THE IMPLICATIONS OF NATURAL FOOD IN THE DEVELOPMENT OF THE INFANT'S IMMUNE SYSTEM

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Abstract: *The immune system of the newborn is immature making the risk of infection to be very large. The breast milk compensates the lack of the immunologic defence, being considered a vital element for the integrity of the growth of the infant and its immune system integrity, at least during the first 6 months of life. The breast milk factors, such as secretor IgA, lactoferrin, carbohydrates, anti-secretor factor, alpha-lactalbumin, offers to infant the resistance against the microbial exposure soon after birth. Studies have shown the significant differences of the immune system between breast-fed infants and those with no breast-fed. Not least, the breast milk seems to develop a probiotic-like microflora, containing bacterial antigens, which essentially participates to the maturation of the infant immune system.*

INTRODUCTION

Since the newborn's adaptive immune system is immature, by ineffective phagocytes responses, serum low levels of IgA or lack of enough antibodies, the infectious risk in the neonatal period is very high.(1)

Proinflammatory activity of IgG, by activating the complement system and phagocytes, transferred transplacentally to the newborn, is significantly controlled by natural nutrition through the immune components of breast milk, thus compensating for the ineffectiveness of the newborn's defense system.(1)

The significant differences between severity and susceptibility to develop various types of infections (gastric, respiratory, urinary tract), according to several studies including breast-fed infants and artificially fed infants, further highlight the essential role that breastfeeding has during the first 6 months of life, giving the newborn a true barrier of antimicrobial and viral resistance.(2)

Breastfeeding provides the infant a resistance to microbial exposure during the first few months of life, even if the immune system is not mature, by the following factors: secretor IgA, lactoferrin, carbohydrates, anti-secretor factor, alpha-lactalbumin, other protection and anti-inflammatory factors.(3)

The *IgA* concentration in mature breast milk is 80-90% (approximative 1g/L); a similar concentration is found in colostrum (about 10 g / L). IgA is considered the most important antibody.(3) Secretor IgA acts as a barrier at the level of intestinal mucosa, against the pathogen agents of the intestinal flora of the mother, in front of which the newborn is exposed after birth.(3) The most important antibacterial role, protector of secretor IgA is to bind the microorganisms to the digestive mucosal epithelial cells, blocking the adhesion and penetration of microorganisms at this level.(3)

Lactoferrin, a major glycoprotein belonging to the transferrin family, is present in the highest concentration in colostrum, followed by breast milk.(3) It functions as an immune modulator, having multiple effects: antibacterial-bacteriostatic and bactericidal for gram positive and gram-negative bacteria, antiviral effect by the ability to inhibit cell-wall binding of the virus and antifungal effect against Candida albicans. It has the capacity to promote the development of probiotic bacteria, such as Bifidobacteria and to inhibit the propagation of other pathogenic microbes, such as Haemophilus influenzae as well as the mucosal adhesion of E. coli.(3) It has an anti-inflammatory role by its ability to penetrate in the leukocytes core, linking bacterial wall components; prevents the initiation and development of inflammation by inhibiting NF-kappaB transcription - a protein complex that is involved in cellular response by reducing the release of pro-inflammatory cytokines (IL-1beta, TNFalpha, IL-6 and IL-8).(3) Lactaderin is another glycoprotein, gastro-resistant, with anti-viral function, especially against rotavirus. It reduces inflammation, especially that of the intestine, by stopping TLR4 and NF-kB signals that have a strong inflammatory action, as well as favouring the tolerogenic phenotype in macrophages and intestinal cells.(4)

Carbohydrates, nutrients contained in breast milk, protect the mucosa from microbial adherence.(3) Oligosaccharides, representing a large solid fraction of the breast milk, are produced in the mammary glands and play an important role in stabilizing an optimal intestinal flora, the breast-fed infants presenting lower bacterial infections (E. coli, Klebsiella) than artificially fed infants. The pathogenic bacterium attaches to a certain oligosaccharide, partially at the cell surface level (there are over 90 types of oligosaccharides), binding giving it a specificity character. The carbohydrates annihilate this adhesion effect of microbial products to mucosal cells, acting in the form of analogous receptors.(3) Oligosaccharides in human milk act as "prebiotic" agents that stimulate the growth of probiotic factors, functioning as receptors that inhibit the adherence of pathogens at the level of intestinal surface of the newborn.(1)

The *anti-secretor factor* (also having an anti-inflammatory role) intervenes in preventing the development of certain conditions, such as mastitis and acute diarrhea, according to several studies.(3)

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Alpha-lactalbumin, with antitumoral effect, reduces the risk of developing leukemia in childhood, and for the mother the risk of developing breast cancer.(3)

The presence of *Il-7* in breast milk, as well as increased concentrations of CD8 + cells (2), are directly proportional with the size of the thymus, these being doubled in naturally-fed infants compared to those artificially fed, significantly reducing infectious risk.(3)

Another additional protective and anti-inflammatory factor, in addition to other cytokines, is the growth factor-beta transformant.(3)

