Review Article

Inflammation in Schizophrenia? A Review of Alterations in Patients

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Abstract

Schizophrenia is a psychotic psychiatric disorder that significantly impacts the social life of the patient. A better understanding of pathogenesis of this disorder is of utmost importance to caregivers. Recent studies have shown evidence of inflammatory reactions involving the pathogenesis of Schizophrenia. Biochemical analysis of CSF has reported an increased count of IL-6 and IL-8 along with other inflammatory substances. Histopathological studies of brain of the affected individuals have presented microglial dysfunction along with several other changes, observed by different researchers. Also, mothers suffering from any particular condition that involved inflammation in the gestational period have been observed to lead to the development of Schizophrenia or related disorders in offspring. Gut-Brain Axis has recently acquired a huge interest among medical researchers. A lot of psychiatric conditions are nowadays being attributed to gut microbiota. Gut microbiota analysis among Schizophrenia patients has shown significant alteration of gut microflora, for example, an increased number of *Lactobacillus* sp. All these studies, when taken into consideration, can give a holistic approach towards the way the pathology of Schizophrenia being viewed, and thus allow professionals to provide better care to the patients.

Keywords: *Schizophrenia, Pathogenesis, CSF, Histopathology, Gestation, Gut-Microflora*

Introduction

Schizophrenia is a psychiatric disorder accompanied by positive and negative symptoms. It is typically considered a psychotic disorder and has significant impact on the life of a patient and his or her family and surroundings. Positive symptoms are those which are added, like hallucinations, delusions (as of punishment), and so on. Negative symptoms typically include removal, for example of social behaviour and emotional responses. It can also be accompanied by Catatonia, like a catatonic stupor. Pathophysiology of Schizophrenia has attracted a lot of interest recently. A better understanding of the pathophysiology of the condition can pave the way for new dimensions of treatment. Typically, excessive action of neurotransmitters like Dopamine and reduced action of Glutamate is associated with this disorder. Theories involving inflammatory responses as a part of the pathogenesis of Schizophrenia and related psychotic disorders are being excessively worked upon. This review tries to study and analyse research works regarding the same. Majority of the studies mentioned here were on human patients with diagnosed schizophrenia, first episode psychosis, multiple episode psychosis or psychotic symptoms (mentioned individually). Relevant animal experiments have been mentioned in their respective contexts. Some of the presented works are original studies conducted on patients, representing the population suffering from Schizophrenia and related disorders, while some are review works.

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The mentioned studies have been conducted in geographically different regions, on different populations. Points significant and relevant to the present study have been mentioned along with.

Biochemical Changes in CSF:

Significant studies have been enlisted below:

Sl no	Author	Sample Size	Observation
1	Tatiana Oviedo-Salcedo (2021)	A total of 331 patients were included. In all, 40% were FEP patient and 60% were Multi episode psychosis patients	1. Elevated CSF protein levels were found in 19.8% and elevated CSF or serum albumin ratios were found in 29.4 % 2. Pleocytosis was found in 6.1% of patients 3. MEP patients showed significantly higher mean - Q Alb compared with FEP patient's which didn't remain significant after correcting for age. 4. Q-Alb elevation occurred most frequently in men
2	Mattia Campana et al (2021)	314 FEP Patients	1. 42.7% patients showed CSF Alterations. 2. Oligoclonal Bands in the CSF were present in 21.8% of patients with 12.4% presenting OCBs type 2 or 3. 3. 15.8% of cohort revealed signs of blood brain barrier dysfunction with increased albumin rations. 4. Mean serum CRP levels were 2.4 mg/l. CRP elevation was present in 41.4% cases. 5. Even though several inflammatory alterations were found both in CSF and in blood tests, no significant relationship was found between peripheral inflammation and inflammatory CSF.

Histopathological Changes in Brain:

Bayer et al (2017), Hercher et al (2014), suggests there is evidence of microglial dysfunction in Schizophrenia. MR Weinstein (1954) find:

1. In choroid plexus analysis with general linear model demonstrated a significant effect of diagnosis on somal width, demonstrating increased somal width in sz without psychotic medication but not in medicates sz cases. No effects observed in calcification.

