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Infantile Colic: An Overview

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Abstract

Infantile colic is a common problem faced by pediatricians in their routine Outdoor patient department. Multi-factorial etiology of infantile colic is known. Many drugs and probiotics are empirically used to treat infantile colic. Proper diagnosis and treatment is important. Parental counseling plays a major role in the treatment. This is an overview of current literature available on management of this condition.

Keywords: Infantile colic; Probiotic

Introduction

Infantile colic is a common problem faced by pediatricians in their routine Outdoor patient department. Multi-factorial etiology of infantile colic is known. Many drugs and probiotics are empirically used to treat infantile colic. Proper diagnosis and treatment is important. Parental counseling plays a major role in the treatment. This is an overview of current literature available on management of this condition.

Many definitions of infantile colic are proposed in studies [1] uniformity in criteria to diagnose infantile colic was reinforced in Rome III [2] criteria. Rule of 3 i.e. crying more than 3 hours a day, for more than 3 days a week and for more than 3 weeks was changed in Rome IV [3]. Current Rome IV criteria to diagnose infantile colic are more parent centric. The factors that have been shown to cause distress in parents i.e. prolonged hard to soothe or unexplained nature of the crying behavior are reinforced [4].

Diagnostic Criteria for Infantile Colic

An infant who is <5 months of age when symptoms start and stop in recurrent and prolonged periods of infant crying, fussing or irritability reported by care giver that occurs without obvious cause and cannot be prevented or resolved by caregivers [3].

No evidence of infant failure to thrive, fever or illness. All of the above should be present to diagnose infantile colic.

Infantile colic is a clinical diagnosis. No unnecessary investigations are required. Organic etiologies must be ruled out.

Prevalence and Etiology-Pathogenesis

Infantile colic is commonly diagnosed. The variable prevalence is noted in studies. Some studies have noted 2-73% with median of 17.7% as prevalence [5]. Based on prospective data some noted it to be 3-28% [6]. Based on Rome 3 criteria, studied prevalence is between 5.9-10.4% in different studies [7] Un-doubted, it is common phenomenon but difficult to diagnose and treat.

Normal crying curve in infant is studied and reported in 1990 [8]. A progressive increase in crying is noted to peak during 2nd month of life. Diurnal rhythm of clustering of crying episode more in the evening is noted in the study [8]. Preterms too behave similarly with peak and evening clustering of crying episodes at 6 weeks of corrected gestational age [9]. Possibility of missing organic etiologies in well diagnosed infantile colic is about 5% [10]. More the infant is away from 2nd month of life less likely is the diagnosis of infantile colic. Obvious red flags like abdominal distension, recurrent vomiting, icterus, blood in stool, bilious vomiting certainly refutes the diagnosis of infantile colic.

Exact cause of infantile colic is still not known [11]. Multiple hypotheses are proposed. Infantile colic can be a clinical phenomenon of upper end of normal crying curve of healthy infant. Central nervous system cause is also proposed as underlying predisposing factor. Food allergies do confabulate the spectrum. Maturing gastro-intestinal tract with discomfort can be a contributing factor too. There is a growing evidence that gut microbia is linked to infantile colic [12]. Microbial interactions and regulation of enteric immune system is proposed to be an important factor. Various cytokines were studied and noted to be increased in infants with infantile colic [13]. Gut inflammations and immune dysregulation are critical [14].

CD4+ T cells are important in gut to understand this immune mediated pathology. In humans the level of helios expression is positively associated with CD25 expression [15]. Upon interaction with TGF-β, CD4+ T cell up regulate both Th17 cells (RORγt) and regulatory T cells and (FOXP3). The balance between Th17 (RORrt) T cells and (FOXP3) regulatory T cell is proposed to be important mediator of gut immune dysregulation [16] Retinoid related orphan receptor-r (RORγ) and Fork head box P3 (FOXP3) messenger RNA levels are studied in peripheral blood [17]. More Th17 response can be a contributing factor to infantile colic.

Measuring fecal calprotectin is one of the markers for gut inflammation, however efficacy of this marker is doubted in breast feed infants [18]. No group till now has performed endoscopy or colonoscopy to study gut inflammation in infants for infantile colic. The concept of dysbiosis, gut inflammation and probiotics use in infantile colic is challenging and needs more studies to understand underlying pathology in infantile colic.

