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Role of Gut-Brain Axis in the Aetiology of Neurodevelopmental Disorders with Reference to Autism

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Abstract

Neurodevelopmental disorders, especially in children, result in brain and nervous system damage. These may result from environmental contaminants, intrauterine environment, infectious diseases or exposure to nanoparticles that cross the blood brain barrier. Gut microbiota directly influence the immune system, nervous system and brain development during microbial colonisation of the newborn (microbiota gut-brain axis) and are controlled and modulated by different endogenous and exogenous factors. Of these factors feeding with human milk creates a healthy microbiota in the infant gut and reduces incidence and severity of infections and promotes normal gastrointestinal function. In addition there is a direct correlation between maternal vaginal and intestinal bacteria, gut microbiota composition, and increased rates of obesity, metabolic and neuropathological disorders such as autism. Gut-brain factors secondary to alterations in gut microbiome by antibiotics or diet may influence brain function in patients with Autism Spectral Disorders (ASD). Children with ASD ingest food products that provide high carbohydrates for bacterial fermentation to produce propionic acid through the bacterial strain Clostridium difficile, which is associated with diarrhoea. Treatment strategies to reduce Clostridium difficile include probiotics, prebiotics, faecal transplantation and hyperbaric oxygen therapy. Studies of microbiota-gut-brain axis could provide a deeper understanding of the relationship between the intestinal bacteria and their hosts which could help to suggest potential therapeutic strategies through affecting the composition of gut microbiota.

Introduction

It is quite known that defects in brain function especially in children usually may result in neuro-developmental disorders such as intellectual disability, Attention-Deficit/Hyperactivity Disorder (ADHD), autism, and learning disabilities which is reflected in disabilities to communicate, move or behave. These symptoms usually change with age, although some children may develop permanent disabilities. Diagnosis and treatment of neurodevelopmental disorders often involves a combination of professional therapy, pharmaceuticals, and home- and school-based programs, though, achievement of successful results is difficult [1].

It was previously reported that the child's developing brain and nervous system are susceptible to damage as a result of exposure to environmental pollutants such as lead [2-4], methyl mercury [5] and Polychlorinated Biphenyls (PCBs) [6]. These developmental disorders include reduced cognitive development, lowered intelligence and behavioural deficits and brain trauma. The latter occurs in over 400,000 injuries per year in the US alone, without clarifying the number that may further produce developmental sequellae. It may be subdivided into two major categories, first, injury occurring in infancy or childhood and second, congenital injury (uncomplicated premature birth) resulting from asphyxia (obstruction of the trachea), hypoxia (lack of oxygen to the brain) or the mechanical trauma of the birth process itself [7].

It should be pointed out that fetal development is affected by the intrauterine environment and any disruptions in the latter may eventually lead to various learning, behavioural, and neurological disorders in childhood, as well as complex diseases such as obesity, stress and cardiovascular problems later in life [8], in addition to certain infectious diseases such as schizophrenia [9], or congenital toxoplasmosis. This latter parasite may result in formation of cysts in the brain and other organs, and even though there is a marked maternal IgG immune response, the parasite was found to continue proliferation in the brain [10]. Other diseases include congenital syphilis and measles which may progress to neurosyphilis and subacute sclerosing panencephalitis respectively in addition to multiple other symptoms.

Furthermore, since the placenta is at a literal interface between maternal and fetal cells, maternal and fetal cells reside in the placenta and also maternal or intrauterine environment are necessarily conveyed to the developing embryo via the placenta. Consequently, the placenta is likely to play a critical role in modulating immune protection and the availability of nutrients and endocrine factors to the offspring. However, factors as autoimmunity, growth restriction and hypoxia implicate the role of the placenta and its involvement in development of neurological complications [11]. In this concern, early prenatal insults are usually involved in the occurrence of neuro-developmental disorders such as schizophrenia, autism and cerebral palsy.

Most recently, exposure to nanoparticles have been shown to accumulate in organs, cross the Blood-Brain Barrier (BBB) and placenta, and have the potential to elicit Developmental Neurotoxicity (DNT).

