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Research Article

A Clinical Study of the Brain-Gut Relationship in Autism Spectrum Disorder (ASD)

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Abstract

We have examined from the clinical point of view 75 patients, from 3 - 15 years old, diagnosed with autism spectrum disorder. They showed disconnected brain and social isolation (80%), creative child (Asperger syndrome) (10%), and hyperconnected ones (5%). Some of these patients (10%) exhibited gastrointestinal diseases, such as esophageal atresia, gastritis, diarrhea, neonatal jaundice, constipation, and viral hepatitis. The results are discussed in relationship with organelle cell abnormalities, oxidative stress, pathology of endothelial junctions in the blood-brain barrier, abnormalities in main grain centers, neuroimmunes system, nerve cell transmission at the tenth cranial nerve, and the metabolic changes induced by the intestinal bacteria and microbial-derived neurotransmitters.

Keywords: *Autism; Brain-Gut Axis; Gastrointestinal Diseases*

Introduction

Gastrointestinal symptoms are present in patients with autism spectrum disorders (ASD), but their pathogenesis and relationship with ASD are not clearly defined. Besides, alteration in gut microbiome has been considered one of the main pathogenetic mechanisms of ASD [1]. The aethiology of ASD disorders remains unknow until now, and the relationship with ASD have been emphasized because patients with ASD exhibit gastrointestinal diseases [2-6].

The gastrointestinal pathology in ASD could be correlated with gut dysbiosis and appear to correspond to a typical gut-brain axis disruption [7]. Gut microbes influence to the nervous system by means of nervous, endocrine, and immunological pathways. The brain can influence the gut microbiome by means of autonomic nervous system, regulating intestinal peristalsis, through hormones that regulate microbial gene expression [8].

New advances indicate that the microbiota participate in the abnormal pathology of inflammation, immunological abnormalities dysfunction, and the breakdown of gut-brain axis, which contribute to autism spectrum disorder [9-11].

In the present clinical study we analyze from the clinical point of view the relationship of gut dysbiosis and ASD in an attempt to provide further insight and support into their physiopathogenesis.

Materials and Methods

75 infant patients ranging from 3 to 15 years-old with autism spectrum disorder were examined from the clinical point of view at the Clinical Neuroscience Outpatient Clinic at San Rafael Clinical Home of Maracaibo. Venezuela [3]. They were previously examined from the psychological point at different public Psychology Centers of Maracaibo. We have taking into account the criteria established in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the principles of Helsinki Declaration for Research in Human Beings.

Results

We found ASD children and young patients exhibiting gastrointestinal diseases (10%), such as esophageal atresia, gastritis, diarrhea, neonatal jaundice, constipation and viral hepatitis. They showed disconnected brain and social isolation (80%), creative child (Asperger syndrome) (10%), and hyperconnected ones (5%). Some exhibit stereotyped movements of hands and body trunk (10%), learning and memory deficit (10%), aggression and self-aggression (10%), language disorders, such as delay in the onset of language, regressive changes of language, mutism, gestural language, escatologic language, and digital language (5%), psychomotor delay (5%), neurobehavioral changes, such as separation anxiety due to parent migration from the home country (1%), mood disorders, anxiety and depression (3%), routinized patterns of though and fantastic thoughts (2%), and sleep disorders (5%), tactile hypersensitivity and atopic dermatitis, crisis of cry (1%), photophobia (1%), and loss of weight (1%). The following associated risk factors were found: hyperactivity and attention deficit (10%) perinatal hypoxia (75%), low weight at birth, and parenteral abuse of child, allergic reaction, and bronchial asthma.

Some non-nervous system comorbidities, such as hyperactivity and attention deficit (10%), atopic dermatitis, and some locomotor abnormalities as genus valgo and flat feet were also observed. The mothers exhibited during pregnancy the following risk factors: urinary infections, behavioral disturbances like anxiety, phobias, hyperactivity, toxoplasmosis and Zika virus infections, hyperemesis, oligohydramnios and loss of amniotic fluid, twin pregnancy, pre-eclampsia, aging placenta, cesarean surgery, high blood pressure, maternal sepsis, diabetes, hepatic coma, hypothyroidism, viral hepatitis, obesity and social parenteral problems, such as excessive work, low economy and poor social conditions, environmental contamination, and labor and conjugal stress.