2. The epithelial cells that were examined were attached to the CP fibrous surface, so width expansion describes the primary methods for these cells to expand with adherence to this surface in SZ. The interaction of antipsychotic medication and diagnosis demonstrates that this is an illness-specific change mediated through the DA system with likely neuronal origin. CP alterations were not found in MDD where they are instead generally associated with heightened allostatic load that was unknown in this cohort.

Other significant findings are presented hereby:

Table 2.

Sl No.	Author	Sample Size	Observations
1	Kirschbaum and Heilbrun(1944)	11	Swelling and shrinkage of cytoplasm like that in chronic infection and metabolic disorders (in all 11). Cytoplasmic and fibrous changes in the cortical microglial cells were observed in 5. Oligodendroglial changes in 4. In 6, increase in lipid content of glial cells.
2	Rupp and Wilson (1949)	4	Chronic Cell Changes and Reactive Gliosis
3	Ferraro (1934)		Acute swelling of Oligodendroglial Cells and Glial Proliferation especially in areas of demyelination.
4	Winkelman and Book (1949)	20	Moderate Gliosis without signs of inflammation, with a proportionate increase of astroglial elements and damage to and loss of nerve cells.
5	Papez and Bateman (1949)	34	Live actively moving organisms looking like inclusion bodies. They believed it to be a phase of the life cycle of a capsulated parasite of nerve cells.
6	Papez (1952)	30	Great numbers of living, reproducing colonial organisms in filamentous, rod-like, globular, lashing, cystic, sac-like, and other forms, in neurons, extracellularly and within erythrocytes. Papez describes a complex reproductive cycle, intracellular and erythrocytic phases, and large colonies resembling the Nostoc blue-green algae and states that the granular forms previously described in stained preparations were "old, dead zooid organisms surrounded by fats."

Gestational health of mother and schizophrenia in offspring:

Argel Aguilar-Valles et al (2021) reviewed that maternal immune activation (MIA) with bacteria or virus led to the activation of immune cells that release cytokines, including interleukin 6 (IL-6) and, in turn, IL-17a. Both of these cytokines affected brain development in the fetus, increasing the risk for neurodevelopmental disorders, such as SCZ. These cytokines can act indirectly on the placenta, or in the case of IL-6 through the induction of hypoferremia, a reduction in circulating non-heme iron. Adipose tissue can also release hormones such as leptin, which affects fetal development. The study showed that SCZ in the offspring is significantly associated with maternal infections using individual biomarkers of illness in the maternal serum or clinical diagnoses. These included respiratory infections, influenza, rubella, *Toxoplasma gonodii*, herpes simplex virus-2, maternal genital or reproductive infections, and maternal bacterial infections. It has been hypothesized that maternal immune activation (MIA), and the inflammatory mediators released following all types of infections, may be fundamentally involved (Argel Aguilar-Valles et al, 2021). Epidemiological studies have provided some evidence supporting this hypothesis. Increased levels of maternal pro-inflammatory cytokines, specifically interleukin (IL)-8, tumor necrosis factor (TNF)α, IL-6, C-reactive protein are associated with a higher risk of psychosis or SCZ in the offspring. Several animal models have

been developed to investigate the immunological and neurobiological link between MIA and altered behavior in the offspring, with a heavy emphasis on behavioural alterations. Pinku Mani Talukdar et al (2021) conducted a study where Sprague-Dawley rats were divided into three groups (n = 15/group) and were injected with poly (I: C), LPS, and saline at gestational day (GD)-12. Except IL-1B, plasma levels of IL-6, TNF-a, and IL-17A assessed after 24 h were significantly elevated in both the poly (I:C)- and LPS-treated pregnant rats, indicating MIA. The rats born to dams treated with poly (I:C) and LPS displayed increased anxiety-like behaviours and significant deficits in social behaviours. Furthermore, the hippocampus of the offspring rats of both the poly (I: C)- and LPS-treated groups showed increased signs of lipid peroxidation, diminished total antioxidant content, and differentially upregulated expression of inflammatory (TNFa, IL6, and IL1B), and apoptotic (Bax, Cas3, and Cas9) genes but decreased expression of neuroprotective (BDNF and Bcl2) genes. They suggested that Maternal Immune Activation can cause Schizophrenia-like behaviors in the offspring through activation of immune-inflammatory, oxidative and apoptotic pathways, and lowered antioxidant defense and neuroprotection.

