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Impact of the Gut Microbiome on the Central Nervous System

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Abstract:- The human gut microbiota is composed of trillions microorganisms with own gene. The gut microbes influence various aspect of Central nervous system through multiple mechanisms whereas vagus nerve connects the gut and brain by neural connections. To transmit signals they directly stimulate afferent neurons of the enteric nervous to the brain by vagus nerve. It is essential in alteration of neurotransmitter levels, if there is any disruption in the gut microbe it affect brain function, and finally it affects the neurological health sometimes it lead to disorders like leaky gut syndrome. They also play a key role in health issues which leads to depression, and disease like autism spectrum through activity of the gut-brain axis. The alteration in the bacterial composition guts microbiota lead to dysfunction of the digestive system such as bowl diseases, obesity, immune and neurological diseases. The gut microbes promote the digestion by facilitating the absorption of nutrients and also help the digestive system to function properly. Gut microbiome play defense role in the development of the immune system by creating a barrier against pathogens and toxins.

Keywords:- *Gut Microbiota, Homeostasis, Dysbiosis, Catecholamines, Neurogenerative, Vagus Nerve.*

I. INTRODUCTION

The human gut microbiota is a complex ecosystem with an extensive metabolic activity that helps in the host's health by protecting against pathogens because they are linked to indicators of health and disease. The gut microbiome consists of exclusive assemblages of microorganism it encourages vigorous neurobiological programming in early development which connect with brain function and behavior Amara, et. al. (2008). The gut microbes produce short-chain fatty acids that may exert neurotoxicity and also helps in nutrient processing which are important beneficial metabolites. Bacterial proteins could cross-react with human antigens to stimulate dysfunctional responses of the adaptive immune system Belkaid (2014). They standardize numerous immune activity, and various activity like gut motility, nutrient absorption, fat distribution. Gut microbes involves in stimulation of angiogenesis, and maintain homeostasis of the intestinal barrier. If there is any alteration in nutritional tools in the gut microbiome there will be an alteration in diet, probiotics, and prebiotics Bhostti (2015). The gut microbiome impacts human brain health and it stimulates the low-grade tonic of the innate immune system De Palma, et. al. (2015). The gut microbe leads to extreme stimulation due to bacterial dysbiosis or overgrowth in the small intestine which causes inflammation in CNS Gonzalez et. al. (2012). These gut microbes help to form the blood-brain barrier and also produce neurotoxic metabolites such as D-lactic acid and ammonia by Douglass (2012). The gut microbiome also exchanges the information with the CNS through bidirectional signaling along with the autonomic nervous system, neuroimmune and neuroendocrine pathways by Stilling et al. (2014). Gut microbiota helps to form blood-brain barrier and it is essential for standardizing brain development, immune function, and hypothalamus–pituitary–adrenal (HPA) axis programming by Konturek et. al. (2011).

II. FUNCTIONS OF THE GUT MICROBIOME

Gut microbes involve in the production of hormones, and neurotransmitters that are identical to those produced by humans and they involve in the development of the gut and mucosal immune system by Flint et. al. (2008). The growth and virulence of the microorganism are influenced by bacterial receptors and they directly stimulate afferent neurons of the enteric nervous. The gut microbes also regulate the sleep and stress reactivity of the hypothalamic-pituitary-adrenal axis by Gill et. al. (2006). They are essential for normative brain development, immune function, hypothalamus–pituitary–adrenal (HPA), and axis programming Douglas (2012). The crucial periods of neural and behavioral development, particularly adolescence was influenced by the gut microbes. If there is any alteration in microbial presence in gut region it will leads to the intestinal permeability Desbonnet, et. al. (2008). Under normal condition the gut microbiota have mutual coexistence with the body and plays key role in human health and physiology as shown in the fig (1).

