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Supplements

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Supplementary Paper

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LITERATURE REVIEW

The importance of gut health in early life for long term health

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Abstract

Introduction. The gut microbiota plays an important role in the normal functioning of the host organism. The microbiota of healthy newborn affected by many factors such as prenatal exposures, maternal nutrition, mode of delivery, type of feeding, introduction to solid food and its type, geography, and antibiotics consumption; and its composition continues to mature until reaching 3 years of age. Normal gut microbiota is essential in gut health, and play an important role in our homeostasis. Therefore, gut microbiota is considered a crucial factor for proper early life development and lifelong health. Prebiotics, along with probiotics, may alter gut microbiota composition thus play a role in the prevention of various diseases associated with dysbiosis condition.

Methods. Advanced search for relevant literatures in PubMed, Cochrane, and Willey was conducted. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Conclusions. Accumulating evidence from different studies has shown that the occurrence of a disease is often preceded by early alterations of the microbiota. Many studies established correlation between gut microbiota dysbiosis with diseases pathogenesis i.e obesity and other metabolic syndrome, asthma and allergies, also stress-related disorder. Prebiotic supplementation has proven to be effective in obesity, asthma and allergies management, also beneficial for immune system.

Keywords gut microbiota, gut health, gut brain axis, prebiotic

Introduction

Gut microbiota has been widely studied and well-recognized in many studies to have an important role in human health. Normal gut microbiota was not only play role in gastrointestinal health but also has great impact on proper early life development and lifelong health. Exposure to bacteria and their by-products has been shown to occur during fetal development, during delivery, and early feeding regime, and is modified by antibiotic exposure, all of which shape the microbiota composition and host's tolerance.[1,2,3,4,5] Microbial interventions, using prebiotics and probiotics supplementation, beginning before birth and in early infancy are widely discussed in the context of underlying mechanisms and the establishment of gut colonization as a critical early homeostatic influence. These interventions may have beneficial effect in normalize gut microbiota and prevent development of various chronic diseases in the future.

The primary aim of this literature review is to summarize the role of gut microbiota in early life and its implication on long term health. Furthermore, this review discussed about prebiotic supplementations to prevent various diseases associated with dysbiosis condition.

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Methods

Advanced search for relevant literatures in PubMed, Cochrane Library, and Wiley Online Library was conducted on prebiotics in early life and its health impact, with time windows from 2000 to 2021. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Discussion

Gut health in early life

In the beginning of life, newborns intestines is in aerobic environment. This condition will only allow the facultative anaerobic microbiota to reproduce, namely the Enterobacteriaceae family. However, within a few days, the lumen intestines will turn into anaerobic and allow for the colonization of microbiota such as Bifidobacterium, Clostridium, and Bacteriodes. Later in the first few weeks, the microbiota of the newborn gut resembles the maternal skin and vaginal microbiome, with predominant bacterial such as Enterococcaceae, Streptococcaceae, Lactobacillaceae, Clostridiaceae, and Bifidobacteriaceae. Bifidobacteriaceae most likey will be majority of bacteria found in the lumen for the next few months due to its nature as milk oligosaccharide fermenters. Weaning and introduction of solid foods will mark another change in gut microbiota, which increase in abundance of Bacteroides, Clostridium, Ruminococcus, and a decrease in Bifidobacterium and Enterobacteriaceae. The human gut microbiome continues to mature until the child reaches 2 to 3 years of age, after which its composition stabilizes. [1,2,3,4]

Gut microbiome affected by some factors such as prenatal exposures and maternal nutrition, mode of delivery, type of feeding (breastmilk vs. formula), introduction to solid food, geography, and antibiotics consumption.[1]

For decades, the human fetal environment has been considered sterile under physiological conditions. But recently many studies have proven the presence of bacteria in the placenta and amniotic fluid. Prenatal exposure to fecal microbes is likely a natural part of in utero development.[5]

Other studies showed that diversity and colonization pattern of the gut microbiota were significantly associated to the mode of delivery, in which the first microbiotas of human infants are determined mainly by their mode of delivery, and differences in the bacterial populations within the infant gut are resembling to the type of microbiota that the child encounters at birth. Previous studies have demonstrated that strains originating from the maternal gut and vagina are transferred to the infant's gut in case of a vaginal delivery, while infants born by cesarean section are suggested to be initially colonized by bacteria from the environment such as from maternal skin, hospital staff or other neonates.[6,7,8,9]

Human breast-milk covert its own microbial taxonomy that is passed on to the infant along with complex non-digestible human milk oligosaccharides (HMOs) that promote the proliferation of specific gut microbes. An infant who consumes human breast-milk is thought to ingest commensal bacteria, however, the origin of these commensals remains unclear. Bacterial transfer may happen during breastfeeding from the mother's skin, but a number of studies also support the entero-mammary pathway hypothesis, wherein bacteria from the maternal gut may reach the mammary glands via maternal dendritic cells and macrophages.[1,5,10]

Shifts in diet can significantly alter the gut microbiota due to the presence of new substrates that promote the survival and proliferation of varied types of microbial species thus introduction of solid food will alter gut microbiome based on the type of food consumed. Clostridium group XIVa was much more abundant in the microbiotas of the children that were fed meat, while Bifidobacteria and Rothia, as well as Lactobacillus decreased over time with Bacteroides remaining the most abundant in children fed iron-only fortifified cereals.[11]

Intestinal microbiota differs by geographical location for a number of reasons. Different ethnogeographic populations may have different genetic backgrounds, regional diets, and cultural practices. Also, availability or access to better sanitation and good healthcare will also determine bacterial species inhabiting in one region.[1,11]

Over usage of broad spectrum antibiotic became a trend to watch out for. Gut microbiota can be

severely altered if exposed to antibiotics too early in its development and/or for long periods of time. This ecological disruption combined with the decreased microbial diversity of the infant gut can provide opportunities for enteric pathogens, also may play a role in emergence of numerous diseases later in life.

Gut microbiota role and health impact in children

Gut microbiota play important roles in our homeostasis, including providing essential nutrients, metabolizing dietary fiber into short chain fatty acids, and ensuring proper development of the immune system. Therefore, gut microbiota is considered a crucial factor for proper early life development and lifelong health. Emerging evidence suggests that the colonization of microbes in the human body during early life plays a critical role in the establishment and maturation of developmental pathways and that disruption of this optimal microbial succession may contribute to lifelong and intergenerational deficits in growth and development. Dysbiosis, defines as imbalances or alterations in microbial composition or activity, can influence health and is implicated in various diseases. The factors that can disturb the balance of intestinal microbiota include lifestyle, antibiotic treatments and pathogens. Diseases such as obesity, type 2 diabetes, asthma, allergies and inflammatory bowel disease (IBD), have been associated with dysbiosis of the gut microbial ecosystem.[12]

Obesity

Obesity results from the accumulation of excess adipose tissue, which caused by behavioral and environmental factors, such as excessive consumption of energy-dense foods and a sedentary lifestyle. But studies support that intestinal microbiota take part in the development of obesity and subsequent insulin resistance.[13]

Gut microbiota metabolites, namely acetate and butyrate, bind to free fatty acid receptor 2 (FFAR2 or GPR43) and free fatty acid receptor 3 (FFAR3 or GPR41) and control eating behavior by increasing satiety and reduced food intake. Several studies also confirmed an increased Firmicutes / Bacteroidetes ratio in obese individuals. This microbiota strongly affects gastrointestinal genes expression involving the regulation of intestinal barrier function, energy balance, the regulation of intestinal barrier function, intestinal satiety hormones release stimulation, bile acids metabolic activity modulation, absorption of nutrients by intestinal mucosa, and the generation of short-chain fatty acids (SCFAs) which contributing significantly to human physiology and metabolism.[14]

Type 2 Diabetes Mellitus

Although common pathway in diabetes mellitus pathogenesis has been established, few studies conducted in connection with gut microbiome shown that proliferation of some bacterial species belonging to Proteobacteria may cause the development of diabetes. The Enterobacter cloacae B29 isolated from the obese human faeces, can induce obesity and insulin resistance in germ-free mice model at a monocolonization manner. This result prove that gut microbiota might play a causative role in metabolic disorder, but still need further researches.[15]

Asthma and allergies

The atopic diseases (atopic dermatitis, allergic rhinitis, allergic conjunctivitis, anaphylaxis, and asthma) are characterized by IgE-mediated hypersensitivity to an external antigen. The hypothesis is there are critical interactions that occur between gut microbiota and immune system in early life in order to circumvent the development of hypersensitivities. Studies in animal model show that restoration of gut microbiota caused a shift toward a TH1 and TH17 dominated immune phenotype, suggesting that the gut microbiota is important in establishing the balance between the TH1/TH2 subtypes in early life. Another study by Abrahamsson *et al*., 2014 shown that low gut microbiota diversity during the first month of life has been associated with asthma in school age.[16]

Gut brain axis concept

The microbiota-gut-brain axis is a bi-directional communication network encompassing the central nervous system (CNS), sympathetic and parasympathetic branches of the autonomic nervous