Management of Infantile Colic

Infantile colic is a clinical diagnosis. Parent counseling and home support is important. Mother and family should be counseled regarding colic process. Various drugs are available in the market for the treatment of infantile colic.

Oral hypertonic glucose solution was noted to be better than placebo in a study [19]. Herbal agents [20] are moderate quality evidence but exact content in these and culture specificity are uncertain factors. Simethicone is not more effective than placebo. Sucrose [20] has very low quality evidence for the management of infantile colic. Dicyclomine [20] though studied but has side effects. Cimetropium bromide has very low quality study but safety is controversial. Cochrane database of systemic review have concluded that no robust evidence supporting pain reliving agents for treatment of infantile colic [20].

Chiropractic manipulation of infants was also studied without any definite evidence and variable results [21,22]. Infant formula supplementation with probiotics does not raise safety concern but is of poor evidence to manage infantile colic [23].

Parental reassurance and education about the benign nature of colic constitute the most important part of the management. Mother's diet modification with reduced allergenic feeds may have some role [24-26]. In a recent randomized control trial multi-strain probiotics during pregnancy is found to affect cytokines and improve colic symptoms in infants [27] more studies are needed.

Recent interest in molecules like probiotics *Lactobacillus returi* DSM 17938 has generated new understanding in management of infantile colic. In earlier studies, lack of blinding, unclear sequence generation, unbalanced baseline characteristics, mother elimination diet and lack of objective measures of crying made result analysis difficult [28,29]. Roos, et al. showed that addition of lactobacillus reutri DSM17938 did not affect the global composition of the bacterial community in gastrointestinal tract [30] Fatheree, et al. in a double blind placebo controlled randomized clinical trial have shown *L. returi* to be safe in newborn with colic [31]. There is no increase in rate of infection, lactic acidosis, gastrointestinal symptoms or other adverse events. In Feb 2017 World Gastroenterology Organization global guideline [32] on returi DSM17938 recommended a dose of 10^8 CFU once daily for 21 days as level I evidence in colic. Lacto-bacllius reuteri DSM 17938 as Preventive strategy of infantile colic as level I evidence is also proposed. LGG 10^{10}-10^{11} twice daily is another probiotic recommended for prevention of infantile colic.

Controversies in Management

Savino, et al. [33] and Szajewska, et al. [34] have shown *L. returi* to be beneficial in double blind, placebo controlled trial in 2010 and 2013 respectively. Sung, et al. in 2013 [29] and 2014 [35] published data and meta-analysis with uncertain benefits. The difference in these studies may be due to different sample size inclusion criteria. Savino and colleagues involved breast fed infants and breast feeding mothers were required to avoid cow's milk while Sung and colleagues included both breast feeds, formula fed infants, breast feeding mothers were not required to avoid cow's milk.

Sung group [36] in 2017 November studied and published impact of *Lactobacillus returi* colonization on gut micorflora and infantile colic noted no difference in crying time at day 28 between infants colonized or not colonized by *L. returi*. They have noted positive relationship between *L. returi* density and crying time. No association between *L. returi* and stool calprotectin was noted. Overall reduction in median crying time was noted regardless of *L. returi* colonization status. They attribute these variable results probably to geographic factors and type of feedings.

Savino group 17 in January 2018 studied and published immunological basis and management of infantile colic by *L. returi*. They found increase in FOXP3 mRNA and reduced RORr/FOXP3 ratio which suggested reduced gut inflammation post *L. returi* ingestion. They concluded *L. returi* significantly reduces crying time and calprotectin in children with infantile colic while in another study by Fatheree et al. published found no change in FOX P3+ Tregs in peripheral blood but the percentages of CD25+ and helios + populations among FOX3+ Tregs were lower with *L. reutri* strain DSM 17938 as compared to placebo and 66% of infants in placebo group has resolution of colic by 3 weeks.

Infantile colic etiology is not certain and is multi-factorial. Epigenetic modifications and differentiation of RORγtvs. FOXP3 lineage, an immunological balance with other metabolic signaling pathway need to be further studied. There are definite geographic variations, type of feeding practices breast feedvs. formula which do change the outcome of infantile colic. Management WGO guidelines 32 published earlier in 2017 have shown that *L. returi* reducing crying time in breast fed infants with colic. Recent trials post these guideline as discussed have variable results. Individualization of treatment in each infant is important. More studies are needed keeping in mind differential outcome.

Management of infantile colic is defiantly challenging and interesting with scope for further research.

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