Another factor that contributes to brain development and behaviour, and also influences the nervous system, is the gut microbiota especially during microbial colonisation of the new born. Studies of microbiota-gut-brain axis could provide a deeper understanding of the

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relationship between the intestinal bacteria and their hosts which could help to suggest potential therapeutic strategies through affecting the composition of gut microbiota.

This information initiate our interest to review all studies related to the role of gut microbiota, gut-brain axis and microbiome-host interaction in the aetiology of different neurodevelopmental disorders with special reference to autism. Understanding these aspects could help in early diagnosis, treatment or prevention of neurodevelopmental disorders.

Gut Microbiota

Normal gut microbiota

Bacterial species diversity in the gut largely derives from colonic transit time and the availability of different carbon substrates and energy sources which is the reason for the marked differences in species-level diversity found between individuals. However, the core members of microbiota are presented by, *Ruminococcus, Eubacterium* and *Dorea* (phylum Firmicutes); *Bacteroides* and *Alistipes* (phylum Bacteroidetes); and *Bifidobacterium* (phylum Actinobacteria) [12]. The composition and metabolic activities of majority of these members of gut microbiota depend on carbohydrate availability as the main nutritional factor and thus utilize saccharolytic metabolisms as the predominant pathway [13,14]. Most (95%) of the Firmicutes sequences examined by were members of the Clostridia class, which contains a substantial number of butyrate- producing bacteria that compose the clostridial clusters IV, XIVa and XVI [15]. *Roseburia intestinalis* and *Eubacterium rectale* have been reported to play dominant roles in butyrate synthesis, which is essential for the maintenance and protection of the normal colonic epithelium, whereas another butyrate producer, *Faecalibacterium prausnitzii*, is only weakly correlated with fecal butyrate concentrations [16]. On the other hand and differently, *Bifidobacterium* has been reported to produce lactate and acetate whereas *R. bromii* produces acetate, ethanol and hydrogen [17]. Schwiertz et al. [18] analyzed the fecal Short Chain Fatty Acid (SCFA) concentrations of lean and obese individuals and reported a 20% higher level of SCFAs in obese individuals, with the largest increase in propionate (41%), followed by butyrate (29%).

Moreover, Zhang et al. [19] hypothesized that in the gastrointestinal tracts of obese individuals, the coexistence of hydrogen-producing bacteria with relatively high numbers of hydrogen-utilizing methanogenic archaea could lead to an interspecies hydrogen transfer between bacterial and archaeal species. This may force the large intestine to an increase in the energy uptake in these individuals. It should be noted, however, that the "energy harvest" hypothesis suggests a protective effect of high intakes of dietary fibres (the main source of SCFAs) for enhancing weight loss or maintenance of a healthier body and thus reduces obesity.

At-birth gut microbiota

Microbial colonization commences immediately after birth, and all infants are initially colonized by *Escherichia coli* and streptococci. The anaerobic genera *Bacteroides, Bifidobacterium* and *Clostridium* are established by the end of the first week of life. During the first months and years of life the neonatal gastrointestinal tract is colonized with an adult-type pattern of indigenous gut microflora finally comprising approximately 10^{14} microorganisms, that is 10 times more than the number of eukaryotic cells in the adult body [20]. The development of the neonates gut microbiota is also controlled and modulated by different interacting mechanisms such as, genetic endowment, intrinsic biological regulatory functions, environment influences and last but not least, the diet influence. Considered together with other endogenous and exogenous factors the type of feeding may interfere greatly in the regulation of the intestinal microbiota. The bacterial microbiota differs among formula-fed and breast-fed infants. In the former *Atopobium spp.* was found in significant counts and the numbers of *Bifidobacterium* dropped followed by increasing numbers in *Bacteroides* population. Moreover, under formula feeding the infants microbiota was more diverse [21]. Breast-fed infants harbour a fecal microbiota by more than two times increase in numbers of *Bifidobacterium* cells and also lacobacilli when compared to formula-fed infants [22]. The gut microbiota including *Bifidobacteria* constantly helps in successful maturation of the gut mucosal adaptive immune system [23-25].