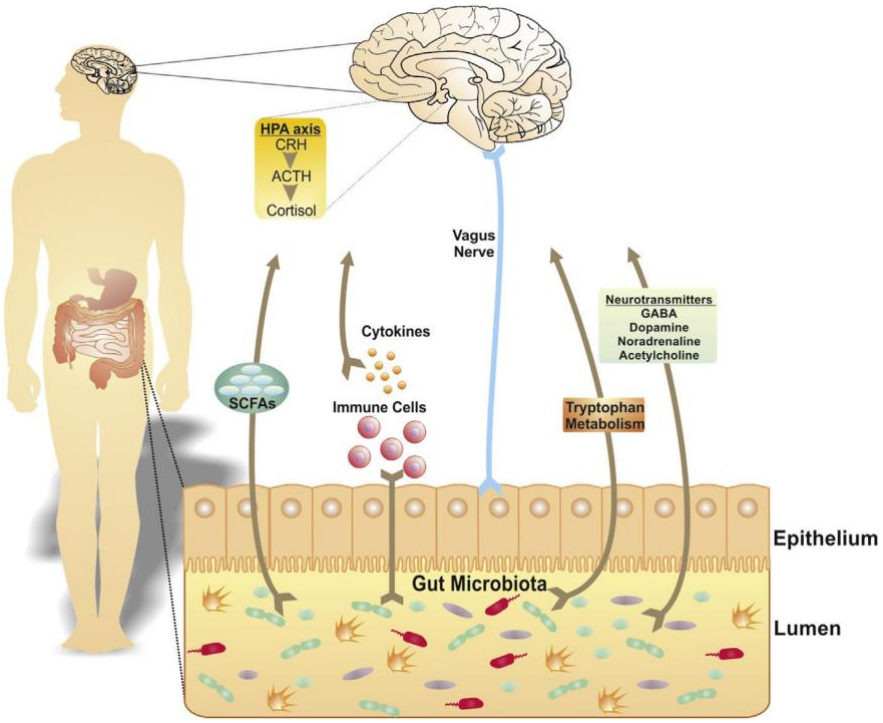

Figure 1. The microbiome-brain-gut axis and its variety of pathways.
(ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone; GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; SFCAs, short chain fatty acids).
(© Kennedy / Macmillan Publishers Limited, Source: Kennedy et al., 2016)

system (ANS), the enteric nervous system (ENS), neuroendocrine and neuroimmune pathways, and the gut microbiota.[17]

Neurodevelopment will be influenced by the individual genetic predisposition and by the influence of external factors (social, environmental, lifestyle) and dietary factors (diet, probiotics, prebiotics). There are several evidences showing mutual mechanisms between central nervous system (CNS) and gut microbiota, which involve the vagus nerve, the hypothalamic-pituitary-adrenal (HPA) axis modulation and the immune system.[18] Microbiota and microbial products may potentially affect gastrointestinal homeostasis via enteric glial cells. Furthermore, enteric glial cells link microbial cues with the host's nervous system.[19]

The vagus nerve is able to sense the microbiota metabolites, such as peptide YY, glucagon-like peptide 1, or cholecystokinin through its afferents and to transfer this gut information to the CNS, where it will generate an adapted or inappropriate response. Most likely CNS modulate microbiota composition by cholinergic anti-inflammatory pathway through vagus nerve fibers.[18]

Hypothalamic-pituitary-adrenal (HPA) axis activity is governed by the secretion of adrenocorticotrophic hormone-releasing factor and vasopressin from hypothalamus, which in turns activates the secretion of adrenocorticotrophic hormone (ACTH) from pituitary, which finally stimulates the secretion of glucocorticoids (cortisol) from the adrenal cortex. Studies, both in animal and human subjects, showed commensal microbiota, influenced by diet, had beneficial psychological effects with a decrease in serum cortisol thus plays a crucial role against the development of stress-related disorders, such as anxiety and depression.

Gut microbiota provides a broad variety of metabolites from the anaerobic fermentation of undigested dietary components, as well as endogenous material generated by the microorganism and host interaction. Gut microbes ferment dietary polysaccharides resulting in the production of monosaccharides and short chain fatty

acids (SCFA), includes acetic acid, butyric acid and propionic acid, which are important energy sources not only for the gut microbiota itself, but also for intestinal epithelial cells. Study by Ernie et al. shows that SCFA, produced by gut microbiota, is essential for microglia maintenance. Several studies also identified SCFA as inhibitors of histone deacetylases, a crucial regulator of the inactivated nuclear factor- κB activity and pro-inflammatory innate immune responses.

Optimize gut microbiota and gut health through prebiotic

Orally supplied prebiotics and probiotics are the most common ways to influence intestinal microbiota development in early life stages. WHO (World Health Organization) described prebiotics as a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota.

Potential prebiotic should fulfill some criterias. The first criteria assumes that prebiotics are not digested or just partially digested in the upper segments of the alimentary tract. As the prebiotic compound reach the colon, it will be selectively fermented by potentially beneficial bacteria, which is the second criteria. The fermentation may lead to the increased production or a change in the relative abundance of different short-chain fatty acids (SCFAs), increased stool mass, reduction of colon pH, reduction of nitrous end products and fecal enzymes, and an improvement of the immunological system, which is beneficial for the host thus fulfill the third criteria. Selective stimulation of growth and/or activity of the intestinal bacteria potentially associated with health protection and wellbeing is considered another criteria. The last criteria are a prebiotic must be able to withstand food processing conditions and remained unchanged, non-degraded, or chemically unaltered and available for bacterial metabolism in the intestine. Huebner et al. (2008) tested several commercially available prebiotics using various processing conditions. They found no significant changes of the prebiotic activity of the tested substances in various processing conditions. Prebiotics may be used as an alternative to probiotics or as an additional support for probiotics.[21,22]

Most prebiotics are non-digestible oligosaccharides such as manno-, pectic-, soybean-, isomalto-, (trans)galacto-, and xylooligosaccharides. The vast majority of prebiotic studies have focused on inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS). FOS and inulin usually can be found in daily diet such as onion, garlic, wheat, banana, chicory, and some cereals; while GOS have a dairy origin and are produced by the enzymatic conversion of lactose using beta-galactosidase.[20] The main effects of inulin, FOS, and/or GOS is that, even consumtion in small amounts (0,24–0,8 gr/100 ml formula in infants or 1.5–5 gr/day in young children), able to stimulate the growth of Bifidobacterium and Lactobacillus species.[23]

Based on in vitro model system investigation, prebiotic administration and propagation of beneficial bacteria will produce organic acids and resulted in a reduction in luminal pH, inhibiting growth of pathogens.[24]

Among the fermentative products of prebiotics produced from the microbiota, short chain fatty acids (SCFAs) are studied most intensively. SCFAs are mainly composed of acetate, propionate and butyrate, and many other metabolites. SCFAs can act as energy sources absorbed through colonic mucosa. Among these, acetate is mainly metabolized in muscle, kidneys, heart, and brain. Propionate undergoes metabolism in the liver and is a neoglucogenic substrate that may inhibit cholesterol synthesis and regulate lipogenesis in adipose tissue. Meanwhile butyrate is mainly metabolized by the colonic commensal bacteria, where it acts as a preferential substrate and regulates cell growth and differentiation by different mechanisms.

There is also an evidence that prebiotic administration may modulate TH2 responses and may be beneficial in allergy cases. Study by Moro et al. 2006 and Ivakhnenko 2013 shows that administration of GOS and long-chain FOS in infant formula given in a double-blind, randomized, placebo-controlled trial in 259 infants was associated with a reduction in incidence of atopic dermatitis, wheezing and urticaria to less than 50% of the incidence in non-prebiotic formula-fed infants.[25]

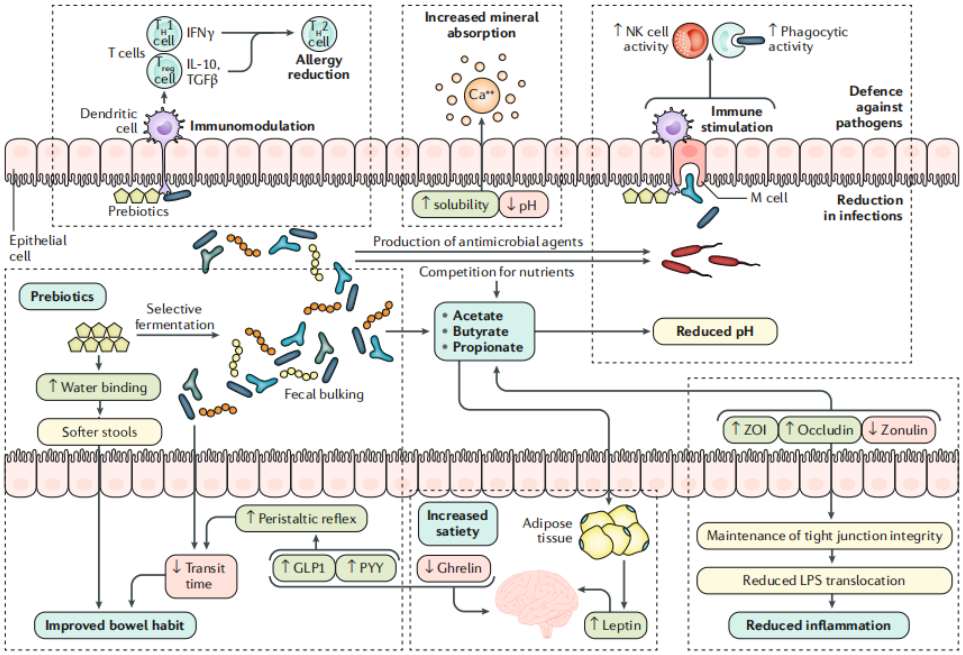

Figure 2. Prebiotic mechanism of action.
(GLP1, glucagon like peptide1; M cell, microfold cell; NK cell, natural killer cell; PYY, peptide YY; TGFβ, transforming growth factor-β; TH1 cell, type 1 T helper cell; TH2 cell, type 2 T helper cell; Treg cell, regulatory T cell; ZO1, zonula occludens 1)
Source: Sanders et al., 2019

Prebiotics enter the gut and are selectively utilized. This step increases bacterial growth and functionality of specific bacteria genus or species. Fecal bulking and improved bowel habits occur due to microbial growth. Immune regulation can be influenced by increased biomass and cell wall components of the bacteria. Metabolic products include organic acids, which lower intestinal pH and have concomitant effects upon microbial pathogens and mineral absorption. Metabolic products can also influence epithelial integrity and hormonal regulation. Bacteria that respond to prebiotic intake can influence the microbiota composition through elaboration of antimicrobial agents (for example, peptides) and competitive interactions, possibly reducing infections and bacteria containing lipopolysaccharide (LPS).