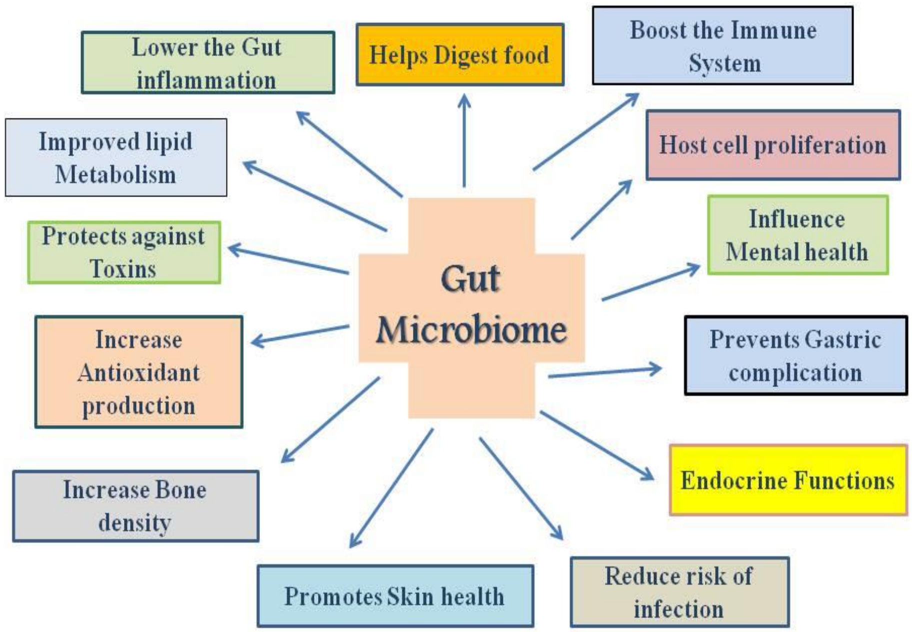

Fig 1:- Representation of the Influence of Gut Microbiome

III. THE CENTRAL NERVOUS SYSTEM AND GUT MICROBIOME

The neurodevelopment process is controlled by both intrinsic and extrinsic signals which are complex processes. The gut is our largest portal to the molecular universe and the gut microbes play a significant role in neurogenerative processes such as myelination, neurogenesis, and microglia maturation by Clarke, et. al. (2013). The brain-gut signaling system enables the brain to influence GI functions, including motility, permeability, secretion, and much production. The brain-gut–microbiota axis includes the CNS, the endocrine-immune system, the hypothalamus–pituitary–adrenal (HPA) axis, and the sympathetic–parasympathetic system which is the main components by Higham (2011). The bidirectional communication network enables top-down signaling from the brain to influence the motor, sensory, and secretary modalities of the GI tract by Savage (1977).

The immune responses such as inflammation, including cytokine production by cells of the mucosal immune system are modulated by gut microbes. During abnormal conditions like stress and depression, there is an alteration in the progress of chronic GI illnesses such as inflammatory bowel diseases and irritable bowel syndrome (IBS) by the brain-gut by Foster (2018). Physical and emotional factors concerning anxiety alter gut motility, the integrity of the intestinal epithelium and, secretions, and mucin production, which express to shifting the process, functions, and activity and promoting alterations in microbial composition Lee et. al. (2012). During stress, the release of catecholamines into the gut may influence the microbial community by interfering with inter-bacterial signaling and with bacterial virulence gene expression by Steinbreche et. al. (1996). And also involved in traditional functions of the gut microbiome, such as protection against pathogens, shielding the intestinal epithelial wall, discharge of IgA, and facilitating nutrient assimilation Ferreiro et. al. (2018). Diverse dietary mechanisms have been shown to interrelate directly with the developing brain and to encourage functional alterations in the mature brain and there is now mounting evidence for a role of the gut micro-organisms in directing and facilitating developmental processes in the brain with extensive implications for health which either promote or rearrange immunologic abnormal Budhwani (2018).

IV. BLOOD-BRAIN-BARRIER

During gestation, the blood-brain barrier serves as a selective barrier between the brain and circulation by Stewart et. al. (2005). The microbiome-gut-brain axis is emerging as an essential pathway for modulating behavior and regulating the permeability of the BBB through the expression of proteins by Yano et. al. (2015). In the deficiency of gut microorganisms, the BBB is more permeable to macromolecules, mediated by declined expression of key tight-junction proteins in the brain endothelium by Sudo (2004). It helps during pregnancy by preventing seizure provoking serum which is acquired by the deficiency of severe electrolyte imbalances by Ley et. al. (2006). The distinction in maternal microbial populations has been suggested to adapt the microbiome, neurodevelopment, and behavior of the offspring by Steiner (2011). The beneficial behavior and physiological effects of some bacteria like *Lactobacillus* are mediated by the vagus nerve by Yu et. al. 2016. The signaling mediators of the immune system can signal to the brain by cytokines and chemokine (Collins, et. al. 2013). During gestation, the immune activation has severe implications on physiology, neuropathology, and behavior, as well as the microbiome in offspring Hendricks et. al. (2015).

V. MICROBIOTA SIGNALLING SYSTEM AT BRAIN-GUT AXIS

Oxidative stress within the intestines can arise from psychosocial stressors where as the gut microbiota can manipulate all aspects of physiology, such as brain-gut communication and brain function as well as cognition and performance significantly by Tillisch et. al. (2013). The human fetal gut is sterile and the colonization begins during and immediately after birth which indicates the absence of normal gut microbiota Crumeyrolle, et, al. (2014). The babies in the womb encounter no microbes until they were born. The restoration of neurochemical profile was less resistant in normal gut flora of their future life by Schafer et. al. (2016). Early-life gut microbiome dysbiosis in high-risk infants leads to the accumulation of stress and physiologically traumatic events, which potentially lead to severe effects such as constipation, diarrhea, and gas bloating by Perez et. al. (2013). It specifically leads to subsequent psychopathology like bipolar disorder, social anxiety, disorder, and major depressive disorder through the brain-gut–microbiota axis by Tim et. al. (2015).