It was previously reported that the mode of delivery strongly influences microbial colonization of infants including the gut [26]. Vaginally delivered infants acquire bacterial communities resembling mother's vaginal microbiota dominated by *Lactobacillus*, *Prevotella*, or *Sneathia spp*., while caesarean delivery (C-section) infants harbor bacterial communities similar to those found on skin, dominated by *Staph, Corynebacteria*, and *Proprionibacterium spp*. In addition, the mode of delivery may have, possibly via gut microbiota development, significant effects on immunological functions in the infant since the total number of immunoglobulins IgA-, IgG- and IgM-secreting cells was found to be lower in infants born by vaginal delivery than in those born by C-section, possibly reflecting excessive antigen exposure across the vulnerable gut barrier. Also autism risk is influenced by the mode of delivery; a previous study has shown that C-section may double the risk of autism [27].

Furthermore, the size of healthy neonates vaginally born at term greatly affects the composition of gut microbiota and in turn the development of the immune system. The prevalence of Gram-negative Proteobacteria was higher in neonates born with Large Gestational Age (LGA), whereas Gram-positive Firmicutes was more prevalent in neonates born with appropriate gestational age (AGA). For this reason, appropriate care with pregnant woman and newborns should be considered as a preventive strategy of children diseases [28].

Functions of human milk bacteria in the infant gut: Human milk bacteria play a vital role in reducing incidence of infection breast-fed infants. This may occur by different mechanisms such as improvement of the intestinal barrier function by increasing mucine production and reducing intestinal permeability, competitive exclusion [29], or production of antimicrobial compounds [30-32].The role of different bacterial strains in milk was previously reported. In this connection, administration of a human milk Lactobacillus strain to infants during 6 months led to 46%, 27%, and 30% reductions in the incidence rates of gastrointestinal infections, upper respiratory tract infections, and total number of infections, respectively [33]. Hospital environment resulting in undesired pathogens to infants or oral colonization by methicillin-resistant *S. aureus* in high-risk newborns may be inhibited by commensal coagulase-negative staphylococci and viridans streptococci provided by breast milk [34]. In fact, some *Staphylococcus epidermidis* strains that play such role have been postulated as a future strategy to eradicate such pathogens from the mucosal surfaces [35,36]. Breast milk bacteria may also participate in the correct maturation of the infant immune system since it was previously reportd that some strains are able to modulate both natural and acquired immune responses in mice and humans with flexibility depending on the conditions found in the gut environment [37-39]. As an example, *Lactobacillus salivarius* CECT 5713 and *Lactobacillus fermentum* CECT 5716 enhanced macrophage production of Th1 cytokines, such as IL-2 and IL-12 and

the inflammatory mediator TNF- α, in the absence of an inflammatory stimulus.

The glycobiome of some lactobacilli and bifidobacteria, including those of species isolated from human milk, may help to achieve a specific "healthy" microbiota in the infant gut [40,41]. These microorganisms are metabolically active in the infant gut by increasing the production of functional metabolites such as butyrate, which is the main energy source for colonocytes and a relevant compound in the modulation of intestinal function through the breakdown of sugars and proteins [42,43].Taking in account that transit of food through the gastrointestinal tract is shorter in infants than in adults and, that the pH of the infant's stomach is higher than that of the adult, human milk lactobacilli strains may improve the intestinal habit, with an increase in fecal moisture, and in stool frequency and volume.

Development of the Microbiome

Diversity in the Gastrointestinal (GI) bacterial strains increases rapidly over the first few years of life [44,45]. The relatively few species GI strains that are first detected in infants, acquired from the mothers' vagina and skin, are replaced by other strains of less certain origin [46-48]. However, the reason for this diversity is unknown: it is possible that new bacteria are incorporated at a constant rate as they are experienced in the environment, or that growing a larger gastrointestinal tract provide more distinct niches for bacteria, or a larger habitat for them to live in. Another alternative is that increasing functional complexity produces taxonomic complexity, until states of equilibrium are reached. Even though, it was found that within a single baby, the consortia of bacterial taxa is not random, at any given time point, indicating that the microbes depend on each other within the consortium. Therefore, during infancy groups of microbes rapidly colonize and may change in response to events such as illness [45]. This pattern of microbial diversity provides an efficient means for adaptation to the changing circumstances of development over an individual's lifetime such as changes in lifestyle, illness, puberty, and others. Interestingly, human family members tend to have more similar microbiota.

