

Psychosis and its Association with Autoimmune Disorders: A Review

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ABSTRACT

Psychosis is a psychological disorder that causes an imbalance in social functioning, perception, and thought. Several genetic and environmental factors are in accordance with the progression of psychosis. Schizophrenia, severe depression, and bipolar disorder causes severe mental illness psychosis. Schizophrenia is a multisystem disorder that causes several immune dysfunctions such as abnormal levels of circulating cytokines. Bipolar disorder is associated with immune dysfunctions and increases the rate of inflammatory medical comorbidities, including cardiovascular disease, chronic infections, autoimmune disorders, and metabolic disorders. In psychosis, a single relapse occurs that causes the disability of facial expressions. Emotion processing deficit persists in the acute phase of schizophrenia and the symptomatic recovery. Furthermore, psychosis acts like an autoimmune disease that leads to CNS autoimmune and inflammatory diseases, like grave's diseases, multiple sclerosis, diabetes, systemic lupus erythematosus, autoimmune vasculatures, and sarcoidosis. This review deals with the genetic association in psychosis and the relation between psychosis and autoimmune disorders.

Abbreviations: MHC: Major Histocompatibility Complex; CSF: Cerebrospinal Fluids; TNF: Tumor Necrosis Factor; IL: Interleukin, TGF: Transforming Growth Factor; BP: Bipolar Disorder; BCIS: Beck Cognitive Insight; NNAI: Non-Neurological Autoimmune; SLE: Systemic Lupus Erythematosus; GAD: Glutamic Acid Decarboxylase; GABA: Gamma-Aminobutyric Acid

Introduction

Psychosis is a common disorder that leads to an imbalance in social functioning, perception, and thought. In the worst cases, the disease becomes life-threatening [1]. Schizophrenia is a psychotic illness commonly present in 1% of the population. The disease begins in early adulthood and persists throughout life. The common features are relapse and progression that become serious over time [2,3]. For the treatment, early interference with the medical and psychosocial trends is efficacious but better comprehension of the disease lowers the psychosis onset in schizophrenia [4]. Factors that cause psychosis in schizophrenia and bipolar disorder include:

- 1) Genetic factor,
- 2) Hormone change,
- 3) Change in brain chemicals.

Over the centuries, the relationship between autoimmune disorder and psychosis has been explored. In autoimmune diseases, the tissue damage is mediated by the T cells and antibodies that induce various symptoms. These symptoms affect the different body parts [5]. Recent studies have shown that the excess of co-occurrence causes two disorders to develop, such as schizophrenia

and autoimmune diseases [6,7]. Both of the diseases are heritable and have a close association with each other [8,9]. Both diseases are immune-related to major histocompatibility complex (MHC) [9]. The close association indicates that the schizophrenia involves the immune system and the genetic signals are present on chromosome 6p, where the MHC gene is also located [10]. Moreover, immune alteration in psychosis patients has also been observed. It indicates the elevated level of inflammatory markers in both cerebrospinal fluids (CSF) and blood and active microglia in the brain. These inflammations can cause autoimmunity and are considered as a risk factor for the psychosis [11,12].

Psychosis as an Autoimmune Disease

Autoimmunity has emerged as a potential disease mechanism [13]. It focuses on adaptive immunity against psychosis. The criteria for the autoimmune disease includes 1) the evidence of diseases for particular adaptive immune response in the specific tissues, organs, or blood; 2) the passive transfer of the autoreactive cells and antibodies replicates in human by in-utero maternofetal transfer or transplant procedures and 3) family history of autoimmune disease [14].

The Relationship between Psychosis and Autoimmune Disorder

In psychotic illness, various courses occur. These courses range from the single episode of illness to relapse and cause disability. The degree of overlap varies from time and causes central nervous system infectious disorder like multiple sclerosis [15]. Psychosis is associated with neuropsychiatric or systemic symptoms. The CNS autoimmune and inflammatory disorder leads to multiple sclerosis, systemic lupus erythematosus, autoimmune vasculatures, and sarcoidosis [16-19]. In these disorders, the mechanism of the underlying psychotic symptom remains unknown. However, systemic lupus erythematosus is an exception in which the relation between psychosis and autoantibodies has been described. But these are not proven scientific theories of lupus psychosis [20-23].

