REVIEW ARTICLE

INFANTILE COLIC –DO WE UNDERSTAND THE ETIOLOGY?

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Abstract
Infantile colic is a commonly encountered, benign self-limited condition which causes much distress to the caregivers. The etio-pathogenesis is inconclusive and myriad theories abound. Gut hormones, gut probiota, lactose malabsorption, food hypersensitivity and psychosocial factors have been implicated. The diagnosis is mainly clinical and treatment includes antispasmodics, probiotics, food modification and herbal preparations. Some long term effects have been observed on follow up of colicky infants.

Introduction

Crying is a reflex phenomenon and is the only means by which the infant can communicate his needs to his mother. However, when the infant cries continuously, inconsolably, for no apparent reason, on a regular basis, we need to make a diagnosis of infantile colic.

The prevalence of infantile colic ranges between 10-30% of infants. (1) Although the condition is well recognized, its exact etiology is not defined. Various hypotheses have been suggested for the causation of the colic. The classical features of infantile colic is best described by the rule of 3, as suggested by Wessel - The period of crying lasts for 3 hours or more, lasting for 3 or more days per week for a minimum of 3 months. (1) The infant is otherwise healthy, active and thriving, with no other features suggestive of underlying disorders. The infant is calm throughout the day, and the paroxysmal crying begins towards the evening. The cry is described as a high pitched, aversive, piercing loud cry that is associated with tensing of the abdominal muscles, flexing of the legs, lifting up the head, flushed face, clenched fingers and passage of flatus. According to Illingworth, (2) the term "evening colic" is preferred for this condition, as it demonstrates a characteristic circardian rhythm.

Etiopathogenesis of infantile colic

The sheer multitude of theories point towards the confusion that surrounds it and no single reason has been found to be the cause of colic. Most of the theories revolve around disturbances of the gastrointestinal tract.

Gut microbes

The gut microflora play an important role in stabilizing the intestinal environment, which has a major bearing on the future occurrence of disease, atopy and intolerance. The infant's gut is sterile at birth and colonization begins soon after birth. The variety of colonizers depends on the mode of delivery, as those infants born by vaginal delivery differ from those born by caesarean section (C-section). Studies conducted by Grölund et al has shown that, in infants born by C-section, the fecal colonization by bifidobacterium like bacteria and lactobacillus like bacteria was delayed , and reached the levels similar to the vaginally delivered infants only around the age of 40 days. (3) The infants born vaginally tend to have bacteria similar to that of the maternal vaginal canal with a predominance of the Lactobacillus, Atopobium, Prevotella and Sneathia species, while those born by C-section tended to have organisms resembling that found on the maternal skin, like Staphylococcus, Corynebacterium and Propionobacterium species. (4) The inadequate numbers of lactobacilli, together with high levels of coliforms in the immature gut can affect fermentation resulting in excessive intra intestinal gas production resulting in colic. (5). Studies have shown the presence of L. acidophilus only in non-colicky infants, while those with colic had L. lactis and L. brevis. These are both hetero fermenting species that produce ethyl alcohol, lactic acid, carbon dioxide and ATP, which alters the intestinal motility and results in abdominal distension, and flatulence characteristic of infantile colic. Oral supplementation of probiotics, especially Lactobacillus, has been shown to improve the symptoms and decrease the duration of crying. (5) The probiotics contribute to the anti-inflammatory tone of the intestinal environment, modulating the immune responses and the motility of the infantile gut. (7) They also have a direct calming effect on the visceral pain. (5)

Lactose malabsorption

Infants maybe intolerant to lactose in the food due to which significant amounts of lactose enters the colon where it acts as a substrate for lactobacilli and bifidobacteria. Due to fermentation of the sugar by the bacteria, there is rapid production of hydrogen and lactic acid in the gut. Both these have deleterious effects. The lactic acid induces osmotic pressure, favoring the influx of water, which causes gut distension. The hydrogen gas also distends the colon and results in pain. (1) This gas is excreted in the breath and can be measured, as an index of unabsorbed carbohydrate in the intestine. (8) Studies have shown elevated breath hydrogen levels in infants with colic, thus corroborating the hypothesis that the colicky infants have carbohydrate mal-absorption causing colic. However, the difference in the breath hydrogen levels between the colicky and control group could depend on other factors like the nature of the bowel flora, colonic bacterial metabolic pathways, partial pressure of hydrogen in the colon, gut perfusion and incomplete monosaccharide absorption in the gut. Hence, by omitting lactose in the diet, could it be possible to resolve the colic? Infante et al attempted to provide clinical as well as biochemical evidence of the efficacy of an adapted formula in twenty infants who were on formula feeds and had presented with symptoms suggestive of infantile colic. (9) They were placed on an adapted formula after doing a breath hydrogen test. The formula had a low lactose concentration of 7g/100 ml. The second breath hydrogen test was done after 2weeks of this formula, and it was found that the duration of crying reduced in