Several meta-analysis have been conducted to have better understanding about metabolic effect from prebiotic administration. Prebiotic intervention, mainly GOS and inulin, has a positive effect on glucose homeostasis, inflammation and blood lipid profile in humans. Studies have shown that consumption by young adolescents of a mixture of FOS and inulin or GOS can result in marked increases in absorption and calcium mineralized into bone, thus may prevent osteoporosis later in life.[25,26,27] Prebiotic administration also may induce satiety and regulate appetite because SCFAs produced by fermentation in the gut can interact with specific fatty acid receptors, FFAR2 and FFAR3, and regulate lipolysis and release of the incretin glucagon-like peptide-1.[24]

Conclusion

Microbiota is part of gut health and has been formed since the pre-natal period. Gut microbiota in individuals is influenced by many factors, for example maternal factors, type of delivery, type of feeding, antibiotic consumption, and many else. An optimal microbiota balance in the body will provide

a good level of health, while disruption of the gut microbiota, known as dysbiosis, can cause health and immune system disorders either directly or in the future. Many studies prove that dysbiosis plays a role in the pathogenesis of IBD, asthma and allergies, obesity and other metabolic syndromes. The microbiota-gut-brain axis also emphasizes the importance of the good gut microbiome in neurodevelopmental development, as well as many studies that emphasize the relationship between the microbiota and neurological cases.

Intervention of gut microbiota can be done with supplementation of probiotics and / or prebiotics. Prebiotic administration has shown evidence of beneficial effects on the immune system, asthma and allergies, and obesity. Future studies might be needed to explain the mechanisms of actions of prebiotics and its interaction with gut microbiota, which may confer a beneficial effect on human health.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Social-emotional development in early life: what happens and how to optimize it

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Abstract

The Physical, metabolic, emotional, cognitive, and social development all begin to develop during early years of childhood.. Social and emotional competencies are increasingly recognized as critical for children's success, in school and in later phases of life into adulthood. According to new research, changes in the gastrointestinal tract's development during the early postnatal period can affect brain development and vice versa., collectively called the gut-brain axis. The gut microbiota has an impact on a variety of mental processes and phenomena, as well as being involved in the pathophysiology of a variety of mental and neurological diseases.. Insights in this area can be targeted through dietary treatments to improve cognitive outcomes in newborns by optimizing the link between the gastrointestinal system and the brain. Further, having a healthy and happy human life could be ensured by acquiring adequate and balance microbiota.

Keywords gut brain axis, gut microbiota, socio-emotional

Introduction

Early childhood is characterized by the successful acquisition of social-emotional skills.[1,2] Early childhood research has highlighted the importance of a child's first five years of life on his/her social emotional development.[3] The basis for perceptual, cognitive, and emotional capacities is laid during the early postnatal period, which is known as critical for the creation of long-term cognitive and behavioral talents. . Recently, the first 1,000 days have been highlighted as a window of opportunity to alter a child's cognitive results.[4]

The quality and stability of a child's human relationships in the early years lay the foundation for a wide range of later developmental outcomes, e.g. self-confidence, motivation to learn, achievement in school and later in life, the ability to control aggressive impulses and resolve conflicts in nonviolent ways, knowing the difference between right and wrong, capable to develop and sustain casual friendships and intimate relationships, and to be a successful parent oneself.[1,5,6] Child development specialists across multiple disciplines acknowledge the importance of positive social-emotional development (SED) to overall child well-being.[6] Therefore, this review provides an overview of key literature related to understanding and optimizing SED in early life. Then, we discuss the concept of gut-brain axis (GBA) and its role in critical window of early postnatal period, and its stimulations to increase the SED in children.

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Social-emotional development in early childhood

Social-emotional development is defined as 'a child's developing capacity to (i) experience, manage and express the full range of positive and negative emotions; (ii) develop close, satisfying relationships with other children and adults; and (iii) actively explore their environment and learn. As

social-emotional skills form the foundation for later functioning in school and for building lasting relationships with other people, the need to assess such skills in young children is now widely accepted.[7]

It is commonly assumed that infants have emotion concepts by about six months of age, as evidenced by their ability to discriminate between posed facial configurations that are stereotypes of facial expressions anger, sadness, fear, and happiness categories.[8] A study examined infants' responding to others' emotional displays across 5 discrete emotions. The results revealed that infants use different functional behaviors in response to discrete emotions and were clearest in the 24-month-old infants.[9]

Psychopathology in infants and toddlers (ages 0–24 months old) is often found within the social-emotional domains and tends to persist over time.[7] Psychopathology in early childhood is associated with concurrent global impairment, and there is evidence for specific relationships between disorders and functioning domains; young children with autism spectrum disorder (ASD) and oppositional defiant disorder show impairment in peer relationships, family functioning and parent-child relationships, and behavioral functioning. [10]

Physiology of social-emotional development

Social interaction is governed by several subcortical forebrain structures such as the prefrontal cortex (PFC), anterior cingulate cortex, amygdala (AMG), hippocampus, and hypothalamus, which form part of an integral interconnected network to facilitate this complex behavior. Damage or dysfunction to any one of these brain regions can give rise to perturbations in social behavior. Indeed, the neurobiology of regions such as the AMG and PFC have been shown to be altered in disorders of the social brain such as autism spectrum disorders (ASDs).[11]

The key brain region for social functioning is the AMG. Damage to the AMG impairs individuals' abilities to recognize complex social emotions in facial expressions. AMG volume and functional connectivity with cortical regions correlates with social network size in young adults, and alterations to AMG circuitry contribute to social processing deficits in many disorders, such as ASDs and anxiety disorders.[12]

Neuronal circuits in the brain are shaped by experience during 'critical periods' in early postnatal life.[13] A young and developing brain has an increased flexibility of the circuitry. Once a particular circuitry pattern becomes established, it is difficult for the effects of new and different experiences to alter that architecture. This means that early experience has a unique advantage in shaping the architecture of developing brain circuits before they are fully mature and stabilized (Fig.1).[14]

How to optimize social emotional development in early life

It was recently discovered that children who are institutionalized at birth have IQs in the low 70s, despite the fact that they are otherwise developing normally. However, placing such children in high quality foster care before the age of two years

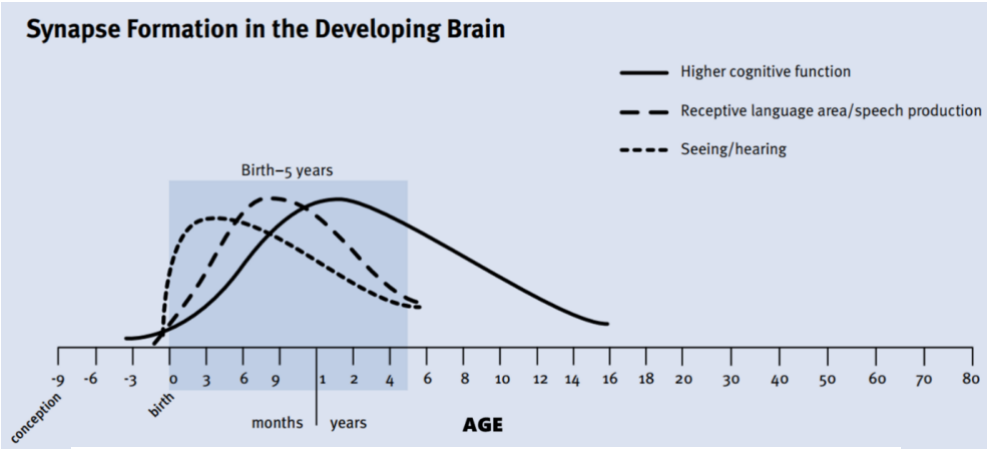

Figure 1. Synapse Formation in the Developing Brain

increases IQ significantly. A similar trend also occurs for language, and the development of the electroencephalogram (EEG) power and coherence. The influence of childhood environment is far more evident in such basic cognitive processes as sensory perception, and the foundation of brain architecture must lay in the early formative years.[15]

It is important that experiences provided in the earliest years are appropriate for the young child's stage of development. Reading a picture book with a toddler who is learning to speak, for example, provides an important opportunity to point to and talk about the pictures, not to focus on the written words. The ability to decode written language comes later, when the appropriate, higher level brain circuitry will be built. Because low-level circuits mature early and high-level circuits mature later, different kinds of experiences are critical at different ages for optimal brain development, a concept called age-appropriate experience. Soon after birth, basic sensory, social, and emotional experiences are essential for optimizing the architecture of low-level circuits. At later ages, more sophisticated kinds of experiences are critical for shaping higher-level circuits. When adults or communities expect young children to master skills for which the necessary brain circuits have not yet been formed, they waste time and resources, and may even impair healthy brain development by inducing excessive stress in the child.[14]

Gut-brain axis (GBA)

In the last several years, interest in the interactions among the gut microbiome, brain, and behavior has exploded.[11,16] The microbes residing in our gut harvest energy from the food we eat, train our immune system, and release metabolites and hormones important for regulating our physiology. Chemical signals from our microbiota can act locally within the gut, and can also have larger systemic effects.[17]

Preclinical evidence supports a role of the gut microbiome in behavioral responses associated with pain, emotion, social interactions, and food intake. Converging evidence suggests that the brain and the gut microbiota are in bidirectional communication.[16] Collectively, this bidirectional pathway is known as the microbiota-GBA.[11,18,19] Interactions between gut microbes and established psychoneuroimmunologic pathways allow for gut-brain communication., including immunological (cytokines), endocrine (hypothalamic-pituitary-adrenal), and neural (vagus) pathways.[20-22]

Both the gut microbiota and the central nervous system undergo fast changes throughout the first two years of life.[20] The early window for gut microbial establishment is critical. Mode of delivery is known to play a significant role in the natural assembly of the neonate gut microbiota in term infants, where the pioneer colonizers of vaginally delivered full term infants resemble the mother's vaginal microbiota.[23] Advances in sequencing technologies are revealing that the early developmental microbiota signature influences almost every aspect of the organism's physiology.[21]

To date, there is limited high-quality evidence regarding alterations in microbial ecology or production of microbial-derived metabolic products in human patients with brain or brain gut disorders. For example, there is inconclusive evidence from human studies regarding the beneficial effects of manipulating the microbiota with prebiotics and antibiotics in patients with irritable bowel syndrome, even though meta-analyses suggest a small therapeutic effect for probiotics. Furthermore, it is not clear whether alterations observed in the microbiota of patients with these disorders arise from primary alterations at the gut microbial interface (bottom-up effects) and/or changes in brain-gut signaling (top-down effects).[16]

