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Letter to the Editor

On The Effectiveness of Probiotic as Treatment Strategy of Autism

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Abbreviations: SCFAs: Short Chain Fatty Acids; LPS: Lip Polysaccharides; TNF-α: Tumor Necrosis Factor-α; IL-6: Inter leukin-6; TNF-α: Tumor Necrosis Factor-α; BBB: Blood Brain Barrier; GABA: Gamma Amino Butyric Acid; GI: Gastro Intestinal

Introduction

The gut micro biota and its metabolites play important roles in the body physiology, including the brain. Dysbiosis or micro biota alterations are involved in numerous pathologies, including neuro developmental disorders. The frequent occurrence of gastrointestinal symptoms in autistic patients could suggest the possible involvement of impaired gut micro biota as etiological mechanism in autism. Up to our understanding of the etiological mechanisms of autism through our clinical and experimental research, it was interesting to relate altered gut micro biota to neuro inflammation, oxidative stress, heavy metal toxicity, autoimmunity, and glutamate excitotoxicity to clarify the possibility of targeting gut micro biota to ameliorate these contributed pathologic signaling and thus treat autism. The gut micro biota can indirectly affect the brain through the circulating pro-inflammatory and anti-inflammatory cytokines or through the production of metabolites among which is short chain fatty acids (SCFAs). SCFAs such as acetate, butyrate, and propionate can modulate the innate immune system and the sympathetic nervous system [1]. Alteration in the intestinal bacteria is related to reduced integrity of the intestinal barrier, leading to increased absorption of toxic metabolites from the gut and leakage of lip polysaccharides (LPS) and fatty acids. These toxic molecules can activate systemic inflammation [2], and finally affects the brain. Multiple records indicate that neuro inflammation biomarkers, such as Inter leukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) are greatly involved as etiological mechanism in autism [3].

Heberling et al. [4] hypothesized that overgrowth of Clostridia and/or *Desulfovibrio* and a decrease in Bifidobacterium which is involved in autism pathogenesis can be related to oxidative stress and impaired sulfur metabolism. Together with increased intestinal permeability, disruption of the blood brain barrier (BBB), increased blood circulation of bacterial metabolites and toxins can induce neuro inflammation. Since, autistic patients are poor detoxifiers and they have a burden of lead and mercury levels, it was very interesting to discuss the probiotic-mediated detoxification mechanism [5-7]. Comparative study on conventional against germ-free animals have shown the protective role of gut micro biota against mercury and lead intoxication [8]. This natural protective effect can clearly have demonstrated through the remarkable increase of the probiotic *lactobacilli* in response to heavy metal [9]. Although certain pathogenic bacteria such as *Clostridia* and *Desulfovibrio* as methyl atorscan convert the less toxic organic mercury into the more toxic methyl mercury [10-12], there are certain probiotic strains that have active enzymatic pathways for detoxification, such as mercury reduction and demethylation [13].

Glutamate release, uptake, metabolism and signaling disorders are described to contribute to the etiology of autism [14-17]. Dysregulation of the enteric glutamatergic neurotransmitter is also among the several pathological mechanisms related to autism. Up to molecular mimicry between early life over grown micro biota and human proteins, auto antibodies against the receptors of the Gamma Amino Butyric Acid (GABA), as well as important immune-related enzymes such as transglutaminase-2 can be related to glutamate excitotoxicity. Up to Heberling et al. [4] hypothesis relating oxidative stress, impaired sulfur metabolism, overgrowth of pathogenic bacteria and increased gut permeability to each

other as four etiological mechanisms in autism, it was suggested that all these mechanisms should be targeted as treatment strategy. Combining folinic acid, betaine, and methyl vitamin B12, as treatment of impaired sulfur metabolism, vancomycin as treatment to *clostridia* overgrowth, aztreonam as treatment of *Desulfovibrio* overgrowth, zonulin as treatment of loosening of tight junctions could have great potential in treating autism symptoms [18-20].