all infants and the level of expired hydrogen decreased significantly from 35+/-3.1ppm to 10+/-2.5ppm. Similar results of higher breath hydrogen levels in colicky infants was demonstrated in studies conducted by Miller et al. (8) However, these results do not explain the occurrence of colic in breast fed infants. Kanabar et al conducted a double blind randomized placebo controlled crossover study in infants with colic. (10) The feed was pre-incubated with lactase and given to the study group, and the breath hydrogen levels were checked. Results showed a 45% lower level of breath hydrogen as well as crying time compared to the placebo group. This response was only found in 26% of the full trial group and 38% of the compliers, which indicates that lactose intolerance is not the only reason for infantile colic, but in those with transient lactose intolerance, pretreatment with lactase resulted in considerable symptomatic relief. According to Ståhlberg et al, healthy infants may have transient physiologic lactase deficiency, but infantile colic is not a symptom of lactose malabsorption. (11)

Gut hormones

There are several hormones that affect the gut functions and motility especially motilin, cholecystokinin, gastrin, vasoactive intestinal peptide (VIP) and ghrelin. Motilin is a 22 amino acid hormone, which is produced in jejunal and duodenal mucosa and is present everywhere in the GI tract of humans. (12) It enhances gastric emptying, increases small bowel peristalsis and decreases the transit time. (1) It also stimulates inter-digestive migrating contractions. (13) In infantile colic, higher basal motilin levels may be responsible for propulsive gut contractions that trigger the symptoms of colic. Motilin has been found in breast milk and may trigger the endogenous release in breast fed infants stimulating gut contractions. Maternal smoking, which is a recognized risk factor for colic, is associated with elevated levels of motilin. (12) Besides the direct effects on the intestinal smooth muscles, the vagal impulses also effect changes in motilin levels. (12) According to the results of studies conducted by Lothe et al, the basal motilin levels are raised from the first day of life in infants who subsequently develop colic, indicating that the GIT is affected even before the symptoms of colic appear. (14) Atropine and similar anti-cholinergics, antagonize the effects of motilin. Cholecystokinin levels are reduced in colicky infants, and its effect is poorly understood. (13) Due to impaired central regulation of satiety and behavior, it may be responsible for the symptoms of distress. Ghrelin, the hunger hormone has been found to be associated with infantile colic. (7) In a study conducted by Savino et al, it was found that colicky infants had higher serum ghrelin levels (2534.2+/-600.0 pg/ml) as compared to controls (2126.1+/-281.3g/ml). (15) Ghrelin may promote abnormal hyperperistalsis and appetite, typically seen in colicky infants. (1) Gastrin and VIP are also involved in the regulation of gut motility. However, studies have not shown any correlation between the levels of these hormones and infantile colic. (16)

Another hypothesis put forth by Weissbluth et al suggests that serotonin which reaches its peak serum concentration in the evening, is responsible for intestinal cramps due to smooth muscle contraction. (17) Melatonin, on the other hand, has the opposite effect, causing smooth muscle relaxation. Both these have a circadian rhythm. However, only the serotonin circadian rhythms are present at birth, while the melatonin rhythm appears only at 3 months of age. Hence, the unopposed activity of serotonin in the initial months of life is responsible for the occurrence of evening colic in infants.

