EDITORIAL

MICROBIOME AND MENTAL HEALTH: THE GUT FEELING OR THE 'FEELING GUT'?

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Since the time of ancient Greek medicine there has been an emphasis on the connection between the gut and mental illness. Constipation, a generic term for disturbances related to gut was referred to as 'Umm ul amraaz', the mother of all diseases, in Hikmat, the subcontinent version and mix of Greek and Vedic Medicine. It was thought to be linked with changes in mood, temperament, and even confusional states. This relationship was exploited in the inhumane settings of asylums of yore. Patients of mental illness were regularly 'treated' with laxatives and enemas.

There has recently been growing academic interest on the role of gut microbiota and role of the microbiome-gut–brain axis in causing illness in humans. A number of studies have measured variations in gut flora between people with various psychiatric and neurological conditions[1].

The human microbiome refers to the total genetic material of the symbiotic microorganisms that reside in the human body. The majority of these microorganisms reside in the human gut. Current research suggests that the human in utero is "sterile". Humans acquire a microbiome through their passage from the birth canal and then throughout life with their interactions with the world around them. Just like their individual interactions, each human's microbiome is as unique as a fingerprint. While one human's genome is 99.9% identical to any other human on the planet, the human microbiome of any individual is 80-90% different from any other. There are various estimates on the ratio of outside microorganisms in the body to human cells, and this may be any where between 3:1 to 1:1. It stands to reason, therefore, that the impact of the microbiome cannot be ignored[2].

The human gut microbiota plays an important role in maintaining homeostasis and its imbalance may lead to various diseases[3]. The first scientific reporting of a gut-brain link can be traced in literature to a publication in British Journal of Psychiatry in 1910 (Philips 1910). The lactic acid bacillus was used for the treatment of melancholia, what psychotic depression was referred to as, at the time. The same organism was used in 1923 to augment the treatment of psychosis. For the next fifty years, Celiac disease, and certain types of bread were linked with schizophrenia in literature. The "cereal" hypothesis of etiopathogenesis of schizophrenia, based on the results of an epidemiological study on the risk of 'de-developing schizophrenia' and the consumption of cereal products. Bender observed a decrease in hospitalization for schizophrenia in the countries that had been forced to reduce consumption of bread during the Second World War, suggesting a possible link between the level of bread consumption and the incidence of schizophrenia. Singh and Kay described subsequent reports on this topic in the journal Science in 1976. They remarked that in people with schizophrenia who were on a gluten and casein-free diet, administration of gluten interrupted the progress of therapy. Upon stopping of the gluten intake, the mental state of patients improved again. In another study, Dohan et al. showed that only two patients with chronic schizophrenia were found among 65,000 adults who were observed in the Pacific Islands, where cereals had not originally been consumed. As soon as these people partially succumbed to Western influence and began to consume wheat products and barley beer, the prevalence of the disease reached the European level[4].

Newer research has made it clear that the maintenance of gut homeostasis is important for the prevention and treatment of various neuropsychiatric disorders[5,6]. Studies have linked the gut microbiome with multiple illnesses; people with post-traumatic stress disorder had lower than normal levels of three types of gut bacteria; altering gut microbiome may be a potential treatment option for polycystic ovary syndrome (PCOS); microbiota dysbiosis may lead to increased gut permeability and bacterial translocation, which are risk factors for Alzheimer's disease[7-9].

The link between the gastrointestinal system and the brain is bidirectional and it is performed through several pathways. As the brain might affect functioning of the gut, modify microbial habitat and hence influence the microbiota composition (Bruce-Keller et al., 2018), at the same time, any disturbance of the microbial flora on the surface of intestinal mucosa might lead to a number of neuropsychiatric conditions (Petra et al., 2015; Zhu et al., 2017). Based on the above observations, the relationship between the brain and the gut has become a target for the research on the pathogenesis and treatment of several illnesses.

In a review article by Clapp et al. (2017) the bidirectional link between gut and brain has been referred to as the gut-brain-axis. The microbiota is implicated as the common link in causing extragastrointestinal and gastrointestinal conditions. The hypothesis suggests that depression and anxiety disorders may be caused through the dysbiosis and inflammation of the gut caused by microbiota. In this hypothesis, the probiotics are seen as 'anti-anxiety, and anti-depressant' agents, that have preventive and therapeutic efficacy. A healthy gut is seen to play a vital role in maintenance of a healthy nervous system. Gut is considered here as an extension of the well known hypothalamic-pituitary-adrenal axis, with cortisol releasing factor (CRF) having direct influence on the enteric musculature, and the gut epithelium which are also influenced by the vagus nerve. This hypothesis turns the gut as a common play

ground for the sympathetic and parasympathetic nervous systems that becomes even more important during chronic stress, which in turn is known to have a central role in anxiety and depression.

Despite the growing body of data, there is not enough evidence to use the microbiome gut-brain axis to make clinical decisions. For example, it is work on the relationship between gut flora and anxiety disorders and mood disorders, as well as trying to influence that relationship using probiotics or prebiotics (called "psychobiotics"), was at an early stage, with insufficient evidence to draw conclusions about a causal role for gut flora changes in these conditions, or about the efficacy of any probiotic or prebiotic treatment[10,11]. Additionally, while much work had been done as of 2016 to characterize various neurotransmitters known to be involved in mental disorders that gut flora can produce (for example, Escherichia, Bacillus, and Saccharomyces species can produce noradrenalin; Candida, Streptococcus, and Escherichia species can produce serotonin, etc.); the interrelationships and pathways by which the gut flora might affect mental health is yet unclear[12].

The main goal in discovering the role of the microbiome-gut-brain axis is to potentially modulate treatment. It is based on the dream that one day, having mapped the entire human microbiome, we may be able to tweak it with our food habits causing improvement in our mental health. We may also be able to have more respect for our patients that already seem to appreciate this connection when they tell us "pait se gas damagh ko charh jaati hai".

The study of the human microbiome may have another unintended effect in a nation like Pakistan. We, as a nation of somatisers, may feel validated by all the data due to having all our feelings in our gut. Despite the growing body of data, however, there is not yet enough evidence to use the microbiome gut brain axis to make clinical decisions. We must wait for more studies done on humans, before we can make a move in this direction in our clinical practice.

On a related note, we in the subcontinent have traditionally linked our spiritual and psychic experiences with longstanding fasting and maintaining hunger for days. The models of a Buddha reduced to bones under a Banyan tree and the consequent light, is linked with his reflection as much as his ability to stay hungry throughout his search for enlightenment. Many sufi traditions are known to propose hunger and thirst by choice as integral to their development of Nafs, a means of improved mental health, to acquire attributes like patience and perseverance, and to experience spiritual ecstasy. Even the most worldly of us may be forced to look inward and find insight during the month of Ramzan.

Given our nation's historical interest and cultural proximity to this theme, Pakistan could become the perfect "breeding ground" to undertake research on this exciting new area of the microbiome-gut-brain axis.

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