet that included these foods (n=77). Bottle fed infants on modified CM formula (Enfalac) or hypoallergenic formula (Progestimil) (n=38)	25% reduction in crying time, not resolution of colic was used as outcome measure, but 2/3 infants still had colic by Wessel's definition at end of the 7 day trial/method of randomisation not discussed; unblinded trial may have created significant bias.
Lothe and Lindberg and Jakobsson[22]	Intervention/N=60 infants 2-12 weeks of age/32 given casein hydrolysate formula (Nutramigen) replaced CM infant formula	Crying time reported by parents reduced significantly after 5 days. Authors concluded that colicky infants turn into children afflicted with cow's milk protein allergy or intolerance.
Berseth, et al.[24]	Randomised double blind parallel group study/158 infants 1-8 weeks of age of parent-defined fussy or extremely fussy infants randomised to soy formula (SF) or partially hydrolysed formula (PHF) for 28 days	Results recorded on electronic diary including fussiness, gas, spit-up, crying time and bowel habits; no intention-to-treat analysis. Significant reductions in fussiness rating and crying times in both groups at 28 days, but crying time still >3 hours. True blinding may not have occurred due to recognisable odour. Natural history not taken into account in 28 day trial. Dropout of 28% (SF) and 18% (PHF) is high but acceptable.

Table 1. Summary of studies investigating infant colic and cow's milk protein allergy.

may have occurred because the inclusion criteria required "severe" colic. Those eliminated were due to the lack of severe symptoms. There was no evidence of randomization. It seems likely that many of those in the study didn't, in fact, have colic, but may have had CMPA. In the final analysis, 13 infants (2% of total infant population) were identified as "colic" babies, a number not inconsistent with the number expected to experience CMPA. Eleven of those 13 had a positive family history of atopy and all had crying that was more extensive and more sporadic than usually defined as common colic, seeming to an observer that these children may have responded to a change in formula because they actually were afflicted with CMPA/soy sensitivity and not colic. That said, the study's results cannot be considered reliable because of the skewed, nonrandomised sample, no blinding of the parents, the usage of a non-validated record sheet and sample size too small to trust conclusions along with no intention-to-treat analysis and a 41% drop out rate which allowed significant bias into the study.

Estep and Kulczycki reported two trials of six infants each; standard formula milk was replaced with hydrolysed formula for four days which resulted in a reduction in crying time by 45%[16] and mother's milk was replaced with hydrolysed formula also significantly reducing crying time.[17] Although the significant reduction in crying with change to a hydrolysed formula may at first seem clinically useful, a sample of six is too small to generalize to the total population. Furthermore, the fact that there was no blinding and parents knew what formula they were receiving increases the reporting bias. The crying was reduced to a minimum of 148 minutes daily, which is 23% more than two hours, which is the crying time considered normal. Some authors agree that a minimum time period needed to evaluate a change in formula is 2-4 weeks[18] as a change in formula generally has some at least short-term effect.[23]

The only trial recruiting exclusively breast fed babies was Evans.[19] This trial eliminated cow's milk in the mother's

Infant Colic	Cow's Milk Allergy
• Excessive crying, more than 3 hours a day at least 3 days a week, more than 3 weeks	• Excessive crying, more than 3 hours a day at least 3 days a week, more than 3 weeks
• Crying is inconsolable and more prominent at end of day	• Crying, wailing, irritability more prominent after feeds, but occurs throughout the day/night, with disrupted sleep
• Occurs in both breast and formula fed infants	• Occurs in both breast and formula fed infants
• Begins at 5-10 days of age	• Can begin anytime, generally 4 weeks onward or within 1 week of receiving CMP
• Flailing of arms	• Frequent regurgitation, vomiting, food refusal
• Pulling up legs	• Diarrhoea or constipation (blood in stool)
• Apparent pain, pained facies	• Atopic dermatitis, eczema, urticaria, pruritis
• Healthy infant	• One first degree relative with allergy/asthma
• Sleep is not affected	• May have some or all GI, cutaneous, respiratory symptoms, which may be progressive over time
	• Failure to thrive

Table 2. Pertinent features of infant colic and cow's milk allergy.