VI. HEALTHY GUT MICROBIOME FOR NEONATES

Facultative anaerobes plays an important role in gut microbial colonization in newborns starting with facultative anaerobes, followed by the establishment of anaerobic genera, such as *Bifidobacterium*, *Bacteroides*, and *Clostridium* . Whereas it is a predominant microorganism in the intestine within a week after birth by Weiss et. al. (2010). Neonatal gut microbiome development is complex by Serpero et. al. (2013). The breast feed infant have conspicuous microbiota through milk and contact with the mother's skin. Six *Bifidobacterium* strains have been isolated from human breast milk showing phenotypical and genotypical characteristics of commercial probiotics, which are significant exclusively for newborns and also probable for use in targeting interventions, such as probiotics for infants by Steenbergen et. al. (2015). *Bifidobacterium* act as a primary colonizer, and they, are mainly involved in the modulation of immunological development Dabritz, et. al (2013). They are also involved in the production of metabolites that grant physiological benefits. The gut microbiome is different in preterm infants and healthy-term infants where they are normally obtained from their mother during birth by Walser et. al. (1959). The development of commensal bacteria in preterm infants was slow and improved colonization by potentially pathogenic microorganisms, performance reduced microbiota diversity which helps in the lowering risk for chronic disease and neurodevelopmental disorders by O'Mahony et. al. (2011).

VII. CONCLUSION

The review explains that the gut microbe's is essential for mental health and mood. Whereas the gut and brain is connected through millions of nerves exclusively vagus nerve. The complex interaction between nutrients and microbiome will reflects on the host health because they play an significant role in bidirectional interaction between brain and the nervous system. The gut microbiome probably influences the brain by various mechanisms because they produce neurotransmitters. Sometime they affect the metabolism by producing serotonin. In general review concludes that the gut microbe is a master regulator of key neurophysiological process. Gut microbes involve in the production of neurotoxic metabolites and activation of afferent neurons of the enteric nervous system to send signal to brain by vagus nerve.

REFERNCES

[1]. Amaral, F,A., Sachs, F, A., Costa, F, A. 2008. Commensal microbiota is fundamental for the development of inflammatory pain. *Proceedings of National Academy of Sciences of USA.*105:2193–7.
[2]. Belkaid, Y., Hand, T,W. 2014. Role of the microbiota in immunity and inflammation. *Cell*. 157:121–41.
[3]. Boschetti, G., Gornero, P. 2015. Accuracies of serum and fecal S100 proteins (calprotectin and calgranulin C) to predict the response to TNF antagonists in patients with Crohn's disease. *Inflammatory Bowel Disease*. 21(2):331-336.
[4]. Budhwani, M., Mazzieri., Dolcetti. 2018. Plasticity of type I interferon-mediated responses in cancer therapy: from anti-tumor immunity to resistance. *Frontiers in Oncology*. 8:322.
[5]. Clarke, G., Grenham, S. 2013. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Molecular Psychiatry*. 18:666–673.
[6]. Collins, S,M., Bercik, P. 2013. Gut microbiota: Intestinal bacteria influence brain activity in healthy humans. *Nature Review Gastroenterology and Hepatology*. 10(6):326-327.
[7]. Crumeyrolle, A, M., Jaglin, M., Bruneau, A. 2014. Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. *Psychoneuroendocrinology*. 42:207–217.
[8]. Dabritz, J., Foell, D., Wirth, A. 2013. Fecal S100A12: identifying intestinal distress in very-low-birth-weight infants. *Journal of Pediatric Gastroenterology and Nutrition.* 57(2):204-210.
[9]. De Palm, G., Blennerhassett, P., Deng. 2015. Microbiota and host determinants of the behavioral phenotype in maternally separated mice. *Nature Communications*. 6:7735.