Clinical findings of gut-brain axis theory

A number of experimental approaches have been employed to study the modulatory effects of gut microbiota on gut-brain interactions in experimental animals, including treatment with antibiotics, fecal microbial transplant, germ-free (GF) animal models, and treatment with probiotics. Microbiota-related effects have been reported in relation to anxiety-like behavior, depression-like behavior, nociceptive responses, stress responsiveness, feeding behavior, and taste preferences. Despite the extensive remodeling of biological systems in the GF animal, the fact that some observed behaviors and brain changes could be reversed by reconstitution of pathogen-free microbiota (conventionalization)

validates some of the conclusions drawn.[16,18] Nevertheless, as the GF animal has no counterpart in human brain development, premature conclusions about the translational relevance of these findings to humans should be avoided.[16]

Ongoing recognition of the role of the gut microbiota in preclinical models of disease, especially neuropsychiatric, demands evaluation in clinical settings.[16] ADHD is the most prevalent neurodevelopmental disorder and is highly heritable with other contributing environmental factors such as diet and microbiome also influencing risk. ADHD individuals had an increase of *Actinobacteria* mainly at the expense of *Firmicutes* and *Bifidobacterium* within the phylum *Actinobacteria* compared to the healthy controls.[23]

There is a high heterogeneity in the findings of altered microbial profiles in ASD. It is reported that there are alterations in the microbial communities in ASD but conflicting results are reported in the prevalence of *Firmicutes*, *Bacteroidetes* and *Proteobacteria*, *Bifidobacterium, Clostridium*, and *Bifidobacterium* between children with ASD and controls. The incidence of schizophrenia is positively correlated with preterm birth and associated with microbiota changes, suggesting that schizophrenia is a neuropsychiatric disorder where microbiome early in life might be involved in the disease process.[23]

Increasing the social-emotional development via gut-brain axis

Throughout one's lifetime, the gut-brain, brain, and mentality develop practically in lockstep. (Fig.2). Improvement of psychology, neuroscience, and psychiatry will all benefit from gut-brain psychology. Various microbiota-improving methods including fecal microbiota transplantation (FMT), probiotics, prebiotics, a balance and healthy diet, also healthy lifestyle have all been demonstrated to improve the function of the gut-brain, microbiota–GBA, and brain. In the future, it will be feasible to utilize the gut microbiota to improve brain and mental health, as well as to prevent and treat disorders associated with them.[19]

Pathogen infection quickly induces sickness behavior, with infected subjects showing fatigue, social avoidance, decreased appetite, and increased anxiety-like behavior. Supplementing with certain probiotics,[24] prebiotics, or fermented foods reduces negative behaviors and improves these emotions.[19] Surgency and extraversion are linked to phylogenetic diversity in toddlers.[25] A healthy microbiota helps the host cope with stress, whereas an aberrant microbiome lowers resistance and makes the host more susceptible to stress-related ailments.[19]

Gut-brain psychology will play a role to the development of general psychology, such as character, memory, and behavior. Its clinical application, such as managing the brain and behavior through gut microbiota intervention, is likely to have a greater impact.. There are mainly seven recognized microbiota interventions: the GF technique, pathogen infection, antibiotics, FMT,[26] probiotics,[24] prebiotics, and diet; All of the methods have showed considerable promise in terms of mind and behavior regulation.. Among these methods, the first two are only possible in animals' experiments, whereas the third one is commonly utilizedin anti-infection treatments, and the last four are all promising in microbiota improvement.[19]

The healthy diet promotes the function of the microbiota–GBA and leads to improvements in health and well-being.[19] Nutritional psychology will connect the microbiota–GBA with psychology.[27] Food is the most important component affecting the gut microbiota, and it has an impact that lasts a lifetime. Through the microbiota–GBA, a balance and healthy diet leads to a healthy gut microbiota and gut-brain, and supports brain and mental health.[19]

Sarris et al. (2015) suggested nutritional psychiatry; they believed that diet is a key modifiable intervention target for prevention of the initial incidence of common mental disorders. Convincing data suggest that select nutrient-based supplements (in isolation, or in combination, e.g. omega-3 fatty acids, zinc, B vitamins, and vitamin D), might provide neurochemical modulatory activities that are beneficial in the management of mental disorders (e.g. bipolar depression, post-traumatic stress disorder, and major depression).[28] The happiness and quality of life among caregiver and families/parents are also studied plays role in improving the child's gut health and effectiveness of nutrition intervention, hence need to be put into

serious consideration in the future.[29] Moreover, combining diet therapy with other interventions, including drug treatment, psychotherapy, and exercise, has shown some good effects in mental therapy.[19]

Conclusion

During the first 1,000 days of life, children learn progressively to regulate their impulses, get along with others, understand and respond to emotions, focus their attention on salient stimuli, follow rules, and engage in culturally appropriate social interactions. Negative early experiences can impair children's mental health and effect their cognitive, behavioral, social-emotional development.

The GBA pathway suggests that microbial signals are important for healthy neurodevelopment and programming of social behaviors in the brain. It is noteworthy that the microbiota is more "medically" accessible and modifiable than the human genome. This fact provides a promising opportunity for preventing or treating neuropsychiatric conditions.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Nutritional opportunity and brain development among fetus and infant

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Abstract

The right for optimal cognitive, social, and emotional behavioral development is fundamental for every child. The cognitive, social, and emotional parts of the brain continue to develop across the lifespan. An immense portion of the brain's structure and capacity is shaped early in life. Nevertheless, a cautious approach must be undertaken to ensure optimal development with long-term consequences during this sensitive period. Among the identified factors for optimal brain development, provision of optimal nutrition shared its portion as one of the fundamentals. This article will review the essential features of nutrients in the fetal, postnatal, and infancy period in relation to brain development.

Keywords brain development, cognitive, nutrient, nutrition

Introduction

The brain, arguably one of the essential organs in the body, requires a high level of nutrition to grow and function optimally. In fact, the brain utilizes 60% of the total intake in the body. To ensure that the neural substrates are incorporated during development, proper maternal and infant nutrition is needed. It is important to note that each nutrient has its period (sensitive period) and their deficiency, subsequently, can cause a detrimental effect on brain development.[1, 2]

The early years of life are fundamental for children's development of foundational cognitive and socioemotional characteristics. Globally, one-third of children failed to reach their developmental potential by pre-school age. In areas of the world where risk factors, such as infection, malnutrition, poverty, and lack of availability to high-quality healthcare and educational services were still present, low development scores were expected.[3] For better development, several of these risk factors can be alleviated through proper nutrition.

Several nutrients that have been studied with respect to nutrition and brain development are folate, iodine, iron, vitamin D, choline, and docosahexaenoic acid (DHA), to name a few. In this review scope, the authors will focus mainly on the six nutrients listed above with the aim to review recent literature regarding the evidence for a health benefit of nutrition in the development of the brain in infants.

Physiological brain development

Brain development is a protracted process that begins about two weeks after conception and continues into young adulthood 20 years later. Prenatal brain growth is primarily under genetic and environmental control (i.e., folic acid), all of which can affect the developing brain. In contrast, much of brain development that occurs postnatally is experience-dependent and characterized by gene-environment interactions.[4]

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Neurulation

After forming a three-layered, spherical structure from a developing embryo, the cells thicken to form a neural plate, followed by forming a neural tube. The neural tube becomes a three-vesicle structure after completion and briefly a five-vesicle structure. The anterior portion of the tube will become the forebrain, the diencephalon, and the basal ganglia. The cells around the middle vesicle will become the midbrain, connecting the diencephalon to the hindbrain. The hindbrain, which consists of the medulla oblongata, the pons, and the cerebellum, will emerge from the tube's back end.[4, 5]

Proliferation

Once the general structure of the neural tube has been set out, the cells that line the innermost part of the tube (ventricular zone) proliferate at a logarithmic rate. A second zone (marginal zone) forms as these cells multiply, containing axons and dendrites. This stage lasts a long time, yielding in a newborn brain with far more neurons than an adult brain. The overproduction of neurons is gradually balanced out by the process of apoptosis (or programmed cell death).[4]

Cell migration

After the cells are born, they migrate to their final destinations. The cerebral cortex is composed of multilayered tissue several millimeters thick, formed by the movement of cells in an inside-out direction (radial migration). This movement begins in the ventricular zone and migrates through the intermediate zone, with the cells eventually reaching their final destination outside the developing brain.[4]

Differentiation

When a neuron reaches its destination, it can either differentiate into a mature neuron with axons and dendrites, or it can be retracted by apoptosis. The development of axons is facilitated by growth cones, tiny structures that emerge at the edge of an axon. Molecular guidance signals and anatomic structures drive the cellular processes that occur at the growth cone promoting growth toward specific targets and away from others. Dendrite formation occurs by a slightly different path, which is thought to be influenced by genes that control the calcium-regulated transcription factors.[4]

Synaptogenesis

In general, synapse, the point of contact between two brain cells (i.e., two neurons and frequently a dendrite and an axon), is first seen about the 23rd week of pregnancy, with peak development lasting the first year of life. Similar to the concept of neurons, massive overproduction of synapses is accompanied by a gradual reduction or pruning. It is worth noting that the different structures of the brain reach their peak of synapse output at different times (i.e., visual cortex peak between the 4th and 8th postnatal month, while prefrontal cortex until the 15th postnatal month). The difference in timing in peak synapse production is crucial because it affects the timing of the plasticity of these regions, with later peak synapse production leading to longer plasticity of the region.[4]

Synapse pruning

Following the overproduction of synapses, pruning of the unused and overabundance of the synapses usually ensued. The stages of brain development are mostly gene-mediated before synaptogenesis, yet, after the synapses are eliminated, the balance changes to pruning, which is primarily experience-driven. The timing of synapse pruning, like synaptogenesis, is dependent on the region of the brain where it occurs. Around the fourth and sixth years of life, pruning in areas of the cortex involved in visual and auditory perception is completed, whereas pruning in areas involved in higher cognitive functions continues through adolescence.[4]

Myelination

Myelination is the final step in the brain's growth. In this process, the axons of neurons are wrapped in fatty cells, ultimately facilitating neuronal activity and communication. Myelination takes place in a different region of the brain at different times. Regions of the brain in certain sensory and motor areas are myelinated earlier in a process completed

around the preschool age. In comparison, in regions involved in higher cognitive abilities (i.e., prefrontal cortex), the process is not complete until adolescence or early adulthood.[4]

Brain development and early nutrition effects

The vulnerability of a developing brain process, region, or circuit in the aspect of early life nutrition is determined by two factors: the timing of the nutrition deficiency and the region's requirement for that nutrient at that time. For example, In the pediatric population, the risk of iron deficiency varies, peaking during the fetal/newborn period, 6-24 months of age, and during the adolescent years in menstruating females.[6] **Table 1** summarized the critical process influenced by particular nutrients during neurodevelopment, while **Table 2** summarized the examples of natural sources of nutrients.