Colic

A baby who is crying excessively and inconsolably, most often during the evening, either drawing its knees up to |its abdomen or arching its back, should be assessed for an underlying cause, including infant colic (urgent action). Assessment of excessive and inconsolable crying should include:

- general health of the baby
- antenatal and perinatal history
- onset and length of crying
- nature of the stools
- feeding assessment
- woman's diet if breastfeeding
- family history of allergy
- parent's response to the baby's crying
- any factors which lessen or worsen the crying.

Healthcare professionals should reassure parents of babies with colic that the baby is not rejecting them and that colic is usually a phase that will pass. Parents should be advised that holding the baby through the crying episode, and accessing peer support may be helpful.

Use of hypoallergenic formula in bottle-fed babies should be considered for treating colic, but only under medical guidance.

Dicycloverine (dicyclomine) should not be used in the treatment of colic due to side effects such as breathing difficulties and coma.

Table 3. NICE guidelines for infant colic[25].

diet. Information was not provided about whether the mothers restricted soy protein from their diet as well milk protein. Since soy is the most common substitute for milk protein, the mothers most likely ate soy instead dairy. The range of ages of 3-18 weeks did not rule out natural history of the condition; however, there was no significant reduction in crying with the maternal change in diet. If soy was the substitute, no change in crying would be expected from a change in diet.

The Forsythe trial was the only one restricted to infants less than eight weeks of age, addressing the critique of the natural history confounder.[20] This trial alternated cow's milk formula with hydrolysed formula (HF) on a rotation of four days, repeating it twice. There was less crying recorded on the HF days in the first course, which attenuated on the second. A trial of 17 infants is too small to generalise to the entire colic population and the reduced effect in the second round provides scant evidence of value in dietary change. Again, the time period to test a formula should be between two and four weeks.[18]

Hill solved some of these problems with a larger trial (n=77) including both breast fed and formula fed infants.[21] The results were reported as successful with a 25% reduction in crying time. Although this was significant, two-thirds of the infants were still technically described as having colic according to the Wessell criteria. The crying time, although improved, remained higher than three hours a day. The lack of blinding added bias and with a sample size of 15, the results are too small to generalize. Lothe, Lindberg and Jakobsson randomized 60 infants to be given either CMF or SF.[22] There was no change in 53% of infants when given either, but they did have reduction in symptoms when given a HF (Nutrimagen). The authors maintained that CMP is a major cause of moderate or severe infant colic and that these same "colicky" children become allergic to cow's milk later, some at 6 or 12 months of age. Change in formula is known to produce a temporary positive effect[23] but there was no follow-up to determine if the positive results persisted. There was also no evidence of randomization. This trial highlights the fact that neither milk protein nor soy protein were well tolerated by the infants in this study.

The Berseth study was unique and elegant in its use of parent-defined fussy or extremely fussy babies (without using the more common Wessels' definition of infant colic) and set out to randomise 200 infants replacing cow's milk formula with soy formula or partially hydrolysed formula (PHF) for 28 days.[24] Only 158 entered the trial and there was a dropout rate of 28% (SF) and 18% (PHF). Because of the unique scent of the two different formulas, blinding cannot be said to be held. All infants were rated significantly lower on the fussiness rating scale at the end of the trial; however, on average, most still cried more than three hours a day (the Wessel criteria), so crying, although reduced, was maintained at higher than average levels. The authors suggest that change in formula is an appropriate first line in addressing fussiness in babies.

The NICE guidelines were proposed for routine postnatal care for infants in the UK and suggest consideration of hypoallergenic formula under a doctor's guidance.[25]

Discussion

Change in diet as a strategy in infant colic has a long history. This is probably because most authors who discuss infant colic maintain a connection to the digestive system, although the connection has never been proven.[26] There is even a systematic review of dietary management of infant colic.[27] This review calls for a universal definition of infant colic to improve application of the evidence, which is now confusing. Other systematic reviews of therapeutic trials point out that there is some evidence to support a casein hydrolysate formula in some types of infant colic.[5,7,28] When taking into account the quality of the trials, there is no convincing effect on infant colic of dietary change including changing to soy, hydrolysed, lactose-free or fibre-rich formula. Improvement is not expected if dietary change is from one common allergen to another. Therefore trials which replace milk with soy or lactose-free milk are not appropriate.[18,29] Furthermore, the ESPGHAN committee on nutrition has recommended that soy protein formula should not be used in infants with signs of food allergy/intolerance during the first 6 months of life.[13]