Breast milk has an anti-infectious and anti-inflammatory role through the varied cellular contents: macrophages, T cells, stem cells and lymphocytes.(5)

In colostrum, the largest proportion (80%) is macrophages, that reach in milk through phagocytosis at the mammary epithelium and interfere in the maturation of the infant's immune system by stimulating the activity of T cells.(5,6)

Cytokines are pluripotent polypeptides whose mode of action is autocrine / paracrine by adhering to specific cellular receptors; they pass the intestinal barrier and thus participate in the development of the infant's immune system, being mediators in intercellular communication.(6) The cytokines from breast milk can perform two functions: to reduce inflammation, but also to increase it in the face of microbial exposure.(6)

Chemokines are part of the cytokine class, with a major chemotactic role, ensuring migration of the immune system cells to the inflammation sites.(1)

The most important cytokines are part of the TGF-beta family. They are activated at the gastric level in the presence of acidic pH and have an anti-inflammatory and antiallergenic role by increasing the intestinal tract tolerance.(7)

G-CSF interferes in the prevention of sepsis and intestinal development through cell proliferation, deepening of crypts and growth of cells.

In terms of thymus development, an important role is given by IL-7 in breast milk.(8)

Other pro-inflammatory cytokines are TNF-alpha, IL-6, IL-8 and IFN gamma, with oscillating values depending on lactation periods.(9,10)

The antibodies compensate the fragility of acquired immunity of the newborn, in particular through secretor (early) IgA and IgM and IgG, predominantly in late lactation.(11)

Secretor IgA-antigen complexes are processed at the intestinal level, subsequently intervening as potent anti-inflammatory agents.(1)

Other proteins that fulfil multiple roles are biliary salts.(1) They stimulate lipase (BSSL), whose bioactive component is influenced by glycans and is oscillating during lactation. They have an energy function by breaking up fats from milk and an antiviral function (especially against Norwalk and HIV viruses), by their ability to prevent CD4 + cells activity.(12)

Milk fat globules (MFG) contain several types of mucins that originate in the plasma membrane and whose basic function is anti-infectious defense, each type of mucin acting specifically: MUC1 against rotavirus and HIV, MUC4 together with MUC1 against the Norwalk and Salmonella viruses.(13)

Both long chain polyunsaturated fatty acid (LCPs) and conjugated linoleic acid have recently been recognized as having a role in developing and maturing the immunity of the newborn. The nucleotides participate in the maturation of the immune system by activating macrophages, NK activity and lymphocyte proliferation.(14,15)

Several studies have shown that breast milk, through its complexity, provides protection against several neonatal infections: sepsis, meningitis, severe diarrhea induced by Campylobacter and calicivirus; the mechanism functions due to fucosylated oligosaccharides acting as analogs on the receptors to which microbial agents attach.(3)

Maternal milk compensates for the lack of immune defense of the baby, developing a probiotic-like microflora. The microflora is produces by secretor IgA-mediated entero-maternal linkage, by means of oligosaccharides acting as analogous receptors (inhibiting the adhesion of microbes to the level of intestinal mucosa) and by cytokines with anti-inflammatory action (IL-10 and TGF-beta.

Several studies have shown that secretor IgA from milk has the ability to protect against aggressive viruses, that cause diarrhea in infants and not only (rotavirus, E.coli, Shigella, V.cholerae, G.lamblia). In addition to the beneficial effects of secretor IgA, the anti-secretor factor plays a role in reducing the risk of developing acute diarrhea, according to recent studies.

The microflora contains bacterial antigens that participate in the maturation of the immune system of the infant, against the situation of a suitable flora that engages a cytotoxic response necessary to defense against the intestinal pathogen agents.(16)

An extremely important effect on the development of the immune system during the neonatal critical period has anti-idiopathic antibodies whose particularity is the specificity against other autologous antibodies, being antibodies that bind to the specific antigen-linkage sites of other antibodies, in the case of breastfeeding.

Breast milk contains nutrients and non-nutrients whose function is in creating a perfectly suited immune system for the infant, so that it can respond appropriately to the microbial explosion from the external environment, when it leaves the germ-free intrauterine environment.(16,17)

Also, breast milk has an essential role in developing proper functioning and intestinal immunity, so that the infant can perform its digestive function in an effective way.(17)

Both breast milk composition and intestinal immunity, being so vital elements for the integrity of the immune system and the development of the infant, reducing the risk of infections and mortality and morbidity, require further research in the sense of the development of strategies for the prevention and treatment of intestinal disorders, especially in the case of infants with low birth weight or preterm infants.(1)

CONCLUSIONS

Breast milk has a composition that is perfectly suited for the growth and development needs of the newborn and infant, offering the energy and indispensable nutrients. Representing a balanced diet, it is the only complete feed of the infant, containing an important source of nutrients that ensures a harmonious somatic development, as well as non-nutritive components, bioactive molecules that contribute to optimal health through protection against infections and inflammation, the development and maturation of immunity, the development of tissues and organs, and the contribution to the development of the microbiota.

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