Table 1. Critical processes during neurodevelopment affected by specific nutrients[6]

Neurologic process	Cell type	Function	Nutrient example	At risk during late gestation and 0-3 years
Anatomy				
	Neuron	Division (neurogenesis) Migration Differentiation (Neurite outgrowth; synaptogenesis)	Protein, carbohydrates, iron, copper, zinc, LC-PUFA, iodine, vitamin A, vitamin B6, vitamin D, vitamin C	Global, hippocampus, striatum, cortex, retina
	Oligodendrocyte	Myelination	Protein, carbohydrates, iron, iodine, selenium, zinc, vitamin B6, vitamin B12	Global
Chemistry				
	Neuron astrocyte	Neurotransmitter concentration, receptor, reuptake	Protein, iron, iodine, copper, zinc, selenium, choline, vitamin B6, vitamin D	Global, hippocampus, nucleus accumbens, VTA, cortex, cerebellum
Physiology & Metabolism				
	Neuron oligodendrocyte	Electrical efficiency	Glucose, protein, iron, iodine, zinc, choline, copper	Global

Table 2. Examples of natural sources of selected nutrients[2]

Nutrient	Examples of sources
Folate	Dark leafy greens Legumes Dairy products Grains Poultry Eggs
Iodine	Seaweed Seafood Oysters Legumes Strawberries Iodized salt
Iron	Red meat Spinach Liver Shellfish Legumes
Vitamin D	Sunshine Fatty fish Beef liver Egg yolks Mushrooms
Choline	Eggs Red meat Liver Peanuts Dark leafy greens
Docosahexaenoic acid	Free-range eggs Grass-fed beef Fatty fish Algae

Nutrients

Folate

Folate is one of the recognized nutrients to support normal metabolic, physiological, and neuronal functions and is involved in methylation reactions, nucleotides synthesis, neurotransmitters and myelin, and homocysteine regulation at non-toxic levels.[7] Neural tube defects (ranging from anencephaly to asymptomatic closed spinal lesions), which affect 1 in 10,000 pregnancies in Europe, have been associated with low intake of folate during pregnancy.[8] Based on emerging evidence, folate is now recommended as a necessary nutrient from before conception to later pregnancy.

Myelination of the brain, which occurs at its peak between mid-gestation and the second year of life, is critical for cognitive development. It protects nerve axons and facilitates communication between neurons and may be especially vulnerable to folate deficiency.[9] According to a recent study, folic acid supplementation in the second and third trimester of pregnancy, as recommended in the first trimester, can affect children's cognitive ability and brain function as young as 11 years of age.[10]

Iodine

Iodine is an essential micronutrient required in human diets. The thyroid hormone's effect on brain growth is mediated by iodine, an essential component of the hormone. This micronutrient also maintains the redox balance. Thyroid hormone also influences processes, such as myelination, cell migration and differentiation, synaptogenesis, dendrite structure, transcriptional regulation, and synaptic plasticity.[11, 12]

Synaptic plasticity, along with long-term potentiation, is one of the processes that sustain learning and memory. Synaptic plasticity works by altering the amount of neurotransmitter release or the number of receptors on the postsynaptic cell.[13] Thyroid hormone is thought to play a role in neurotransmitter release throughout fetal development and may even act as neurotransmitters themselves, implying that iodine is needed. Thyroid hormones have also been shown to promote neuronal contact by interacting with other neurotransmitter types such as acetylcholine, norepinephrine, and dopamine.[11]

Iodine deficiency affects all age groups, and a lack of iodine may trigger hypothyroidism and other disorders, classified as iodine deficiency disorders (IDDs). Iodine deficiency can lead to oxidative stress, which can disrupt the function of trophoblastic cells and the placental vascular net. Behavioral abnormalities range from global abnormalities in severe deficiency to more inferior learning and memory, sensory gating, and in milder deficiency, increased anxiety.[11, 14] Iodine supplementation may be recommended to meet individual needs, especially for expectant mothers, in order to prevent potential negative impacts and optimize fetal growth.

Iron

Iron, a structurally essential component of hemoglobin and one of the micronutrients that influences early brain development, has been extensively researched.[15] Iron deficiency is the most common nutritional problem worldwide. Prenatal and early childhood iron deficiency can result in permanent neural issues.[16] Fetal iron sufficiency supports neural energy metabolism, the dendrites and synapses development, neurotransmitters synthesis, and the onset of myelination.[17] In an iron-deficient fetus, brain development does not undergo a typical trajectory and the suboptimal outcomes are almost certainly irreversible even when the iron is replete.[2]

Iron deficiency in the first 30 weeks of pregnancy was linked to a higher prevalence of autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and intellectual disability in children compared to children whose mothers were diagnosed later in pregnancy or were not diagnosed at all, according to a study involving over half a million of children in Sweden.[18] Along with that, iron deficiency anemia during later childhood has been linked to poor cognition and school achievement and in a longitudinal study among adolescents with iron deficiency anemia in childhood continued to score lower in intelligence quotient (IQ), social problems, and inattention compared to non-anemic peers.[9]

Vitamin D

Vitamin D, a lipid-soluble vitamin synthesized in our skin when we are exposed to sunlight. This vitamin has long been recognized for its function in calcium homeostasis and maintaining bone integrity. Vitamin D is essential for neuronal development in the early stages of life. Vitamin D is a neuroactive steroid and vitamin D receptors have also been found in the human brain.[19] Vitamin D plays a role in neuronal proliferation, differentiation, neurotransmission, neuroplasticity, neuroprotection, and myelination, according to data from in vitro, ex vivo, and animal models.[20] This is further reinforced by the fact that vitamin D levels are linked to the levels of many neurotrophic factors, including nerve growth factors (NGFs) and those of neurotrophins, both of which are essential for the maintenance and the growth of neurons.[21]

With the advancement of research, vitamin D has been related to cognitive dysfunction, psychosis, and autism in the interchange of decreased vitamin D levels. In a study of mothers and offspring with vitamin D deficiency, listening, memory disorders, and grooming habits were found to be impaired in early childhood. In specific, vitamin D deficiency in the first trimester of pregnancy predicted worse performance in cognitive and language skills, while during the third trimester, this deficiency affected motor development.[20] According to a recent study on the effect of vitamin D supplementation in the treatment of children with autism spectrum disorders, oxidative stress and mitochondrial dysfunction are common in individuals with autism spectrum disorders, and vitamin D acts as a counter-protective mechanism by protecting the genome from oxidative stress and DNA damage and the regulation of cellular proliferation and differentiation. [22]

Choline

Chemically, choline is closely related to the B-vitamin family. Choline is a precursor that aids in the biosynthesis of a metabolite important for fetal development, especially in the brain. The synthesis of acetylcholine, a neurotransmitter fundamental for synaptogenesis and leukocyte function, also requires enough choline. The downstream metabolites betaine, dimethylglycine, and sarcosine are methyl donors for the regeneration of methionine from homocysteine.[23, 24] Choline is stored in the brain as membrane-bound phospholipids that are hydrolyzed by choline acetyltransferase to yield choline for acetylcholine synthesis, and it passes through the blood-brain barrier through facilitated diffusion regulated by the choline concentration gradient.[24]

Between the 10th week of pregnancy and two years of age, brain phospholipids are thought to increase twofold and threefold in the cortex and white matter, respectively.[23] Choline is also a critical component of membrane synthesis and methylation in fetal hippocampus neural progenitor cells (starter cells). At particular times during fetal development, these cells divide, migrate, proliferate, and undergo apoptosis.[23, 24] A recent analysis of neonatal brain metabolite concentrations using magnetic resonance imaging (MRI) scanning discovered that the advancing concentrations of choline were age-related, which are likely to reflect an increased cell membrane synthesis or turnover rate.[25]

Choline production is boosted by increased estrogen production. While there is a possible increased capacity for the body to synthesize choline during pregnancy, evidence from animal models indicated that fetal and infant demand is so high that maternal stores are exhausted during pregnancy and lactation. Low maternal choline intake has been linked to an increased risk of both neural tube defects and cleft palates during pregnancy.[26]

Docosahexaenoic acid

Long-chain polyunsaturated fatty acids (LC-PUFA), including docosahexaenoic acid (DHA) together with arachidonic acid (AA), are incorporated into membrane phospholipids and are active activators of many gene transcription factors (e.g., peroxisome proliferator activated receptors).[27] The critical role of n-3 LC-PUFA is generally contributed to incorporating DHA in uniquely high levels in the central nervous system.[28, 29] DHA accumulates in the brain throughout the intrauterine and neonatal periods, up to the age of two years, and the high levels of DHA in the brain are maintained throughout life.[27]

The rate of membrane DHA incorporation in early life is determined by maternal transfer, dietary

supply, and endogenous LC-PUFA production due to lack of *de novo* PUFA synthesis. Non-esterified PUFA derived primarily from the maternal circulation is transferred through the placenta to provide intrauterine PUFA. LC-PUFA accumulation in the fetus occurs mainly in the third trimester, starting about the 30th week of pregnancy when weight gain becomes more rapid and growth is followed by fat tissue deposition. Nonetheless, as opposed to the high relative concentrations of LC-PUFAs deposited in the brain, fetal fat tissues contain comparatively low levels of DHA and AA. The maternal transfer of PUFA by breastmilk supports the postnatal accumulation of LC-PUFA in infant tissue, and blood levels of LC-PUFA in breast-fed infants remain higher than maternal levels for some time postnatally.[27]

The formation of neurons is complete at prenatal stages, yet, gliogenesis (the development of astrocytes, oligodendrocytes, and microglial cells) is not completed until after birth. Low DHA availability can affect neurotransmitters such as acetylcholine, dopamine, serotonin, norepinephrine, glutamate, and gamma-aminobutyric acid (GABA). During synaptogenesis, DHA is incorporated into nerve growth cones and synaptosomes, implying that the mother's DHA intake must be adequate for this process to occur at optimal levels. Deficient/lower levels of long-chain omega-3s or DHA were found among children with ADHD, dyspraxia or developmental coordination disorder, autistic spectrum disorder, and mood disorder.[30]

Conclusion

Optimal brain growth and maintenance requires a prime environment, internally and externally, one of them is adequate nutrition. Timing, dose, and duration of nutrient intake are crucial, e.g., folate during the fetal period, while choline and DHA in postnatal and infantile period. Synergistic interaction between nutrients should be considered in the development of an optimal brain. Sensitive periods for action undertaken and care must be sought to avoid profound and irreversible sequelae of nutrient deficiency.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

The role of prebiotics and nutrition in early stages for brain and socio-emotional development : A literature review

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Abstract

Introduction. The first 1000 days of life is the most crucial period for physical and neuro-emotional development. Since prenatal, the organ development had started and affected by many factors. Healthy neurodevelopment is dependent on socioeconomic, interpersonal and/or family, and nutritional factors. Macro- and micro-nutrients deficiencies may disrupt neurodevelopmental process. Iron, zinc, and iodium has been proven to affect brain development intrauterine and continues after birth. Prebiotics also play a role in neurodevelopmental through brain-gut-axis, but also beneficial on overall health.