Another weakness in the trials where breastfeeding mothers were instructed to adopt a milk protein-free diet is that they were not also instructed to avoid soy protein. The majority of dairy-free alternatives are soy products. Others have pointed out that although some help may be perceived by parents when changing formula,[23] some experts recommend a trial of at least 2-4 weeks of allergy free diet.[18] None of the trials evaluated tested a change in formula for a long enough interval to be able to fairly evaluate the results. Moravej et al. in 2010 recommended that the only children who are likely to benefit from a formula change are those with a positive skin prick test.[30] Thus, there is little convincing evidence that infant colic is a form of cow's milk/soy protein allergy. Instead, it is likely that a subgroup of infants who have been diagnosed with colic, in fact, have CMPA. As symptoms develop and therapies do not work and the child does not outgrow colic, then the diagnosis becomes one of exclusion in those infants. In the small number of cases where change to a hypoallergenic formula has subdued symptoms, it is likely that the child's condition had been misdiagnosed as infant colic, and should have been diagnosed as CMPA.

However, the Berseth study does point out that in infants

with inconsolable crying along with digestive difficulties, there may be a place for a formula which does not address an actual CMPA but a cow's milk intolerance.[24] This study found that two different types of formulas, soy and partially hydrolysed, neither of which would be appropriate for actual CMPA, resulted in less crying along with slight reductions in reported gas and spit-up. They concluded that crying with feeding difficulties should be treated with dietary changes, identifying another subset of the excessively crying infant population in addition to simple colic and more complex CMPA. However, the strength of the evidence is weak and it is known that any change in diet may bring about a temporary report of fewer symptoms.[23]

The prevalence of infant colic is most commonly estimated at 21% of all infants.[1] The incidence of CMPA is 2-7.5% in infants in developed countries.[31] It is likely that a proportion of infants who have been diagnosed with colic actually are afflicted with CMPA. Because of broad inclusion criteria of most studies, the latter group may not have been excluded from colic trials; in fact, by including "severe" excessive crying, those suffering from CMPA may have been preferentially admitted to these trials. This may account for the small, but clear response rate in some dietary trials. Deletion of CMP/soy protein from the diet specifically helps those with CMPA and cow's milk intolerance, but not the broader range of colicky babies. This may account for the inconsistent results, depending on the trial and its inclusion criteria.

In cow's milk protein allergy, the condition should be recognized and treated without delay; these infants should not be entered into colic trials. Meticulous inclusion and exclusion criteria are required in future trials. Infants who cry all day along with symptoms of CMPA (integumentary, respiratory,[12] allergic constipation,[32] failure to thrive,[18] along with those with family history of atopy[9]) should be excluded from studies on colic. Those who appear allergic should be offered a skin prick test,[30] a trial of hypoallergenic formula or removal of dairy/soy products from the mother's diet if baby is breast fed. In agreement with Hill, the breastfeeding mother should also consider eliminating the other most common allergens including nuts, eggs, fish and wheat.[18] Colicky infants without CMPA signs or symptoms should not be managed with hypoallergenic formulas.[33,34]

Regarding the answer to the research question, is infant colic an allergic response to cow's milk protein? According to the evidence, the answer is no. However, in a small percentage of infants, allergy/sensitivity to cow's milk is likely one cause of excessive crying of infancy. Despite this, the etiology of colic remains unknown and future studies should define inclusion/exclusion criteria strictly to exclude infants afflicted with CMPA and cow's milk protein intolerance from the studies. Any role for hydrolyzed or amino acid formula is likely to be in a small group of infants who are afflicted with CMPA. Until subgrouping is effectively done in primary care practices and research trials, it is unlikely that infant colic will be fully understood.

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