Food hypersensitivity

Infantile colic represents a transient non-organic behavior dysregulation in an otherwise healthy infant. Breast feeding does not protect the infant from colic. The role of diet in the causation of colic remains controversial, although several studies have shown suggestive results. Cow's milk protein appears to be associated with significant number of cases of infantile colic. (18) Jakobsson et al performed a trial on sixty - six breast feeding mothers whose infants had symptoms of colic. (19) These mothers were placed on a diet free of cow's milk and were followed up. Results showed the disappearance of colic in 53% of the infants, which reappeared upon challenge of cow's milk in 35% of the infants. The intake of a variety of other foods by breast feeding mothers has also been associated with increasing numbers of colic attacks. (20) A randomized controlled study on 107 exclusively breast fed infants who had presented with colic, was conducted by Hill et al (13). The maternal diet was devoid of possible allergenic foods like cow's milk, peanuts, tree nuts, wheat, soy and fish, while the control group was allowed to consume all these foods. The change in cry/fuss patterns per 48 hours was assessed after 7 days of the trial and it was significantly decreased in 74% of the low allergen group as against 37% in the control diet group. This study clearly showed that elimination of certain major food allergens from the maternal diet, does decrease the duration of crying and fussing in the infant, and the maternal food allergens do play a significant role in the pathogenesis of colic. This could be attributed to the increased macromolecular gut permeability that allows food sensitization to occur. Studies conducted by Lothe et al, used human alpha –lactalbumin (LA) as a marker to detect the intestinal absorption of macromolecules in breast fed as well as formula fed infants. (21) Significantly higher levels of alpha-LA were found in breast fed and formula fed infants with colic at all ages. This is corroborated by the detection of antigens of allergens like wheat, cow's milk, peanuts and eggs in the human milk, which stimulates mucosal immune responses and the presence of mucosal IgE containing plasma cells, in infants with colic. (13) However, elimination diets can be recommended only for a limited duration of time in the mothers of breast fed infants with colic, and their nutritional progress has to be closely monitored by an experienced dietitian.

Formula fed infants with colic may benefit from the exclusion of casein in the formula. Lucassen et al studied

forty three thriving Dutch colicky infants on formula feeds which was replaced by a whey hydrolysate formula and followed up for one week. (22) Results showed decrease in the crying times, thus favoring the use of an extensively hydrolyzed formula in the reduction of infantile colic. Savino et al, have recently reported the results of studies using an infant formula containing partially hydrolyzed formula supplemented with fructo- and galacto-oligosacccharides in formula fed infants with colic. (23) Infants fed this formula had significant reduction in the crying episodes as against the standard formula fed infants.

Psychosocial factors

The occurrence of colic has been attributed to personality disorders associated with an irritable and hypersensitive infant. (1)It may be a response of the infant- environment interaction. The mother-infant, father–infant interactions have been studied and found to be less than optimal in families with colicky infants. (24) There were more pronounced problems of interaction between father-infant in the severe colic group. Inter-parental interactions were also dysfunctional and the colicky infants were less competent in interacting with their parents. Inexperienced and anxious parents create a situation for a severely colicky infant. (1)

Laboratory investigations

The diagnosis of infantile colic is usually based on clinical features. The modified Wessel's criteria is usually adequate to confirm the diagnosis of infantile colic. Infantile colic has been postulated to be associated with lactase deficiency causing carbohydrate malabsorption. Due to this, there is an increase in the gut fermentation of the undigested carbohydrate, resulting in elevated levels of hydrogen excreted in the breath. (25) The breath hydrogen test provides a sensitive, reliable and semi quantitative index of incomplete carbohydrate absorption. Tests have shown increased levels of breath hydrogen in colicky infants, in comparison with the control group. However, tests have shown that almost 38% of colicky infants have low breath hydrogen levels, while32% of control group infants have elevated breath hydrogen. The relevance of breath hydrogen tests as a marker of infantile colic is yet undetermined. Some reports have commented on the beneficial effects of higher stool methane levels that is associated with decreased colic. (26) However, its role in the diagnosis of infantile colic is debated. Keen clinical acumen and knowledge is essential to make a definitive diagnosis of infantile colic, as none of the investigations are associated with complete accuracy.