Discussion and Conclusion

In the present paper we have reported gastrointestinal diseases in the patients examined, such as esophageal atresia and gastric reflux, constipation or diarrhea, neonatal jaundice and viral hepatitis. According to Ferguson., *et al.* (2019), the majority children and adolescents with autism spectrum disorder and neurobehavioral disorders experienced constipation, about half experienced stomach aches or stomach pain, and others experienced nausea or diarrhea [12].

According to Li., *et al.* (2017) the altered gut microbiome is observed in inflammatory bowel disease and and mood disorders [13]. The excellent review of Srikantha and Mohajeri (2019) [10] describes alterations of gut microbiota found in autistic patients.

The presence and abundance of bacterial species such as: *Candida*, *Prevotella*, *Streptococcus* and *Veillonella, Bacteroidetes*, *Firmicutes*, *Actinomyces*, *Dorea*, *Lactobacillus*, *Faecalibacterium prausnitzii*, and *Bacteroidetes/Firmicutes, Bifidobacteriales and Bifidobacterium longum* are found in children with ASD and gastrointestinal symptoms [11,14].

According to Baspinar and Yardimci (2020), peptides, toxins, and proinflammatory cytokines pass through the BBB and enter the nervous tissue. As a result of the accumulation of these elements, brain function is adversely affected. According to Baspinar and Yardimci [15]. Peptide act as opioid agonists diminish pain sensation and augment the severity of ASD behavior [15].

Abnormal mitochondrial function, oxidative stress tight junction pathology in the BBB has been found in different central nerve centers [10]. Such pathological changes are observed in permeability changes of intestinal barrier, allowing bacterial toxins pass through the gut barrier and acting upon the children with ASD [16].

According to Israelyan and Margolis (2018) [17], the serotonin have been found in a murine model that exhibit behavioral abnormalities as observed in ASD patients, and also show the mutated serotonin transporter (SERT). New research approaches should be carried out to explore metabolic and immune compounds that provide additional knowledge on autism spectrum disorder [18].

Rose., *et al.* (2018) [19] suggested that patients with ASD, who experience gastrointestinal disorders, have an abnormal immune system, apparently due to metagenomic changes that influence symptoms and clinical evolution.

Vuong., *et al.* (2017) reflected upon the relationship of intestinal bacteria and phenotypes with ASD symptomatology [20].

Consistent with metagenomic analysis, liquid chromatography-mass spectrometry (LC/MS) revealed some of the differential metabolites in ASD were involved in the metabolic network of neurotransmitters including serotonin, dopamine, histidine, and GABA. Furthermore, we found these differences in metabolites were associated with altered abundance of specific bacteria. The study suggested possible future modalities for ASD intervention through targeting the specific bacteria associated with neurotransmitter metabolism [21].

The microbiota and the brain communicate with each other via various routes including the immune system, tryptophan metabolism, the vagus nerve and the enteric nervous system, involving microbial metabolites such as short-chain fatty acids, branched chain amino acids, and peptidoglycans. Many factors can influence microbiota composition in early life, including infection, mode of birth delivery, use of antibiotic medications, the nature of nutritional provision, environmental stressors, and host genetics. At the other extreme of life, microbial diversity diminishes with aging. Stress, in particular, can significantly impact the microbiota-gut-brain axis at all stages of life. Much recent work has implicated the gut microbiota in many conditions including autism, anxiety, obesity, schizophrenia, Parkinson's disease, and Alzheimer's disease [22].

A combination of altered social and feeding behaviors is common in children with autism spectrum disorder (ASD); however, the underlying mechanisms are unknown. Nevertheless, it has been established that several specific neuropeptides are critically involved in the regulation of both feeding and social behavior, such as α-melanocyte-stimulating hormone (α-MSH) and oxytocin, respectively. Moreover, recent data implicated gut microbiota in regulation of host feeding and emotion and revealed its dysbiosis in ASD, suggesting a mechanistic role of altered microbiota-brain axis in ASD [23].

As above described the lifestyle, environmental conditions, maternal pathology and socioeconomic situation are greatly associated with the development of ASD and gut dysbiosis [24].

Sivamaruthi., *et al.* (2020) emphasize about the evidence of altered gut microbial in children with ASD. An unique profile of microbiome has not yet been identified due to the heterogeneity of ASD patients. The supplementation of probiotics seem to improve ASD symptoms [25].

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