Due to the function of gut flora in promoting normal gastrointestinal function, protecting from infection, regulating metabolism and comprising more than 75% of our immune system, so, dysregulated gut flora has been linked to diseases ranging from autism and depression to autoimmune conditions like Hashimoto's, inflammatory bowel disease and type 1 diabetes. This probably explains why babies born via caesarean sections may have increased susceptibility to gut infections, asthma and allergies later in life [49].

Factors affecting gut microbiota during development

The diversity in microbiota among children was shown in a recent study which compared the fecal microbiota of European children (EU) with that of African children from Burkina Faso (BF) in Central Africa. The results revealed significant differences in both biodiversity and richness of microbiota to the favour of BF children ($P<0.01$) [50]. African children fed on high carbohydrates and low protein diet, showed significantly higher levels of SCFAs ($P < 0.001$) and a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0.001$), with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter* which were completely lacking in the EU children while *Enterobacteriaceae* (Shigella and Escherichia) were significantly lacking in African compared to EU children ($P<0.05$) [50]. Of somewhat greater surprise was the observation, that Gram-negative bacteria (mainly Bacteroidetes) were more abundant (58.5%) than Gram-positive bacteria (37.4%) in the BF population, whereas Gram-positive (mainly Firmicutes) were more abundant than Gram-negative bacteria (70.4% vs 29.1% respectively) in the EU population, resulting in a Gram-positive to Gram negative ratio of 37 to 59 in the BF population compared to 70 to 29 in the EU population [50]. These observations regarding the effect of diet on gut microbiota was supported by Wu et al. [51] who investigated the association between dietary variables and gut microbiota in 98 individuals and demonstrated a strong correlation between long-term diet and enterotype. The Bacteroides enterotype was highly associated with the intake of animal protein and saturated fats, suggesting that meat consumption, as typified by a Western diet, characterize this enterotype. This could help to suggest that early dietary and gut microbiological environments have a more complex effect on the metabolic programming of a child than previously anticipated.

It was documented that obesity is greatly contributed the shift of children gut microbiota towards pathogenic composition. In a recent study done by Karlsson et al. [52], twenty 4–5 year old overweight or obese children were compared to twenty children of the same age but with normal body mass index. The burden of the Gram-negative family Enterobacteriaceae was significantly higher in the obese/overweight children and the levels of *Desulfovibrio* and *Akkermansia muciniphila*-like bacteria were significantly lower in the obese/overweight children. No significant differences were found in content of Lactobacillus, Bifidobacterium or the *Bacteroides fragilis* group. It was also observed that the diversity of the dominating bacterial community tended to be less diverse in the obese/overweight group, although the difference was not statistically significant.

A previous study has shown for the first time in human that differences in the gut microbiota may precede overweight development [53]. It was shown that *Bifidobacterium spp*. number was higher in children who exhibited a normal-weight at seven years than in children developing overweight. More importantly they observed that the *Staphylococcus aureus* counting was lower in children who maintain a normal-weight than in children becoming overweight several years later. This could provide evidence that the gut microbiota composition in children could be associated with weight gain and point out the putative role of the Bifidobacteria and Staphylococcus in that context. This is consistent with the recent finding of Barros et al. [54] showing 58% higher prevalence of obesity in young adult Brazilians born by CS than in young adults born vaginally. Because CS-born individuals do not make contact at birth with maternal vaginal and intestinal bacteria, this could lead to long-term changes in the gut microbiota that could contribute to obesity. The size of an infant at birth, a measure of gestational growth, has been recognized for many years as a biomarker of future risk of morbidity. Both being born Small for Gestational Age (SGA) and being born Large for Gestational Age (LGA), are associated with increased rates of obesity and metabolic disorder, as well as a number of mental disorders including attention deficit/hyperactivity disorder, autism, anxiety, and depression [55].This could be related to the transfer of altered microbiota from pregnant mothers to infants which lead to an increased risk of abnormal gestational weight [56], and thus the composition and development of infant gut microbiota are influenced by Body Mass Index (BMI), weight, and weight gain of mothers during pregnancy.