Methods. Advanced search for relevant literatures in PubMed, Cochrane, and Willey was conducted. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Conclusions. Prebiotics supplementation is beneficial in promoting gut health, thus also play a role in immune pathway and influence brain function. Many studies also shown that prebiotics might be used as additional therapy in diseases that related to gut health i.e functional gastrointestinal disorders, obesity, and allergy.

Keywords early development, brain development, nutrition, prebiotics

Introduction

The cognitive, social and emotional parts of the brain continue to develop throughout the child's life. A large part of the ultimate structure and capacity of the brain is shaped early in life, before the age of 3 years, which known as the first 1000 days of life. The first 1000 days of life is undoubtedly the most important period that marked the beginning not only physical development but also socio-emotional development as well. Among the factors that influence early brain development is the provision of optimal nutrition. Nutrition is critical in supporting healthy brain development early in life, with long-lasting, and often, irreversible effects on an individual's cognitive development and life-long mental health Apart from macro-nutrients, micro-nutrients are also essential in brain development, which often overlooked in daily consumption. Prebiotics supplementation also plays an important role in which preclinical as well as clinical research has convincingly shown that early life nutrition can shape the gut microbiota and may affect brain development.

This review summarizes current knowledge on the brain and socio-emotional development in the early stages of life, and discussed the importance of prebiotics and nutrients in critical neuro-developmental windows.

Methods

Advanced search for relevant literatures in PubMed, Cochrane Library, and Wiley Online Library was

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conducted on nutrition and prebiotic role in early brain development with time windows from 2000 to 2021. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Discussions

The first 1000 days of life development

The first 1000 days of human life started as early as in utero for approximately 270 days or 9 months and continues for another 730 days or until reaching two years of age.

Simultaneously with major body structures formation, such as spines, head, arms, and legs, human organs also began to develop since the very beginning. Digestive system, respiratory system, vascular system, urogenital system, and also nervous system begin to develop as early as the fetus reach 3 to 4 weeks old and the development continues during pregnancy, even after birth.

Brain development that occurs during the prenatal months is largely under genetic control, although clearly the environment can play a role; for example, it is well known that the lack of nutrition (e.g. folic acid) and the presence of toxins (e.g. alcohol) can both deleteriously influence the developing brain. In contrast, much of brain development that occurs postnatally is experience-dependent and defined by gene–environment interactions.[1,2]

The development of the different components of the nervous system intra-uterine can be categorized into distinct phases. These include the birth of neurons (neurogenesis), the migration of neurons to their correct location, the differentiation of neurons into different types and their subsequent maturation of connections, and the pruning back of connections and cells themselves. After birth, brain continue to grow and increase its mass during irregular periods commonly called growth spurts. This increase is most likely results from the growth of dendritic processes and myelination. Such an increase in cortical complexity would be expected to correlate with increased complexity in behavioral functions and also significant changes in cognitive development.[1,2]

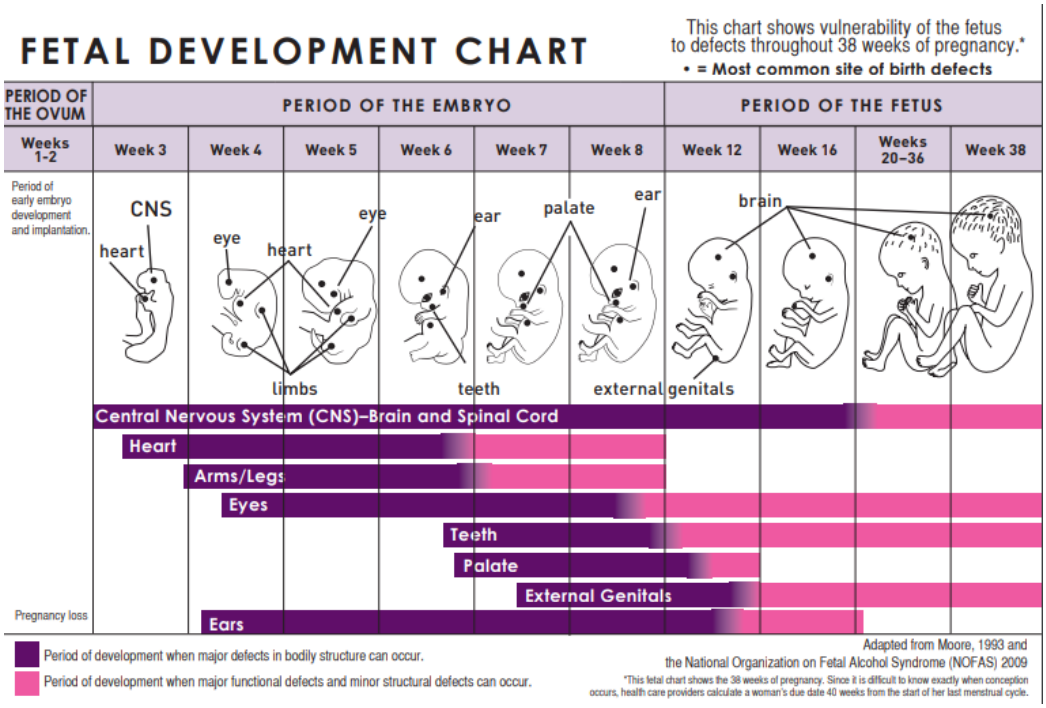


Figure 1. Fetal development chart

Brain development

The period of fetal life and the first 2 years postpartum may be seen as a time of tremendous opportunity for neurodevelopment and a time of great vulnerability. Healthy neurodevelopment is dependent on socioeconomic, interpersonal and/or family, and nutritional factors. The nutritional environment has an effect on whether brain growth and differentiation proceed normally or abnormally. Both adequate overall nutrition (ie, absence of malnutrition) and provision of adequate amounts of key macronutrients and micronutrients at critical periods in development are necessary for normal brain development. Importantly, the definition of malnutrition includes both undernutrition (provision of inadequate amounts of macro- and/or micronutrients) and also obesity (provision of excessive calories, often at the expense of other crucial nutrients). It is important to recognize that many nutrients exhibit a U-shaped risk curve, whereby inadequate or excessive amounts both place the individual at risk.[3]

Other factor that also play an important role in neurodevelopment is interaction between gut and brain, known as gut-brain axis. The brain-gut-microbiota axis is a complex interplay between the CNS, the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic arms of the autonomic nervous system, the enteric nervous system, and the microbiota. The communication throughout this axis is bidirectional, with brain signals affecting gastrointestinal tract motor, sensory and secretory functions, and simultaneous visceral signaling from the GI tract affecting brain function.[5]

Nutrition need in infants and children

A child's diet directly impacts on their growth and development, and later, also on their adult health. Achieving optimal intake will support optimal physical and socioemotional development, and prevent children from various diseases due to nutritional deficiencies. Many dietary recommendations available for children and most recommendation for those aged 2 years and older stress a diet that primarily relies on fruits and vegetables, whole grains, low-fat and nonfat dairy products, beans, fish, and lean meat. A varied and nutritious diet is recommended to assure optimal nutrition both macro and micro-nutrients.

According to Indonesian Recommended Dietary Allowance (RDA) based on age and gender, it is stated that calories needed are 550 kcal for 0–5 months of age, 800 kcal for 6-11 months of age, and 1350 kcal for age 2 to 3 years old per day. These calories estimation are based on a sedentary lifestyle thus increased physical activity will require additional calories from 10-14% per day. Indonesian RDA also continues to recommend diets low in saturated and trans fats. Daily intake should includes carbohydrate from grains, preferably whole grains; lean meat or legumes; vegetables; fruits; and dairy products or milk.

It was recommended that all infants should be breastfed exclusively for the first 6 months of life and continue until the age of 2 years. Breast milk not only meets the nutritional needs of young infants, but also confers other benefits. These include improved sensory and cognitive development, fewer infections, slower, healthier weight gain, improved maternal health, including a lower risk of breast cancer and endometriosis, greater postpartum weight loss and a lower maternal body mass index.[6,7,8]

Nutrition for brain development

All nutrients are important for brain growth and function, but certain ones have particularly significant effects during early development.

