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HiPP Symposium Abstract

in the context of the 6th World Congress of Pediatric Gastroenterology, Hepatology an Nutrition

New insights into the intestinal microbiome in breastfed and formula-fed infants

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The establishment and the functions of the gut micribiota of breastfed infants

The human body is colonised by a vast array of microorganisms, the so-called microbiota. Every ecological niche present in the human body harbours a characteristic microbiota with the gut containing the most complex and diverse microbial community. During the last two decades, with the development of culture-independent techniques such as those based on Next Generation DNA Sequencing, our understanding on the composition and activity of this microbiota has increased rapidly. Now we know that the intestinal microbiota plays a key role for the maintenance health. Several studies have underlined the importance of the early-life microbiota development and a critical factor for a proper infant development and a correct microbiota-induced maturation of the host. Studies underlining the important role of the neonatal microbial colonization will be discussed, since this colonization process will affect the immune and metabolic homeostasis of the infant. Some recent data pointing out at the early days microbiota as a determinant for the later development and weigh-gain of the baby during the first months of life, will be presented. All this evidence substantiate the hypothesis that aberrancies or alterations in the neonatal period may pose important implications for the later health of the individual.

The initial establishment of the microbiome in the newborn, and its further development, is driven by factors such gestational age, delivery mode or the feeding habit, the effects of which are relatively well know. Moreover, this process is further modulated by other perinatal factors whose impact is not well understood yet. The healthy full-term, vaginally delivered, exclusively breast-fed baby has often been considered as the standard of a healthy microbiome, with an appropriate composition and providing the necessary functions for infant development and the maintenance of the physiological homeostasis. Unfortunately, this golden-standard is not always present and then situations like preterm-delivery, C-section delivery, antibiotics exposure, formula feeding, etc., may introduce alterations in the infant gut microbiome development process, a dysbiosis state, with potential consequences for health. Recent data indicate that these alterations are present at both high and low taxonomic levels, then affecting the global microbiota composition at phyla level but also that of specific species and subspecies. In this presentations the microbiota alterations induced by the above mentioned factors in the global microbiota composition, as well as on specific bacterial groups of special relevance in the infant, such as the genera Lactobacillus and Bifidobacterium, will be described. The data presented will allow identifying the key modifications in the global colonization pattern, and on the specific bifidobacterial population, resulting from prematurity, C-section, formula feeding or perinatal antibiotics. After the first months of life weaning and the introduction of complementary foods will further modify the development of the microbiota. This introduction of solid foods together with the cessation of breast-feeding will promote the increase on the levels of some intestinal microbes and the reduction of others. This process of microbial succession phenomena will become stabilized at about 2-3 years of age, when the microbiota of the baby already resembles that of an adult, although some specific microbial groups will continue suffering modifications until the adolescence.

As it can be expected, the above mentioned alterations in the microbial colonization process will impact not just the microbial composition but will also have a reflection at functional level. The production of important compounds, such as the short chain fatty acids, resulting from the microbial metabolism in the gut, will be impaired which will affect the metabolic homeostasis of the host and the gut barrier effect. Moreover, the presence of microbial dysbiosis may also limit the ability of the microbiota to provide the regulatory signals necessary for the immunological homeostasis of the host.

To summarize, our understanding on the process of establishment and development of the microbiome in early-life, and the factors driving it, is increasing very rapidly, mainly due to the technological development associated to DNA sequencing. This accumulating knowledge shall allow the development of intervention strategies for assisting the process of establishment of the microbiome when it is hampered. Such an approach may have long-term consequences during the rest of the life of the individual, resulting in a reduction on the risk of disease.

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A synbiotic infant formula shapes the gut microbiota of non-breastfed infants closer towards that of breastfed infants

Human milk is the natural form of infant nutrition — nurturing the infant in a perfect, most adequate and individualized form. Beside it´s nutrients, human milk also contains different functional ingredients supporting the still developing immune system. Consequently, breastfed infants show lower incidence in infections during the first years of life compared to non-breastfed infants and exclusive breastfeeding is recommended in the first six months of life. One of the non-nutritive factors that may mediate this protection is the human milk microbiome (HMM). The establishment of the infant´s microbiota has a profound influence on the development and maintenance of immunity at a critical developmental time window. Vaginal birth and breastfeeding are two major factors in setting up an ideal microbiota. Breastfed infants develop a protective microbiota that could partially explain the preventive effect of human milk on infections. Beneficial bacteria like e.g. Bifidobacteria or Lactobacilli are transmitted from mother to child at the time of birth and during the breastfeeding period.