It could be suggested that a balance between microbial groups present in the human gut is crucial for maintaining health. When this balance is disturbed, the host microbe relationship can progress toward a disease state. Altered intestinal colonization by commensal microorganisms as well as high inter-individual variability and reduced microbial diversity has been reported in preterm infants increasing the risk to develop later disease [57,58].

Gut –brain axis and aetiology of neuro-developmental disorders

It is well known that gut microbiota can affect the development [59] and function [60] of the central nervous system, thereby, leading to the recent interesting concept of the microbiota gut–brain axis [61] (Figure 1).

Many studies using animal models of different behavioural disorders such as autism, anxiety, cognitive disability and depression proved that microbiota composition greatly influences brain function. Neuroactive compounds in the intestinal lumen can cross the blood-brain barrier and induce many cognitive and behavioural disturbances [62].

The composition of the intestinal microbiota is extremely relevant in neurogastroenterology, as a science deals with the gut–brain axis interactions. Several neuropathological diseases are thought to be associated with the gut microbiota. Autism as a neurodevelopmental disorder often involves GI symptoms. Recent studies related to faecal microbial profiles of autistic patients, indicated 10-fold higher counts of Clostridium spp. compared with healthy controls [63]. Clostridium is known to produce neurotoxins, which could contribute to the development of autistic behaviours. Higher urinary levels of hippurate, phenylacetylglutamine and tryptophan/nicotinic acid metabolism have been reported in autistic children as an aspect of metabolic alteration in gut host–microbial co-metabolism [64,65].

Although many studies have demonstrated altered gut microbiota composition in children with autism compared with control healthy subjects [66-70], such data should be interpreted with care, as autistic patients have a higher incidence of antibiotic usage and often have different diets compared with neurotypical individuals, both of which can alter the composition of the gut microbiota. Interestingly, a recent study also highlights alterations in the faecal concentrations of the short-chain fatty acids in children with autism [71] suggesting that production of such neuroactive microbial metabolites could be related to the mechanism by which bacteria may alter brain function.

Recently, intracerebroventricular or oral administration of neurotoxic doses of Propionic Acid (PPA) to animals was effective in inducing autistic features [72,73]. It is currently unclear whether the doses of propionic acid used in animal studies reflect the potential alterations in short-chain fatty acids observed in autistic individuals [74].

Interestingly, there has been some transient success in using the antibiotic vancomycin in treating some of the symptoms of autism [75]. Although such studies are effective, it needs replication in a greater numbers of patients and controlled clinical trials using more sophisticated bacterial analyses are recommended to assess whether autism is associated with alterations in the gut microbiota and whether such alterations play a part in the gastrointestinal, behavioural and cognitive symptoms seen in autistic children.

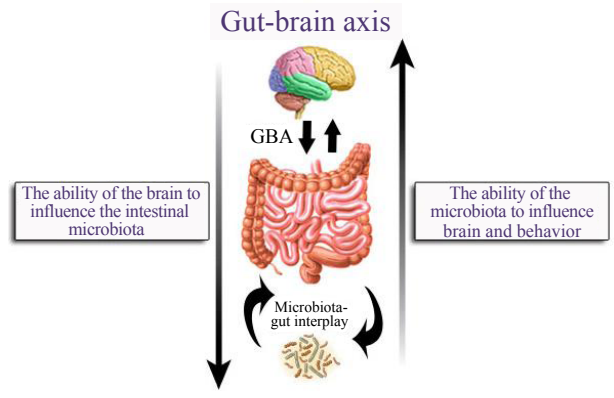

Figure 1: Interaction between gut-brain axis.

Recently, there is a growing interest suggesting that dietary factors might worsen and, in some cases, improve the symptoms of autism. It is well known that SCFAs, such as PPA, are produced by many intestinal bacteria through the breakdown of dietary carbohydrates and amino acids [76]. Special attention is given to Clostridia species as the most infectious causes of ASDs [77]. Clostridial species, as anaerobic, gram-positive and PPA producers [78], are major bacteria that colonize the gut in early life. It is well documented that spore-forming anaerobes and microerophilic bacteria, particularly from Clostridial species, are elevated in patients with autism [79].