Treatment

The etiopathogenesis of infantile colic is myriad, and there is to date no general consensus on its causative factors. Hence there are several variations in the treatment recommended for this condition. It is essential to counsel both the parents as regards their interaction with each other as well as with the infant. Reassurance that the condition is transient and non-pathogenic will go a long way in allaying parental anxieties. (26) Early response to the crying, sucking on a pacifier, using eye contact and interactive playing may be useful behavior modification therapy. (27)

The role of gut microbes has been studied extensively as an etiological agent. Supplementation of probiotics especially lactobacillus species has been shown to have beneficial effects. (28) Studies by Savino et al has shown the usefulness of lactobacillus delbrueckii DSM20074 and L. plantarum MB456 in inhibiting the growth of gas forming coliforms of different species via the production of bacteriocins and inhibitory non –proteinaceous metabolites with antibacterial activity. Other studies have shown the effectiveness of L. reuteri DSM 17938 on decreasing colic by improvement of the gut motility and function, as well as its direct effect on calming the visceral pain. (5) These findings have opened up a new therapeutic approach for the treatment of infantile colic. However further studies are needed to quantify the inhibitory amounts as well as the optimal species of probiotics that would be beneficial in the treatment of colic.

Dietary modifications made by the mother maybe useful in the avoidance of infantile colic. By avoiding potential allergens like cow's milk, egg, peanuts and wheat, it may be possible to decrease the occurrence of infantile colic. This is recommended in breast fed infants with colic.

Since the gut hormone motilin has been found to be elevated in colicky infants, the use of anti-cholinergics like atropine and similar compounds may produce symptomatic relief. Hyoscine and dicyclomine decrease the intestinal spasms and thus produce relief from colic. (27) However, these medications may be associated with unwanted side effects like drowsiness, especially with dicyclomine. (29) Other untoward effects include loose motions or constipation, muscular hypotonia, syncope and breathing difficulties. Another drug which is a semisynthetic derivative of belladonna alkaloid (scopolamine) has been investigated for its effectiveness in treating colic. (1) Cimetropium bromide acts by competitive antagonism of the muscarinic receptors in the visceral smooth muscles, as well as by a direct myolytic action. It has shown significant reduction in the duration of crying but not in the number of episodes of distress. Simethicone, a defoaming agent, has also been studied as colic reliever, but has not been shown to provide beneficial results. (29)

Formula fed infants may benefit from the change of the type of formula used. Extensively hydrolyzed whey containing formulas has been shown to significantly decrease the crying time. (22,29) The use of casein hydrolysate formula has been found to be useful in infants who had symptoms of colic due to protein sensitivity. (29,30) Pre-incubation of lactose containing feeds with lactase has been found to provide 45% relief from the symptoms of colic. (31) Other studies have not shown any advantage of administration of lactase treated milk. (29) According to ESPGHAN guidelines, soy milk is not indicated for use in infants below the age

of 6 months, and hence has no role in the treatment of infantile colic. (32) A recent formula containing partially hydrolyzed proteins and low amounts of lactose supplemented with fructose oligosaccharide (FOS) and galactose oligosaccharide (GOS) has been shown to be useful in combating colic. (23)

A variety of herbs and herbal products have been used with varied results. They are thought to provide relief from flatulence and indigestion, and hence calm the gut of the colicky infant. Products containing zingiber, cumin, cardamom, ginger, fennel, black pepper etc are known to produce relief from colic. (25) Herbal teas containing mixtures of vervain, chamomile, fennel, liquorice and lemon balm maybe useful and are used in many communities globally. (1) A study reported by Savino et al has shown relief from colic in breastfed infants within a week by the use of an extract based on Matricariae recrutita, Foeniculum vulgare and Melissa officinalis. (1)

Long term outcomes

Infantile colic has a favorable and self-containing nature, with resolution by 6 months of age. However, some follow up studies have shown long term effects of infantile colic. These infants may have more sleep problems during as well as after the period of colic. These infants displayed more temper-tantrums and sleep difficulties at the age of three years than those who did not suffer from colic. (33) Children with signs of atopy at 2 years of age, were found to have been colicky infants and hence colic could be considered an early manifestation of subsequent atopy. (34) Further follow up has shown different temperaments by the age of four years. These infants have demonstrated more negative emotions and more negative moods during meal times. (35) There is more susceptibility to recurrent pain abdomen, allergic disorders like atopic eczema, food allergy, respiratory and ocular allergies, as well as psychological disorders of sleep, aggressiveness and fussiness at the age of 10 years. (36) Infantile colic may thus represent the earliest manifestation of a spectrum of common childhood disorders.

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