ISSN No:-2456-2165

[10]. Desbonnet, L., Garrett, L., Clarke, G. 2008. The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. *Journal of Psychiatric Research*. 43:164–174.
[11]. Douglas, E,M., Weiss, M,D. 2012. Biomarkers of brain injury in the premature infant. *Frontiers in Neurolog*y. 3:185.
[12]. Ferreiro, A., Crook, N., Gasparrinni, A. 2018. Multiscale evolutionary dynamics of host-associated microbiomes. *Cell*. 172:1216–1227.
[13]. Flint, H,J., Bayer, E,A., Rincon, M,T. 2008. Polysaccharide utilization by gut bacteria: Potential for new insights from genomic analysis. *Nature Reviews Microbiology*. 6(2):121
[14]. Foster, J,A., Rinaman, L., Cryan, F. 2017. Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of stress*. 7:124–136.
[15]. Gill, S,R. 2006. Metagenomic analysis of the human distal gut microbiome. *Science*. 312(5778):1355–1359.
[16]. Gonzalez, J,M., Lee, G. 2012. Immunomodulatory functions of type I interferons. *Nature Review Immunology*. 2012;12:125–135.
[17]. Hendricks, K,D., Jie Xu, Parikh, H. 2015. Skin-to-Skin Care and the Development of the Preterm Infant Oral Microbiome. *The American Journal of Perinatology*. 32(13):1205-1216.
[18]. Higham, J,P., Bar, S., Hoff, C,H. 2011. Mu-opioid receptor (OPRM1) variation,oxytocin levels and maternal attachment in free-ranging rhesus macaques Macaca mulatta. *Behavioural Neuroscience.* 125(2):131-6.
[19]. Konturek, P,C., Brzozowski, T. 2011. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *Journal of Physiologyical Pharmacology*.2011;62(6):591-9.
[20]. Lee, S,E. 2012. Type I interferons maintain Foxp3 expression and T-regulatory cell functions under inflammatory conditions in mice. *Gastroenterology.*143:145–54.
[21]. Ley, R,E., Daniel, A. 2006. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell.* 124(4):837–848.
[22]. O'Mahony, S,M., Niall, P.H., Timothy, G.H. 2011. Maternal separation as a model of brain-gut axis dysfunction. *Psychopharmacology (Berl).* 214(1):71-88.
[23]. Perez, B,A., Wang, B., Mao, Y,K. 2013. Psychoactive bacteria Lactobacillus rhamnosus (JB-1) elicits rapid frequency facilitation in vagal afferents. *American Journal of Physiology- Gastrointestinal and Liver Physiology*. 304:211–20.
[24]. Savage, D,C., 1977. Microbial ecology of the gastrointestinal tract. *Annual Review of Microbiology*. 31:107–33.
[25]. Schafer, D,P., Heller, C., Gunner, G. 2016. Microglia contributes to circuit defects inMecp2 null mice independent of the microglia-specific loss of Mecp2 expression. *Elife.* 2016;5:15224.
[26]. Serpero, L,D., Bellissima, L., Colivicchi, M. 2013. Next-generation biomarkers for brain injury. *The Journal of Maternal Fetal Neonatal Medicine*. 26(20):44-9.
[27]. Steenbergen, L., Sellaro, R., Hemert, S.V. 2015. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain Behavior and Immunology*. 48:258–264.
[28]. Steinbrecher, H,A. 1999. Urea production in normal breastfed infants was measured with primed/intermittent oral doses of [15N, 15N] urea. *Acta Paediatrica*. 85(6):656–662.
[29]. Steiner, J., Walter, M., Gos, T., Guillemin, G.J. 2011. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for immune-modulated glutamatergic neurotransmission?. *Journal of Neuroinflammation*. 8:94.
[30]. Stewart, G,S., Smith, P,C. 2005. Urea nitrogen salvages mechanisms and their relevance to ruminants, non-ruminants, and man. *Nutrition Research Reviews.* 18(1):49–62.
[31]. Stilling, R,M., Dinan, T,G., Cryan., 2014. Microbial genes, brain & behavior - epigenetic regulation of the gut-brain axis. *Genes, Brain Behavior*. 13(1):69-86.
[32]. Sudo, N., Chida, Y., Aiba., Y. 2004. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *Journal of Physiology.* 558:263–275.
[33]. Tillisch, K., Labus, J., Kilpatrick, L. 2013. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology*. 144(7):1394-401.
[34]. Tim, A., Raith, H., Qian, Y., Forssberg, H. 2015. Host microbiota modulates the development of social preference in mice. *Microbial Ecology in Health and Disease*. 26:29719.
[35]. Walse, M., Bodenlos, L,J. 1959. Urea metabolism in man. *Journal of Clinical Investigation.* 38:1617–1626.
[36]. Weiss, G., Simon, R., Hjerrild, Z. 2010. *Lactobacillus acidophilus* induces virus immune defense genes in murine dendritic cells by a toll-like receptor-2-dependent mechanism. *Immunology.* 131:268–81.
[37]. Yano, J,M., Yu. K., Donaldson, G,P., Shastri, G.G, 2015. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*. 161:264–276.
[38]. Yu, X., Cai, B., Wang, M., Tan, P., Ding, X. 2016. Cross-regulation of two types I interferon signaling pathways in plasmacytoid dendritic cells controls anti-malaria immunity and host mortality. *Immunity*. 45:1093–107.