Additionally, species of *Desulfovibrio*, a gram-negative, non-spore former were recently isolated from the stool of patients with autism, and, to a lesser extent, non-affected siblings. *Desulfovibrio*, in addition to PPA production, is resistant to most common antibiotics and produces the gasotransmitter and potential mitochondrial toxin, hydrogen sulfide. Eradication of these organisms with oritavancin and aztreonam was recently suggested as a possible treatment of ASDs.

Furthermore, ASDs often show comorbidity with a variety of gastrointestinal disorders, such as alterations in gut motility, leaky gut, bacterial dysbiosis, impaired carbohydrate digestion/ absorption, reflux esophagitis [80,81,66]. An association between long-term antibiotic use, hospitalization, abdominal discomfort and the onset of ASD symptoms after normal or near-normal development has also been reported [82-84]. These findings raise the possibility that gut-born factors secondary to alteration of the gut microbiome by antibiotics or diet may affect brain function in patients with autism. Moreover, a compromised gut-blood barrier in case of acquired colitis or impaired colonocyte energy metabolism [85], which use SCFAs as an energy substrate may contribute for greater systemic and brain access for PPA. PPA is also known to have a number of direct effects on gut physiology. As reviewed by MacFabe et al. [80], PPA increases the contraction of colonic smooth muscle, dilates colonic arteries, and increases serotonin release from gut chromaffin cells, and decrease gastric motility, which could be easily related to the gastrointestinal abnormalities frequently observed in many autistic patients. This could explain the observations of some parents of autism that gastrointestinal and behavioural symptoms increase when their children fed high carbohydrate diet or any food that contain PPA as preservative or eradication of PPA-producing bacteria using broad spectrum antibiotics [84,86].

In a recent study done by El-Ansary et al. [73], orally administered PPA was highly potent to induce oxidative stress (lipid peroxidation), coupled with a decrease in Glutathione (GSH) and Glutathione Peroxidase (GPX) and catalase activities. Impaired energy metabolism was also ascertained through the decrease of lactate dehydrogenase and activation of Creatine Kinase (CK). Elevated IL-6, TNFα, IFNγ and heat shock protein 70 (HSP70) confirmed the neuroinflammatory effect of PPA. Moreover, elevation of caspase3 and DNA fragmentation proved the pro-apoptotic and neurotoxic effect of PPA to rat pups received 250mg/kg body weight for 3 days. Their study proved the involvement of PPA in inducing persistent autistic features in rat pups. In fact, El-Ansary et al. [74] previously provided plausible links that related the occurrence of lower PPA in the plasma of autistic patients to elevated

levels of PA in their brain. They attributed the remarkably lower plasma PPA in autistic patients to the high rate of blood to brain influx. In fact, and compared to other fatty acids, PPA was previously reported to cross the Blood Brain Barrier (BBB) with a brain uptake index of 43.53 and a low Km value of 2.03 [87]. Since the lower the Km, the higher the affinity of the transporters for the substrates, then an uptake index of 43.53% and a Km value of 2.03 are enough to facilitate the cross of PPA into the brain cell, which could explain the elevation of this SCFA in the brain homogenates of the treated rats.

In an attempt to prove the relationship between unbalanced gut microbiota and the etiology of autistic features and to confirm the critical role of *Clostridium difficile* as PPA producer, a comparative study of the effect of clindamycin-induced *Clostridium difficile* growth and orally administered PPA was done by El-Ansary et al. [88]. Both treatments were effective to induce biochemical autistic features (Oxidative stress, mitochondrial dysfunction, neuroinflammation, pro-apoptotic) with direct orally administered PPA being more potent compared to the indirect effect, through induction of PPA bacterial producers among which is *Clostridium difficile.*

Clearly, gut microbiota not only exert a local effect on the GI tract but also impact remote organs such as the brain through chemical signaling.

