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FIRST PERSON ACCOUNT

Am I Inflamed? Chicken, Egg, and Psychosis

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This first person account by Hashwin V.S. Ganesh is derived from Experiential Science Talks Series at the Center for Excellence in Youth Mental Health, Douglas Research Center, McGill University. In this series, experts with lived experience share their experiential knowledge to influence new research directions in youth mental health. https://ceymh-cesmj.ca/introducing-the-ceymh-experiential-science-talks/.

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COVID was a blessing in disguise, not just for me but for the field of schizophrenia/psychotic research, in general. Let me explain.

What started as a COVID infection in early 2022, quickly progressed with severe symptoms that included neurological issues, disruption of gut function, sleep loss, anxiety/depression, and self-harm ideation—ending up in an emergency call to the first responders, who rushed me to the emergency in Vancouver, Canada. The attending physician at the emergency department just asked me two questions—(1) If I was hearing voices? (2) Would I describe myself as an anxious person? I was given a prescription for sleep medication and asked to immediately schedule an appointment at a mental health clinic in Vancouver and get in touch with a psychiatrist/psychologist. With the healthcare system under severe stress as a result of COVID leading to wait times extending to weeks/months, my family abroad quickly realized that I was not going to be able to obtain the requisite medical attention in Vancouver. With some helpful intervention from the Indian Embassy officials, I was able to get on a flight and fly back to India.

In India, I was placed under private medical care with a team of specialists. While I have always had issues with sleep, anxiety-depression, emotional blunting, apathy, feeling aloof, etc. right from the age of 13 or 14, it was quickly apparent that the COVID infection caused an acute inflammatory response resulting in an extreme exacerbation of symptoms over a very short time window. I was subjected to a slew of diagnostic tests such as blood tests (extensive panel), Ultrasound scans, whole-body Positron Emission Tomography (PET), and whole-body Computed Tomography (CT). The test results were interesting with an underlying theme of systemic inflammation. For example, the ultrasound sound scans revealed that the "bowel loops appeared mildly edematous compared to elsewhere—likely colitis." The PET-CT scans indicated "hypermetabolism in palatine tonsils—inflammatory." The specialists indicated that I was exhibiting symptoms of inflammatory bowel disease (IBD) and scalp dermatitis, all indicative of inflammation. Furthermore, the blood report also showed severe deficiencies of Vitamin B12 and Vitamin D, both of which are implicated in playing important roles in the inflammatory biochemical pathways. What puzzled me was the following: Why were the test reports indicating underlying systemic inflammation, while I was experiencing neurological/neuropsychiatric/psychotic symptoms? Initially, none of this made any sense to me. I also quickly realized that the team of specialists treating me was also not able to form a cohesive picture of what was happening to me. The psychiatrist prescribed mild anti-psychotics/sleep medication, the gastroenterologist prescribed medication for IBD, the GP prescribed B12 injections and D3 tablets, etc. It was around this time that I decided to take matters into my own hands and decided to delve deeper into research literature, owing to my training as a neuroscientist.

While conducting a literature search, I stumbled upon an exciting report of complete remission of psychosis in a Japanese patient with schizophrenia, following allogeneic bone marrow transplantation (BMT) in 2017.[1] A 24-year-old Japanese man with treatment-resistant schizophrenia, characterized predominantly by severe delusion and hallucination, was treated for acute myeloid leukemia with allogeneic BMT from a healthy donor. Unexpectedly, after BMT, the patient showed a drastic reduction of his psychotic symptoms (reported as a decrease in the Positive and Negative Symptom Scale PANSS), without any neuroleptics administration (*proof of rescue*). The patient also showed remarkable improvement in his social functioning reported as an increase in the Global Assessment of Functioning (GAF) scale. How could this be? If schizophrenia (and other neuropsychiatric illnesses) is a result of a chemical imbalance in the brain, then how can we explain the complete remission of psychotic symptoms following BMT? The only plausible explanation is that BMT, a cellular therapy,

through its immune-modulatory effects counteracts inflammatory processes through immune regulation, resulting in amelioration of psychotic symptoms in treatment-resistant schizophrenia. This report gave me a lot of hope and helped me explain why my own test reports showed an underlying theme of systemic inflammation as well. This finding by the Japanese group also lays the groundwork for utilizing BMT for the possible curative treatment of schizophrenia and by extension, potentially to other psychotic illnesses (requires similar clinical research studies).

Although there have been several research reports for the role of immune activation in autism,[2,3] schizophrenia,[4,5] and the efficacy of BMT in reversing these symptoms in certain neurological diseases such as Rett syndrome, Huntington's disease,[6–8] these reports have all been on animal models. The Japanese study by Tsuyoshi et al is a stand-alone clinical report in literature and the first-of-its-kind clinical case report to the best of our knowledge. As such, the finding needs to be repeated with added subjects to definitively establish the immune pathogenesis of schizophrenia.

Interestingly, in 2015, just 2 years prior to the Japanese case report, another group[9] presented a clinical case report of a patient who contracted severe psychosis following allogeneic BMT from a donor with schizophrenia (*proof of induction*). This clinical report by Sommer et al strongly supports the immune pathogenesis of schizophrenia. This clinical report also suggests that the disease-causing/psychosis-inducing agent was transmitted from the schizophrenic donor to the recipient, via BMT (bone marrow aspirate? plasma?). Based on these two landmark studies, it does appear that schizophrenia (and other psychotic illnesses) could be complex disorders which are fundamentally multifactorial in nature. There is a strong role for the following factors: (1) Inflammation, (2) Oxidative Stress, (3) Gut–Brain Axis, (4) Vasculature, (5) Vitamin/Mineral deficiencies, and (6) Dopamine/Glutamate.

There is a need for concerted research efforts to tackle each of these aspects of the disease etiopathology, preferably, by multiple research groups across the world simultaneously.

The following lines of research inquiry are worth pursuing:

1. Examining the role of Vitamin D, Vitamin B12 in inflammation—oxidative stress pathways? C-reactive protein (CRP) interactions? Kynurenine pathways?
2. Examining the role of gut microbiome in mental/neuropsychiatric illnesses—Is there a perfect mix-proportion of microbes that results in perfect mental health? Lactobacillus vs Faecalibateria vs other strains? Less diverse microbiome vs more diverse microbiome? What's the ideal gut microbiome for ideal mental health? Personalized microbiome for each individual?
3. Examine Gut–Brain axis—Specifically the role of the vagus nerve. How does the gut–brain axis modulate mental health? What Communication pathways—Neural and chemical pathways are involved? Can we generate a gut–brain axis communication network map?
4. Examine vascular abnormalities in brain disorders—glucose/oxygen/nutritional delivery efficiency to the brain? What causes catatonia? Examine the link between blood osmolarity, osmolality, and blood pressure changes associated with symptom manifestation. What causes water dysbiosis and polydipsia in some psychiatric illnesses?

In conclusion, the above research lines of inquiry need to be pursued with a sense of urgency. This will help us answer some of the crucial questions such as—what causes the inflammation in psychotic illnesses such as schizophrenia? What comes first: inflammation (or) psychosis?

While it is indeed a case of the chicken-and-egg and unlike the original metaphor, we might be able to resolve this in the case of inflammation and psychosis, provided there is a concerted global research effort. As a patient who experienced this firsthand, I hope my appeal is considered by the research community.

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