Gut Microbiota of Schizophrenia Patients:

Florence Thirion et al (2023) found SCZ gut microbiota differed significantly from those of healthy control subjects and individuals with metabolic syndrome in terms of richness and global composition. SCZ gut microbiota were notably enriched in *Flavonifractor plautii*, *Collinsella aerofaciens*, *Bilophila wadsworthia*, and *Sellimonas intestinalis*, while depleted in *Faecalibacterium prausnitzii*, *Ruminococcus lactaris*, *Ruminococcus bicirculans*, and *Veillonella rogosae*. The functional potential of gut microbiota accounted for 11% of cognition variability. In particular, the bacterial functional module for synthesizing tyrosine, a precursor for dopamine, was in SCZ cases positively associated with the cognitive score. Feng Zhu et al (2020) carried out shotgun sequencing on fecal samples from 90 medication-free patients and 81 healthy controls to obtain an average of 11.46 Gb sequence data per sample and mapped the high-quality reads onto a comprehensive reference gene catalog of 11.4 million genes. The gut microbiota in schizophrenic patients harboured many facultative anaerobes such as *Lactobacillus fermentum*, *Enterococcus faecium*, *Alkaliphilus oremlandii*, and *Cronobacter sakazakii/turicensis*, which are rare in a healthy gut. Additionally, bacteria that are often present in the oral cavity, such as *Veillonella atypica*, *Veillonella dispar*, *Bifidobacterium dentium*, *Dialister invisus*, *Lactobacillus oris*, and *Streptococcus salivarius* were more abundant in patients with schizophrenia than in healthy controls. John R Kelly et al (2016) found limited evidence of Gut Microbiota with Clozapine response. Significantly decreased microbial richness was observed in Schizophrenia patients compared to control. According to them, the findings in this study are consistent with the idea that clozapine induces alterations to gut microbiome composition, although the possibility that preexisting microbiome differences contribute to treatment resistance cannot be ruled out. These findings suggest that prior reports of microbiome alterations in individuals with chronic schizophrenia may be due to medication or lifestyle factors and that future studies should incorporate these variables in their design and interpretation.

Other findings are as follows:

Table 3.

Sl no.	Author	Observation
1	SONJA ORLOVSKA-WAAST et al (2019)	1. Csf serum albumin ratio was increased in SCH 2. Total CSF protein was elevated 3. IgG ratio increased 4. IgG albumin ratio decreased 5.IL6 and IL8 levels increase significantly.

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2	Wiliams et al (2023)	1. In choroid plexus analysis with general linear model demonstrated a significant effect of diagnosis on somal width, demonstrating increased somal width in sz without psychotic medication but not in medicated sz cases. No effects were observed in calcification. 2. The epithelial cells that were examined were attached to the CP fibrous surface, so width expansion describes the primary methods for these cells to expand with adherence to this surface in SZ. The interaction of antipsychotic medication and diagnosis demonstrates that this is an illness-specific change mediated through the DA system with likely neuronal origin. CP alterations were not found in MDD where they are instead generally associated with heightened allostatic load that was unknown in this cohort.

Conclusions:

In this study we have reviewed several papers concerning Schizophrenia and its immunological aspects. The generalized accepted pathogenesis of Schizophrenia includes hyperactivity of dopaminergic neurons and reduced activity of glutamate. All these studies might hint at alternative aspects of viewing this pathogenesis.