Macro-nutrients that affect early brain development are protein and long chain poly unsaturated fatty acids (LC-PUFA). Protein deficiencies manifested as growth failure, and in fetus known as intrauterine growth restriction. Preclinical models of early life malnutrition indicate that protein or protein–energy restriction results in smaller brains with reduced RNA and DNA contents, fewer neurons, simpler dendritic and synaptic head architecture, and reduced concentrations of neurotransmitters and growth factors. As for LC-PUFA, gestational and early postnatal LC-PUFA supplementation, particularly docosahexaenoic acid (DHA) and arachidonic acid,

has been associated with improved cognition and attention in some studies. Preclinical models show that docosahexaenoic acid is important for neurogenesis and neuronal migration, membrane fatty acid composition and fluidity, and synaptogenesis. On animal models, LC-PUFAs showed a profound effect on visual system and areas of the prefrontal cortex that mediate attention, inhibition, and impulsivity. Willats 2018 and Oyen et al. 2018 prove that enrichment of diet with fatty acids has a positive impact on the child's learning skills, memory, language progress and cognitive competence in general. The insufficient intake of docosahexaenoic acid reduces DHA in the brain, leading to brain damage or abnormal brain disorder.[9,10,11,12]

Many micro-nutrients affect brain development such as zinc, iron, iodine, also vitamin B12, and vitamin D. Zinc is a vital nutrient for the brain, works as co-factor for more than 200 enzymes that regulate diverse metabolic activities in the body, including protein and DNA synthesis. It also plays a role in neurogenesis, maturation and migration of neurons as well as in synapse formation. Preclinical models indicate that zinc is necessary for normal neurogenesis and migration, myelination, synaptogenesis, regulation of neurotransmitter release in gammaaminobutyric acid-ergic neuron and ERK1/2 signaling, particularly in the fetal cortex, hippocampus, cerebellum, and autonomic nervous system. Behaviorally, early life zinc deficiency results in poorer learning, attention, memory, and mood.[9,10,13,14,15]

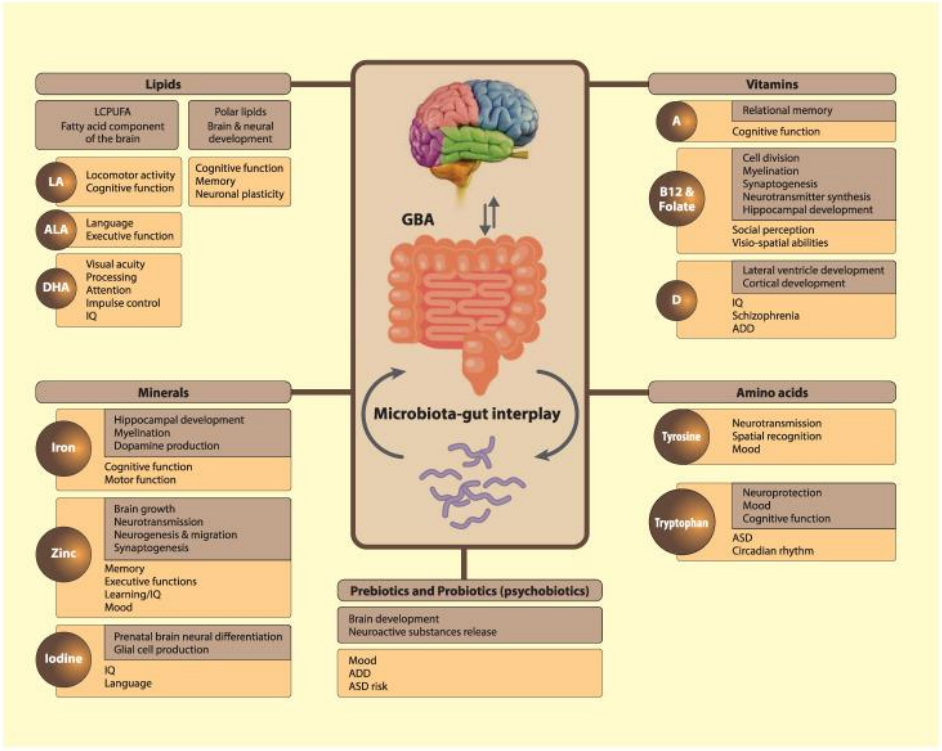
Iron is necessary for normal anatomic development of the fetal brain, myelination, and the development and function of the dopamine, serotonin, and norepinephrine systems. Iron also modifies the epigenetic landscape of the brain. Iron deficiency in early childhood is the most common micronutrient deficiency and can lead to irreversible damage to brain structure and cognitive function, regardless of therapies with iron supplements. Research has shown that iron deficiency can lead to delayed motor development, delayed cognitive processing, altered recognition, memory and executive functions and poorer emotional health later in the adult age. Positive impact of iron supplementation on cognitive function was observed in anemic primary school children.[15]

Iodine is an essential trace element for the biosynthesis of thyroid hormones. The developing fetal brain is most susceptible to iodine deficiency during the first trimester, when fetal triiodothyronine production depends entirely on supply of maternal thyroxine. Severe iodine deficiency during pregnancy is well-known to result in cretinism, marked by deficits in hearing, speech, and gait, and an IQ of approximately 30. Post-natally, iodine continues to play a role in neurocognitive development. The level of iodine in colostrum predicts the motor development capability of infants at 18 months.[15]

Vitamin B12 and vitamin D play a vital role in normal brain development and function.Vitamin B12 serves as a cofactor in numerous catalytic reactions in the human body, which are required for the neurotransmitter synthesis and functioning, and also essential in myelin production. Vitamin B12 and folate are required for cell division and generation of methionine, which is needed to produce neurotransmitters and myelin. Vitamin D deficiency in early pregnancy may correlate with delayed neurocognitive development, including language impairment, mental development and psychomotor development in early childhood. Interestingly, vitamin D also has been shown to be able to upregulate serotonin expression.[15]

Impact of prebiotic as nutrition intervention in children health

Another group of nutritional supplements that may be of interest as potential neuroprotective agents for preterm infants are prebiotics and probiotics. As the gut-brain axis concept becomes more familiar, more researches have been done and prebotics has been proven the benefit of maintaining gut health to better health and also beneficial for brain development.
The current definition of a prebiotic is the one proposed by the International Scientific Association for Probiotics and Prebiotics (ISAPP): a substrate that is selectively utilized by host micro-organisms and confers a health benefit. Prebiotics acting as a fuel source for selective fermentation by normal microorganisms in the gastrointestinal tract, which are required for protective effect against pathogens, or to improve intestinal barrier function, play a role



LCPUFA: long-chain polyunsaturated fatty acid; LA: linoleic acid; ALA: alpha-linolenic acid; DHA: docosahexanoic acid; IQ: intelligence quotient; ASD: autism spectrum disorder; ADD: attention deficit disorder; GBA: Gut-Brain Axis

Figure 2. Function of nutrients and prebiotics in brain development

in immune pathways and also influence brain function.[16,17]

These substance, which able to influence gastrointestinal health, comprise certain non-digestible oligosaccharides (NDOs), soluble fermentable fibres, and human milk oligosaccharides (HMOs). Human milk oligosaccharides are fraction of carbohydrate from human milk and they have been shown to selectively stimulate the growth of bifidobacteria and lactobacilli in the intestines. It is known that bovine milk is almost completely devoid of milk oligosaccharides, but recent biotechnical advances have made it possible to produce some synthetic milk oligosaccharides in large quantities. These advances enable supplementation of infant milk formula with the goal of promoting gut microbiota composition and function that is similar to that of a breast-fed infant. Preparations like galactooligosaccharides (GOS), fructooligosaccharides (FOS), 2'-fucosyllactose, lacto-N-neo-tetraose, inulin, oligofructose and galactofructose are examples of commonly used and studied products. These non-digestible oligosaccharides are widely used as additional supplementation because they provides the opportunity to improve the gut microbial ecosystem, including bacterial populations, biochemical profiles, and physiological effects. Prebiotic oligosaccharides have the potential to improve the infant's intestinal microbiota by promoting growth of Bifidobacteria, which may in turn reduce the burden of potentially pathogenic micro-organisms in the gut.[17,18]

Prebiotics also studied for their effect on neurodevelopmental. Gut microbiota affects the brain through three routes, including neural, endocrine, and immune pathways. The products of prebiotics fermentation can affect the brain by the vagus nerve. Some prebiotics, such as FOS and GOS, have regulatory effects on brain-derived neurotrophic factors, neurotransmitters (e.g., d-

serine), and synaptic proteins. Prebiotics also act as regulator for hormones such as corticosterone and adrenocorticotropic hormone, which in turn may affect mood and stress level. Schmidt et al. tested the intake of fructo-oligosaccharides (FOS) and Bimuno®-galactooligosaccharides (B-GOS), and reported that only B-GOS reduced the waking-cortisol response. Exaggerated waking cortisol is a biomarker of emotional disturbances, such as depression. Other studies on autisms shows that various prebiotics may have therapeutic effects on patients with autism by decreasing the population of Clostridium perfringens and increasing the rate of Bifidobacteria.[19,20,21]

An imbalance and/or reduced microbial diversity has been associated with a wide variety of functional gastrointestinal disease in children such as colic, irritable bowel syndrome (IBS), constipation and diarrhea, but also with other diseases such as allergy. In addition, many diseases later in life seem to be associated with the gut microbiota early in life, for example, inflammatory bowel disease, celiac disease, obesity, and allergic reactions. Prebiotics also shown to be beneficial as additional treatment in these diseases.[22]

Conclusion

Macro-nutrients such as protein and LC-PUFA and micro-nutrients supplementation such as iron, zinc, and iodium has been proven beneficial not only for health in general but for brain development as well. Prebiotics and probiotics supplementation also shown beneficial effect on health. Prebiotics safety profile and convinience in production and formulation process make it more favorable to be added in diets than probiotics. There are many studies on the positive effects of prebiotics on human health; however, accurately designed long-term clinical trials and genomics investigations are needed to confirm the health claims especially to determine whether prebiotics exert a beneficial effect on neurodevelopmental disorders in infants, and to understand the mechanism of action.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Indonesian health care practitioner's perception on gut-brain-axis and social-emotional concept

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Abstract

Background The microbiome-gut-brain-axis (GBA) concept has long been appreciated. It is recognized that the microbes resident in the gastrointestinal tract can influence brain physiology and the social-development competencies, and vice versa. Therefore, it is crucial for health care practitioners (HCPs) to understand this concept, especially in children; however, no study has been reported.

Methods: This study used qualitative methods to explore HCPs' perception and awareness about the microbiome-GBA concept. Data were collected through in-depth interviews using online video calls with HCPs, including general practitioners, pediatricians, and midwives.

Results: We found that responders are aware of the microbiome-GBA concept, as this issue is often discussed in seminars and other events. They realized that gut health is a significant concern, and it is significantly impacting brain health and leads to social and emotional development (SED). This process starts from the early stages of life.