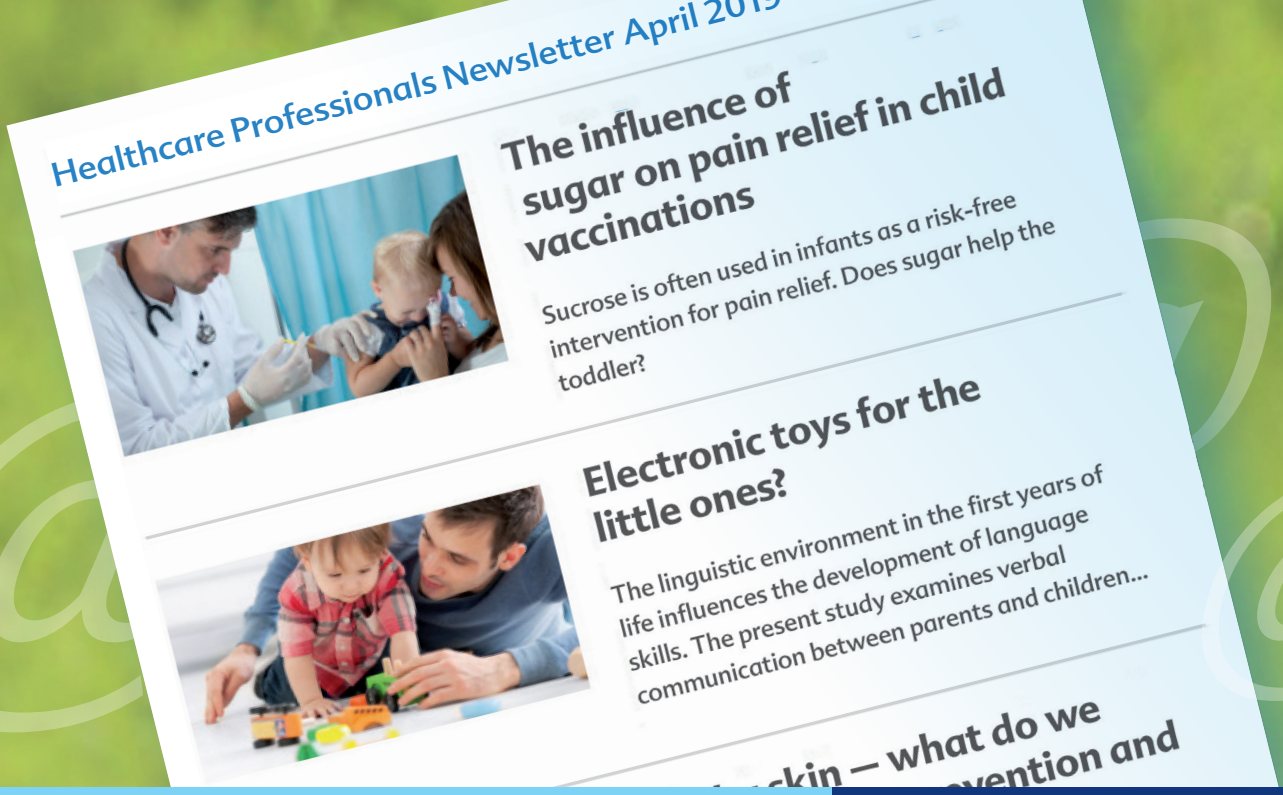
To isolate probiotic strains from human milk is one possibility to transfer these HMM-mediated protection to children who cannot be breastfed for whatever reason. Several trials have shown that some specific strains are able to prevent infections in the first year of life. Limosilactobacillus fermentum (L. fermentum) CECT5716 was isolated from the HMM and could show in vitro, in vivo and in human studies an array of health promoting effects e.g. in the prevention of gastrointestinal and upper respiratory tract infections.

Our recent clinical trial (ClinicalTrials.gov: NCT02221687) aimed to evaluate the effect of a synbiotic infant formula containing L. fermentum CECT5716 and galacto-oligosaccharides (GOS) in the prevention of infectious diseases in formula-fed infants in comparison to a standard infant formula without synbiotics. Breastfed infants were included as a reference group. In this double-blind, randomized, controlled, prospective study, an eleven-month intervention period was combined with a two-year follow-up. A total of 540 infants were included during their first month of life after parental consent. A study population of 503 subjects was included in the final analysis (control formula (CF): n=214, intervention formula (IF): n=214, breastfed (BF): n=75). The incidence rate of infections during the first year of life (gastrointestinal (GI), upper and lower respiratory tracts, otitis media and urinary tract) was assessed. Safety and tolerance of the synbiotic formula were evaluated. Negative binomial models adjusting on mode of delivery, history of breastfeeding and gender (according to the outcome) were applied. Furthermore, fecal GI parameters, including microbiota composition, secretory immunoglobulin A (sIgA), pH, and short chain fatty acids (SCFA) were assessed. Stool samples were analysed via qPCR and 16S analysis.

Results: Both infant formulae were well tolerated and showed comparable growth. Fecal microbiota analysis showed time dependent increase in alpha diversity. At four months of age, the effective richness was lower in breastfed infants compared to both formula interventions and significantly lower in the IF compared to the CF group. At 4 months of age, infant fed with IF showed significantly higher levels (copies per gram feces) of Lactobacillus spp. and therefore resembled more the levels in BF infants, compared to the CF group. Analysis of L. fermentum CECT 5716 on strain level showed that the probiotic was detectable in the IF group at the age of four months and one year. Synbiotic IF significantly increased the abundance of bifidobacteria from four months up to one year of age — comparable to BF infants.

Parameters of GI milieu (fecal pH, short chain fatty acids) and GI immune system (sIgA) were significantly influenced by the synbiotic IF. Fecal pH was significantly lower in the IF group than in the CF group and closer to the BF group at four months of age, while levels of acetate were higher in the IF group compared to the CF group. Fecal sIgA was highest in the BF group, and significantly higher in the IF group compared to the CF group at 12 months of age, showing persistant stimulation of the immune system. The incidence of lower respiratory tract infections was significantly lower in the IF group than in CF. For other infections no clinical significant differences between groups were shown.

Conclusion: These results provide some evidence that a specific synbiotic formula containing L. fermentum CECT5716 and GOS moves the intestinal microbiota profile closer to that of breastfed infants and could reduce the incidence of lower respiratory tract infections during the first year of age. The increased sIgA level in the synbiotic IF group could be linked to the interactions of the synbiotic compounds with the intestinal immune system.



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