Treatment Strategy to Reduce Clostridium Difficile

Probiotics and prebiotics

The antibiotic-associated diarrhoea is mostly due to *C. difficile,* pathogenic bacteria recently reported as etiological factor in the pathophysiology of autism [70]. A randomised double-blind placebo-controlled trial done by Hickson et al. [89] recorded that consumption of a probiotic drink containing *L. casei, L. bulgaricus*, and *S. thermophilus*can reduce *C. difficile* associated Diarrhoea (CDD). Among the randomized patients, 138 received the Lactobacillus and Bifidobacterium strains as probiotic in combination with the antibiotic and the other half received the antibiotic therapy alone for 20 days compared with placebo group. On basis of diarrhoea development, 2.9% of patients' present *C. difficile* associated toxins in their faecal samples versus 7.9% in placebo control. After complete analysis of patient samples, 46% of probiotic patients were toxin-positive compared with 78% of the placebo group. Based on these records, probiotics could be suggested as treatment strategy for autistic patients.

A prebiotic is defined as selectively fermented ingredients that induce specific changes, both in the composition and/or activity in the gut microbiota that confers benefits upon host health [90,91]. In recent years, there is a dramatically increasing interest in the use of prebiotics as functional foods in order to modulate the composition of gut microbiota [92,93].

Faecal transplantation

One of the most important techniques recently considered in treating C. difficile infection is faecal transplantation. This treatment strategy aims to replace the gut microbiota of a diseased individual by transplanting the microbiota from a healthy donor [94]. Meta analyses have recently reported a 90% successful trials when faecal transplantation is used to treat refractory C. difficile infection [95,96] showing that this methodology has potent and reproducible efficacy when broad-spectrum antibiotics, as traditional therapeutic option have failed to treat disease [95]. Recent studies, certainly show that faecal transplants can be effective even when samples that have been previously frozen were used or when the transplant is self-administered suggest that it will be possible to simplify donor recruitment and sample processing steps without reducing the potency [97,98].

The mechanism of action of faecal transplantation has not been established. However, patients with recurrent *C. difficile* Infection (CDI) have been found to have decreased bacterial diversity in their stool microbiome [99,100]. By repopulating the gastrointestinal tract with a healthy microbiome, stool transplantation could be effective in restoring resistance to *C. difficile* growth [95,101].Although fecal transplantation is considered as successful strategy to treat dysbiosis, but it is not widely used because of the time required to identify a suitable donor, the risk of introducing pathogenic bacteria, and a general recepiant dislike [102]. Thus, the development of animal model that have many features of fecal transplantation in humans with recurrent *C. difficile* disease could help to understand the basic mechanisms of successful fecal transplantation and also to develop standardized bacteriotherapy [103].

Hyperbaric Oxygen Therapy (HBOT)

HBOT has been used to decrease the amount of abnormal bacteria in the gut and therefore can function as an antibiotic [104]. In animal studies, HBOT was effective in reducing intestinal bacterial counts after bacteria overgrowth in the distal ileum associated with bile duct ligation [105]. It also shows bactericidal activity against many pathogenic bacteria, including Pseudomonas [106] Salmonella and Proteus, Staphylococcus [107], Mycobacterium tuberculosis [108], and anaerobic bacteria such as Clostridia [109].

Based on the fact that oxygen-dependent killing of *Staphyloccus aureus* by phagocytic leukocytes has been shown to increase by HBOT in animals [110], and that HBOT has also been shown to inhibit the growth of some yeast [111] and to possess virucidal activity against some enveloped viruses [112], HBOT might lead to an improvement in the dysbiosis found in some autistic patients by reducing counts of abnormal pathogens. However, many of the studies had limitations which may have contributed to inconsistent findings across them, including the use of many different standardized and non-standardized instruments, making it difficult to directly compare the results of studies or to know if there are specific areas of behaviour in which HBOT is most effective [113].

In a recent study done by Chiranjit et al. [114], use of HBOT for children appears generally safe, even at pressures up to 2.0 atm for 2 h per day for 40 sessions the atmospheric pressure has a significant impact on the bacterial colonization of the gut and on the ecology of the gut microflora.

Conclusion

The gut microbiota, gut-brain axis and microbiome-host interaction play a significant role in aetiology of different neurodevelopmental disorders, especially autism.

Microbial colonization commences immediately after birth and carbohydrate availability is the most important nutritional factor which could control the composition and metabolic activities of microbiota and bacterial species diversity.

We can hypothesize that understanding these aspects could help in early diagnosis, treatment or prevention of neurodevelopmental disorders such as autism.

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