Consumption of probiotics is now being recommended as an adjuvant for detoxification in patients with autism. In relation to methyl mercury burden in autistic patients, lower *Bifidobacterium spp*. [21] and *clostridia* overgrowth [22], again *Lactobacillus spp*. and *Bifidobacterium spp*. as probiotic species able to transform toxic mercury compounds into metabolites extractable in feces [23]. Interestingly, selected strains of probiotics have been shown to inhibit the growth of different Clostridium species *in vitro* [24] and *in vivo* [25]. Consumption of probiotics may therefore help to maintain or restore the balance of gut micro biota among autistic children [26]. Moreover, *Lactobacillus rhamnosus* was found to reduce anxiety and depression-like behaviors through the amelioration GABAergic system of the brain [27]. Moreover, oral administration of GABA derived from *Lactobacillus hilgardii* fermentation has been shown to have clinical value presented as immune enhancement and anxiety reduction [28].

In relation to all these alterations, Santocchi et al. [29] registered a randomized clinical trial (NCT02708901) on 100 preschooler's autistic patients (18-72 months age) with and without gastro Intestinal (GI) symptoms. Vivomixx® as a probiotic mixture of 8 bacterial strains (*Bifidobacteriumlongum, Bifidobacteriuminfantis, Bifidobacteriumbreve, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus paracasei, Lactobacillus bulgaricus and Streptococcus thermophilus*) was fed for both groups for six months. Both groups of participants were assessed at the baseline, after three months and after six months from the baseline to evaluate the possible changes in GI symptoms, in autism behavioral phenotypes (e.g. social communication; sensory profile), plasmatic, urinary and fecal biomarkers related to abnormal intestinal function and in the electrophysiological patterns. The results of this trial are about to be declared in 2018.

Conclusion

At this point, the role of the gut micro biota as a trigger and modulator of heavy metal toxicity, neuro inflammation, autoimmunity, and glutamate excitotoxicity as etiological mechanisms of autism remains to be formally ascertained. Identification of pathogenic overgrowth of flora (individually or all together) may give new diagnostic tools. More importantly and up to this, new therapeutic strategies could be designed to neutralize the bacterial pathogenic triggers (e.g. bacterial neuro peptide, toxin and metabolites). These would include antimicrobial manipulation by specifically tailored antibiotic protocols, by pre and probiotics. Figure 1 demonstrates the suggested therapeutic effects of probiotics through the amelioration of oxidative stress, neuro inflammation, heavy metal toxicity, glutamate excitotoxicity and autoimmunity. Of course, addressing these etiological mechanisms can improve attention, learning and other autistic behaviors.

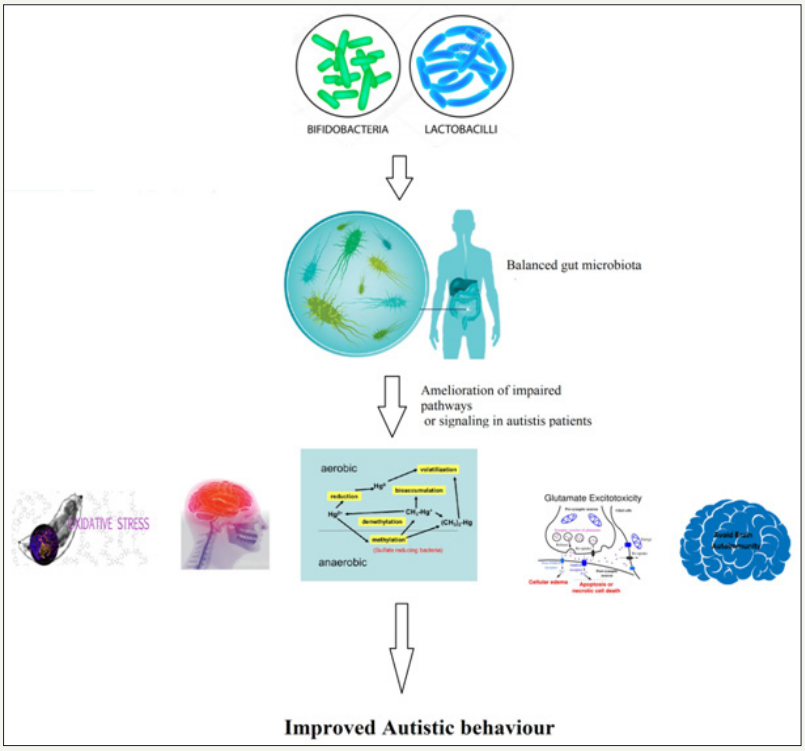

Figure 1: Suggested therapeutic effects of probiotics through the amelioration of oxidative stress, neuro inflammation, heavy metal toxicity, glutamate excitotoxicity, and autoimmunity in autistic patients.

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