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The Role of Intestinal Dysbiosis in the Pathogenesis of Autism: Minireview

Review Article

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Abstract

Autism spectrum disorder is a complex neurodevelopmental disease where gastrointestinal disturbance is commonly reported. Here we review the evidence suggesting that gut microbota my play a role in this disease and summarize comparative studies we found in international literature on the topic. Discussion of results, methodology of the data collection, bias of selection and behavioral interferences lead to the conclusion that changes in the gut microbiota is a significant piece of autism spectrum disorder but further studies are needed to understand this pathogenetic role.

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Introduction

Human microbiota represents one of the most striking cultural revolution in medicine emerged in the last 20 years [1]. Many studies have revealed how the complexity and dynamics of gut microbiota influences normal physiology and contribute to a variety of diseases ranging from obesity to atherosclerosis, allergy and severe neurological disorders [2]. The latter topic is of particular relevance and really revolutionary and is specifically linked to the existence of so-called gut-brain axis: a physiological framework in which the gut microbiota communicates with the CNS and viceversa through neural, endocrine and immune pathways [3]. If this is true then is plausible to expect that the modulation gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders. Autism is definitely one of these disorders.

Autism encompasses a broad spectrum of heterogeneous neurodevelopmental disorders with a prevalence rate of 1:150 and a 4:1 male: female ratio, characterized by qualitative impairment in social communication area and restricted repetitive and stereotyped patterns of behavior interests and activities [4].

The possibility that autism is the consequence of an imperfect development of gut flora is supported by a number of observations like: the frequent coexistence of gastrointestinal symptoms in autistic children; the appearance of the disease after an incidental antimicrobic therapy and the increased levels of urinary biomarkers of specific pathogens of clostridium spp. in the urine of autistic children [2].

SCFAs represent a group of compounds derived from the host microbiome that can induce widespread effects on gut, brain, and behavior, contribute to various neurological processes and are plausibly linked to ASDs [5].

Since the literature about the role played by intestinal dysbiosis in autism is increasing, we felt interesting to summarize the present evidences in this mini review.

Material and Methods

We conducted a database search using Pubmed Plus, Ovid MEDLINE, CINAHL, ISIWeb of Science, PSYCinfo, The Cochrane Database, ALOIS, Google Scholar for the years 1980 to 2013 using the terms: autism, microbiota, dysbiosis, gut flora, gut-brain axis. From this search we reviewed clinical trials, case reports and qualitative observations that used these key words. We considered only comparative studies with a sizeable number of cases. At the end of our process we have identified nine articles fulfilling the selection criteria.

Results

Table1 one summarizes the fundamental features of the studies selected. We identifies nine studied published in the medical literature between 2005 and 2013.

All these studies have targeted fecal microbiota but two (ileal and cecal biopsies) using a wide range of techniques. Five studies have been carried out in USA, four in Australia and one in Italy. All the studies are case-control comparative studies with a small-medium sample size, ranging from 15 to 58 autistic children and from 10 to 53 typicals. The age of the children has a wide range: from 3 to 16 years. As expected there is a strong inhomogeneity as regards the microbiological assay method employed. One group has employed FISH analysis with specific 16SrRna oligonucleo-

Table 1. Comparative studies of intestinal microbiological profile in autism

Authors	Ref.	Country	Study population	Microbiological assay method	Results	Published in
Parracho et al.	6	USA, 2005	58 ASDs children (3-16 years old) VERSUS 10 non-ASDs siblings (2-10 years old) and 10 unrelated healty childrens (3-12 years old)	FISH analysis performed in fecal samples with specific 16S rRNA oligonucleotide probes	Significantly increased incidence of Clostridium histolyticum in ASD group and intermediate non significant difference with sibling group	J Med Microbiol 2005; 54: 987-91.
Finegold et al.	7	USA, 2010	33 ASDs children VERSUS 7 siblings and 8 unrelated healthy children	bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP) in fecal samples	Significantly increases in Bacteroidetes in fecal samples from ASDs children and increases of Firmicutes in control group	Anaerobe 2010; 16:444-53.
Adams et al.	8	USA, 2011	58 ASDs children (mean age 6.91 years) VERSUS 39 unrelated healthy children (mean age 7,7 years)	Bacterial and yeast culture using standard tecniques. Vitek 2 (GN , GP and YST system identification.	Significant lower level of species of Bifidobacter and higher level of Lactobacillus in ASD children. Similar levels of other bacteria and yeast	BMC Gastroenterology 2011; 11: 22.
Wang et al	9	Australia, 2011	23 ASDs children (mean age 123 mo.) VERSUS 22 siblings (mean age 144 mo.) and 9 unrelated healthy children (mean age 114 mo.)	DNA extraction from fecal samples and qRNA analysis performed on a CFX 384TM real-time PCR detection system	Significant lower level of species of Bifidobacterium spp. in ASD children versus siblings and controls and lower level of Akkermansia muciniphila in ASD children versus controls only	Appl Environ Microbiol 2011; 77: 6718-21.
Williams et al.	10	USA, 2011	15 ASDs children (mean age 4.5 years) VERSUS 7 unrelated healthy children (mean age 4.0 years)	DNA extraction from ileal and cecal biopsies and PCR assays (16S rRNA gene pyrosequencing analysis)	Significantly decreases in Bacteroidetes (with increases Firmicutes/ Bacteroidetes ratio) and increases of Betaproteobactera was found in intestinal biopsy samples from ASDs children	PLoS ONE 2011; 6: e24585
Williams et al.	11	USA, 2012	23 ASDs children (3-10 years old) VERSUS 9 unrelated healthy children (3-10 years old)	DNA extraction from ileal and cecal biopsies and PCR assays (16S rRNA gene pyrosequencing analysis)	High level of Sutterella species was found in intestinal biopsy samples from ASDs children	mBio2012; 3: e00261-11
Gondalia et al.	12	Australia, 2012	51 ASDs children VERSUS 53 healty control siblings	bacterial tag-encoded FLX amplicon pyrosequencing	No differencies between ASD and controls	Autism Res 2012; 5: 419-27.
DeAngelis et al.	13	Italy, 2013	20 ASDs children (10 autistic and 10 pervasive e developmental disorder not otherwise specified) (4-10 years old) VERSUS 10 healty control siblings (4-10 years old)	DNA and RNA extraction from fecal samples and 16S rDNA and 16S rRNA analysis	Compared with healthy controls median values of Clostridium, Bacteroides, Prophyromonas and Prevotella, Pseudomonas, Aeromonas and Enterobacteria were higher, instead Enterococcus, Lactobacillus, Streptococcus, Lactococcus, Staphylococcus were lower.	PLoS ONE 2013; 8: e76993
Wang et. Al	14	Australia, 2013	23 ASDs children (mean age 123 mo.) VERSUS 22 siblings (mean age 144 mo.) and 9 unrelated healthy children (mean age 114 mo.)	DNA extraction and qRNA analysis performed on a CFX 384TM real-time PCR detection system	Significant higher level of Sutterella spp.in ASD children versus siblings and controls	Molecular Autism 2013; 4: 42
Kang DW, et al.	15	USA, 2013	20 ASDs children (mean age 6.7 years) VERSUS 20 unrelated healthy children (mean age 8.3 years)	16S rRNA gene pyrosequencing analysis from fecal DNA samples	Significantly lower level of Prevotella, Coprococcus and unclassified Veillonellacea in autistic samples	PloS ONE 2013; 8: e68322