Conclusion: The HCPs in our study have a good perception of the microbiome-GBA concept, e.g., a healthy brain is not possible without a healthy gut. As far as we are concerned, this is the first study to investigate the knowledge of HCPs about bidirectional communication of microbiome-GBA as an essential factor in child management.

Keywords gut microbiota, gut-brain axis, HCP perception, social-emotional

Introduction

Growth and development are central characteristics of childhood with a complex interaction of closely regulated genetic, hormonal, and environmental factors that prepares an organism for survival. [1,2] Up- and downward growth deviations from normal patterns may reflect serious disorders, such as endocrine conditions, infectious or inflammatory diseases, and psychosocial deprivation.[2] Exposures to putative pathogens at an early stage of physical, immunologic, and cognitive development may adversely disrupt a child's potential development trajectory, resulting in long-lasting consequences.[3]

The causes of poor growth and development in early childhood are complex, including a lack of adequate amount or quality of food, early termination of breastfeeding, the inadequate response of the host and the host's gut microbial to caloric insufficiency, and a configuration of the microbiota that is suboptimal for nutrient harvest.[3] It is now widely recognized that early growth and tissue development during the first 1,000 days of human life and beyond are significant predictors of long-term health and performance up to adulthood and old age.[2]

Fetal growth is influenced by maternal, placental, and genetic factors. Poor intrauterine growth is associated with developmental delays and increased risk for different mental health problems.

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Experiences that occur during the first years of life will permanently modify brain structure and function and consequently affect the susceptibility to mental disorders.[4]

Peripartum adverse events are also considerably known to affect neurodevelopmental outcomes.[4] Early microbial colonization triggers processes that result in intestinal maturation and immune priming. Mode and place of delivery are critical to shaping the infant gut microbiota with potential health consequences. The results highlight both the importance of host-microbial contact during the first month of life and the dynamism of the process.[5]

In recent years, we have seen the emergence of microbiota as one of the critical regulators of gut-brain function and has led to a distinct microbiota-gut-brain axis.[6,7] Bidirectional communication between the gut microbiome and the brain can occur across physiological channels, including neuroendocrine and neuroimmune pathways and the autonomic nervous system, and bacteria within the gut can produce neurotransmitters that can also be found within the central nervous system (8-10). For example, evidence suggests that a strain of Lactobacillus brevis can produce GABA. Monoamines play a crucial role in brain-gut-microbiome axis signaling; serotonin, a key target in treating major depression.[9]

Strikingly, initial evidence suggests that the diversity of the gut microbiota may also be related to brain structure. Emerging research suggests that gut microbiota has impacts on social behavior. Evidence of altered social behavior in germ-free animals is complemented by evidence indicating that children with autistic spectrum disorder have a gut microbial profile that differs from controls. The immune pathway within the brain-gut-microbiome axis may be a plausible mediator of the effects of this axis on social behavior, as cytokine-induced sickness behavior is associated with social withdrawal.[9]

Determining the dynamics of the behavior-gut associations in early life is important because many physical and mental health conditions have early life antecedents. The gut microbiome may be more malleable in early life. However, by approximately two years of age, gut microbiota profiles resemble profiles found in adults, which are relatively stable.[11] Early stress in life can also have long-term effects on gut microbiota composition.[8] Thus, assessing the gut microbiome as early as two years of age may provide insight into long-term functioning.[11]

Based on those explanations above, we believe it is crucial for health care practitioners (HCP) to have a proper and in-depth understanding of GBA and SED in early childhood. Surprisingly, as far as we know, no study has been done to investigate this issue yet. Pediatricians, general practitioners, and midwives are front-line HCPs who face infants or toddlers daily. Therefore, it is very important to explore the HCPs' (pediatricians, GPs, and midwives') perception and awareness of the GBA and its relationship with the SED concept among infants or toddlers.

Methods

Study design

As the study focused on investigating perception and awareness, a qualitative design was chosen; this suited the study's exploratory nature and provided the best fit for the research questions.[12] This qualitative study used in-depth interview via online video call with HCPs. Data were collected on January 2021.

Sample and recruitment

Health care practitioners in this study include pediatricians, GPs, and midwives. Their age is between 35 – 60 years old, with experience duration more than six years in their specialization, and either working in a public or private hospital. Randomization of the subject study was based on the year experience, affiliation, and the number of patients. No specific qualification to justify the number per HCP. 12 HCPs were interviewed, consisting of 2 pediatricians, 6 GPs, and 4 midwives; 8 women and 4 males.

Procedure

Expert interviewers ran interviews via online video calls. Subjects were invited to share their perception of GBA and SED concepts in infants or toddlers. All interviews were recorded. Consent was obtained in

writing before the interview, while verbal consent to record the discussion was obtained prior to each session.

Data analysis

All data obtained from in-depth interviews were recorded. A qualitative approach was used to improve the understanding of HCPs' views and perceptions regarding GBA and SED concepts in infants or toddlers.

Results

Overall understanding about GBA and SED concepts among HCPs

The gut-brain axis and its relation with social-emotional development in early life are well known among the HCPs recruited in this study. They said that this issue was often introduced and discussed with them through seminars or other events.

The importance of the GBA and SED concepts

According to the HCPs interviewed, the knowledge about GBA and SED concepts in infants or toddlers is a significant concern. They stated that gut challenges are the main challenges faced in infants' early months. They often face problems such as diarrhea, indigestion, allergies, and others. Therefore, HCPs need to understand these concepts to relate them with daily practices and give appropriate management to patients.

The knowledge of GBA and SED concept among HCPs

Next, we asked the HCPs how far their knowledge about this concept is. They agreed that the idea of GBA is very relevant to their daily practices. They have successfully established the need for gut health in the early stages. Gut health significantly impacts brain health; if the gut is not healthy, nutrients are not well absorbed and will adversely affect brain growth and development. In other words, brain health is not possible without a healthy gut. Furthermore, the HCPs also realized that there is no good SED without physical growth and development of the brain.

What can be improved from the concept according to HCPs

Finally, we asked the HCPs for their suggestions on what can be improved from the concept. The knowledge about GBA and SED itself is not compellingly new. Therefore, they suggested reinforcing the benefit of gut and brain health in the early stages of a child`s life as a reminder to HCPs. Furthermore, it is better to reiterate the examples of contents that have been reported to have a good impact on the concept, such as omega, amino acid, docosahexaenoic acid (DHA) in the right proportions for brain health, and fructooligosaccharides (FOS), galactooligosaccharides (GOS), also prebiotics for gut health. These contents can be found easily in various baby milk or food.

Discussion

This study is the first known to the authors to investigate the perception of HCPs (pediatricians, general practitioners, and midwives) about the strong relationship between healthy gut to support brain and social-emotional. We use qualitative study using in-depth interviews because qualitative methods can help bridge the gap between scientific evidence and clinical practice.[13]

Interestingly, the HCPs involved in this study are well-known with the concept of GBA and its correlation with SED development which starts in early life. They are also aware of the bidirectional communication between gut and brain; gut health is one of the foundations of brain and social-emotional development. The responders have plenty of exposure to this topic. By knowing this important concept, it is expected that the treatment and management of either gastrointestinal (GI) or social-emotional diseases will have better results. It has been proposed that a multidisciplinary treatment approach between biological and psychological processes is most likely to be effective and well-received.[14]

We think the next important task for HCPs is to communicate this message to patients or parents in

practice. Indeed, it has been reported that children whose parents accept a biopsychosocial conceptualization of gastrointestinal problems and their treatment are more likely to experience symptom improvement. Moreover, based on the biopsychosocial model, patients with GI disorders and their families will be equipped with the foundation necessary for reducing symptoms by impacting the brain-gut axis through behavioral strategies.[14]

Next, our responders suggested that the HCPs should be often reminded of this concept for reiterating purposes. Indeed, there are significant associations between physician knowledge and practice outcomes. For example, the knowledge-based certification internists and cardiologists have 19% lower mortality rates of their patients following an acute myocardial infarction.[15] An educational follow-up experiment with knowledge retention measured at assigned time intervals (0–55 days) after an online tutorial showed that mean knowledge scores increased from 50% before the tutorial to 76% among those tested immediately afterward. Score gains were half at 3–8 days, and no significant retention was measurable at 55 days. To achieve longer-term retention, physicians should review or otherwise reinforce new learning after as little as one week.[16] A study was conducted to evaluate the knowledge retention among midwives in Indonesia after providing digestive health (e.g., gut health is an important issue in which there is a role of nutrition to gut health and brain axis), nutrition, and parenting education sessions. At baseline, less than 50% of the subjects had sufficient knowledge of the issues. There were significant improvements in the proportion of adequate knowledge immediately after and after three months, which declined after three months compared to the immediate group.[17] Thus there is a need to do regular and periodic refreshments, especially to topics that are not applied regularly, to retain the knowledge.

Another exciting issue mentioned by the responders is the knowledge of omega, amino acid, docosahexaenoic acid (DHA) in the right proportions for brain health, and FOS, GOS, also prebiotic for gut health. Indeed, there is quite a lot of information about the "good" nutrients for brain or gut health commercially available. Studies have found that prebiotics, such as omega-3 fatty acids and oligosaccharides, change the gut microbiota, improving the GBA function and symptoms of mental illness subjects.[18] Research in humans indicates that DHA, eicosapentaenoic acid, and total omega-3 polyunsaturated fatty acids are lower in people with major depression than controls.[9] Nonetheless, prebiotic supplementation has been demonstrated to reduce stress responsiveness, anxiety, and depressive-like behavior. One of the main classes of prebiotics is dietary fiber, including inulin, FOS, GOS, and resistant starch. Administration of FOS+GOS and GOS has been shown to increase *Bifidobacterium* and reduce stress-induced corticosterone release.[6]

We have shown for the first time that the concept of microbiome-GBA is well-known among HCPs. They realize the importance of this concept in the early stages of life since they face lots of gut challenges in their daily practices, and also many mothers are seeking brain health benefits. Specific knowledge should also be considered to improve and strengthen the HCPs' understanding of the particular role of prebiotic and probiotic in a child's growth and development.[19,20] The bidirectional communication between brain and gut is crucial, so it is also important to constantly remind the HCPs about this for a better social-developmental of children.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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