The above studies have shown an increased population of *Lactobacillus* in the gut of Scz patients as well as elevated levels of IL-6 and 8. John A Williams et al (2022) in a Mendelian randomization study including 20688 participants in the UK Biobank genetically predicted that the levels of interleukin 6 were associated with grey matter volume and cortical thickness primarily in the middle temporal gyrus and superior frontal region. The middle temporal gyrus over-expressed a number of genes relevant to interleukin 6 pathway proteins and neuropsychiatric disorder ontologies, including schizophrenia and autism spectrum disorder. L.M. Rocha-Ramírez et al (2017) suggested that probiotic *Lactobacillus* could stimulate IL-8 (and 6) production. Moïse Coëffier et al (2001) reported that Glutamine decreased interleukin-8 and interleukin- 6, but not nitric oxide and prostaglandins e(2) production by human gut *in vitro*. Ten fasted volunteers received either enteral glutamine or isonitrogenous amino acids over 6 h in a cross-over design. Series of duodenal biopsies were frozen or cultured for 24 h with 0.5 or 5 mM of glutamine or amino acids. IL-6, IL-8 and PGE(2) were measured in culture media by ELISA and nitrites by Griess assay. mRNA levels for IL-6, IL-8, Cyclooxygenase-2 and NO synthase-2 were assessed in biopsies by RT-PCR. Results were compared by the Wilcoxon test. Glutamine decreased IL-8 and IL-6 in *in vitro* production. IL-8 mRNA level also decreased in biopsies cultured with 5 mM glutamine. Concentrations were not significantly affected by glutamine. Nitrites and PGE(2) concentrations were not significantly affected by glutamine. Again, Parrado et al (2012) showed Dopamine agonists upregulate IL-6 and IL-8 production in human keratinocytes. Cells were stimulated with dopamine and the D(2) dopamine receptor agonist cabergoline. Levels of IL-6 and IL-B in culture supernatants were then determined. Cell proliferation was also assessed. Assays were carried out in the presence or absence of the dopaminergic and B-adrenergic receptor antagonists (sulpiride and propranolol, respectively) and ascorbic acid. Dopamine stimulated the production of IL-6 and IL-8 in a concentration-dependent manner. The effects observed on the secretion of IL-6 (Parrado et al, 2012) were more potent than those corresponding to IL-8 and were reduced by ascorbic acid. The dopamine-induced IL-6 secretion was partially reduced by sulpiride and abrogated by propranolol. The latter drug was able to block the effect of dopamine on the secretion of IL-8. The cabergoline-induced IL-6 release was reduced by sulpiride. Cell viability was not affected by any of the drugs. These studies can indicate that increased dopaminergic activity in Scz is upregulating the formation of IL-6 and IL-8. Reduced Glutamate activity is removing the effect

of the same in keeping IL-6 and 8 under check. These factors can explain the increased levels of these inflammatory substances found in CSF of Scz patients. Ece Yazla et al (2022) showed indicator of Blood blood-brain barrier Damage in Scz patients. That can be taken into consideration as a potential cause of inflammation. Souhel Najjar et al (2017) also studied the hyperpermeability of Blood Brain Barrier in Scz. Pollak et al. (2018) reported that the complex nature of BBB dysfunction in schizophrenia may be related to many aspects of the impaired neuronal and synaptic function, including increased permeability to inflammatory molecules, impaired glutamate homoeostasis, and non-response or resistance to antipsychotics. These can explain why peripheral inflammatory substances migrate centrally in Scz and hence the CSF findings of such inflammatory substances.

Possible future studies:

1. Studying inflammatory changes in neurotic conditions.
2. Variation in symptoms of subjects suffering from Schizophrenia, with administration of drugs that alter the relevant gut microflora.
3. Biomarkers in Schizophrenia: A more precise way of diagnosis .

- Effect of antipsychotics on Gut Microbiome.
- Dietary difference between patients of Schizophrenia and Unaffected Control Group.
- Differences in Guy Microbiota across different psychotic conditions.
- Correlation of social well being with inflammatory conditions: a better understanding of the classical bio-psycho-social model.
- Study of gut microbiome in subjects with Schizophrenia or related disorders with that of family members.
- *Lactobacillus* sp. In conditions of inflammation in CNS.
- Alteration of Blood-Brain Barrier across various psychiatric conditions.

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