tide probes; other bacterial tag encoded FLX ampliconpyro sequencing (three studies). Four studies have been carried out using real-time PCR assays on CFX 384TM detection system and only one using bacterial and yeast culture using traditional techniques.

Only one study did not find any difference in microbiological pattern between autistic children and controls.

In the other eight significant differences have been found in increase or decrease of specific bacterial population. For example Parracho [6] et al found significantly increase incidence of Clostridium histoliticum in ASD group and intermediate non significant difference with sibling group. A significantly increase in bacteroidetes and decrease in Firmicutes has been described

by Finegold [7]; while the opposite was true for Williams. This author by the way sampled the mucosa associated bacteria rather than fecal bacteria.

Significantly lower level of Bifidobacteria in autistics were found in two studies (Adams et al and Wang et al) [8, 9].

High level of Sutterella species have been found in intestinal biopsy samples by Williams, and in feces by Wang et al. and this seems particularly noteworthy since Sutterella species have never been described before in human gut. [11-14]

Significantly higher counts of Bacteroides and Prophyromon were found in fecal samples of ASD children by Italian group, and more important a higher median value of Clostridium spp. Enterococcus, Lactobacillus, Streptococcus Lactococcus and Staphylococcus were lower in autism [13].

Discussion

The studies on intestinal dysbiosis associated with ASD open new avenues in the understanding of this dramatic disease. The coexistence of ASD and gastrointestinal disturbances is often overlooked due to the difficulty in eliciting subjective symptoms in a disorder characterized by an impaired communication. It is not surprising therefore that a standardized diagnosis of GI symptoms in ASD is yet to be clearly defined.

In any case the high prevalence of the GI manifestations [16, 17] highlight the possibility that they might may be linked to gut dysbiosis.

There is an increasing body of knowledge pointing out that gut flora influences a variety of social emotional, and anxiety-like behaviors, and contribute to brain development and function in animals [18, 19] and humans [20]. In a recent study carried out by Hsiao et al. these authors demonstrated that a particular model of autistic mouse displays behavioral symptoms relevant to ASD and other neurodevelopmental disorders [21, 22], while also exhibiting defective GI integrity, dysbiosis of the commensal microbiota, and alterations in serum metabolites. The administration of a particular commensal (B. Fragilis) is able to reverse autistic symptoms and metabolic derangement. These findings represent a major breakthrough in the microbiota hypothesis of ASD [23]. Unfortunately they have to be replicated in human being. B.Fragilis is not commonly found in foods, therefore clinical trials need special IND to be carried out.

The studies on intestinal microbiological profile in autism are more or less in their infancy. There are many methodological issues to be resolved, like the standardization of microbiological assay methods, of sampling protocols and mathematical analysis of the results.

An important issue to be addressed is the effect of diet on gut microbiota. The fact that autistic children display very often a "nutrition fixation", i.e a reduced spectrum of food variety, implies that the differences seen in microbiota profile might depend more from particular dietary pattern related to autistic behavior rather than to an intrinsic defect of gut homeostasis. In most published studies authors were unable to make comparisons regarding the diets of the unaffected control children and autistic children since food records are rarely collected both for children with ASDs or controls. Therefore it is unclear if the differences observed in microbiota profile between case and control groups are reflective of their dietary intake or abnormal metabolism or both.

Further studies are therefore needed before the whole issue of gut microbiota can be considered as a hard end point in autism research. Comprehensive studies starting from behavior of mother during pregnancy, bacterial transolocation from mother intestine during pregnancy in fetus organs, early exposure to antibiotics after birth, quality and quantity of breast feeding and urinary metabolomic profile of the newborn in his early development are warranted to make a real step forward in this complex area of research and speculation.

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