Genetic Associations in Schizophrenia

Schizophrenia is a genetic disorder having a heritability estimate of 80% [24]. At an epidemic level, increased chance of autoimmune disorder in psychoses and other psychotic disorders is found. Moreover, people suffering from the autoimmune disorder are at high risk of getting schizophrenia [13,25]. The diagnosis of psychotic disorder is similar to an autoimmune disorder [5]. Rheumatoid arthritis is considered the only autoimmune disease that has a negative association by schizophrenia. Individuals suffering from schizophrenia are at risk greater than 29% to get rheumatoid arthritis [26,27], however, the underlying reasons are not fully understood. A study showed a small robust negative nucleotide polymorphism relation between these disorders [28]. Psychosis shares an environmental risk factor with several other autoimmune diseases like a season of birth latitude effect associated

to the newly born vitamin D status [29].

Abnormal Level of Serum Cytokines in Schizophrenia

Schizophrenia is a multisystem disorder that causes several immune dysfunctions such as abnormal levels of circulating cytokines, mediator of the immune system [30]. The cytokines are connected with behavioral activities. Any change in cytokines causes the potential implications leading to schizophrenia [31]. Serum cytokines influence psychosis in schizophrenia patients [32]. The abnormal level of cytokines is the common manifestation of schizophrenia [33]. The level of cytokines in different SHZ patients have been investigated and the results indicate an increased levels in cytokines such as tumor necrosis factor (TNF)- α , IL-1 β , IL-12, interleukin (IL)-6, and transforming growth factor (TGF)- β [34]. Furthermore, it was observed that symptom severity, aggression, cognitive abilities were linked with an increased level of cytokines [35]. Schizophrenia patients are more prone to sudden cardiac death [36].

Schizophrenia and Bipolar Disorder with Psychosis

In schizophrenia, facial displays of emotions are a well-known impairment [37]. Emotion processing deficit persists in the acute phase of schizophrenia and the symptomatic recovery [38]. The confusion in facial expressions is common in bipolar disorder (BP) [39]. Other neurobehavioral deficits occur in schizophrenia patients with a history of psychosis. The facial deficit becomes prominent in schizophrenia along with other disorders such as bipolar disorder [40]. Various investigations have demonstrated a greater facial deficit in SHZ compared to bipolar patients [41].

Acute Psychosis in Schizophrenia and loss of Sight

The most common effect of schizophrenia is the loss of sight. Insight psychosis causes the multidimensional concept that takes place on a continuum [42,43]. Clinical insight is a common diagnosis and therapy of schizophrenia. However, the concept has few drawbacks. Insight psychosis is linked with dissociation from misinterpretations and reevaluating distorted beliefs [44]. The beck cognitive insight (BCIS) was evolved to investigate the patient's condition [45]. Cognitive insight can be linked to the present symptoms and stage of disease, however, relation between clinical symptoms and cognitive insight is still unknown [46]. A recent study have demonstrated a mild relation between the negative, positive, and self-certainty scale of BCIS patients [47]. Several investigations on understanding the relationship between the cognitive insight in schizophrenia's patients with or without psychotic symptoms have been made. Moreover, the relation between acute symptoms and alteration in cognitive insight was also studied. Results showed that patients having current psychotic symptoms show careless in their perception and were damaged in self-reflectiveness which was decreased in the treatment. No effect was observed on the over-confidence after the symptomatic improvement. The over-confidence with misinterpretations is a more continues feature

which expands beyond psychoactive states in a schizophrenia patient. The patient having no psychotic symptoms showed more self-reflectiveness than a patient having psychotic symptoms [48]. An individual with schizophrenia has overconfidence in their judgment than depressed patients, and delusions patients show high self-certainty [49,50]. Schizophrenia patients decide without any information and are overconfident in their decisions. Overconfidence can be influenced by personality. With better self-esteem and copying styles, the poor insight can be improved. Overconfidence is the common manifestation in delusion-prone schizophrenia individuals rather than acute psychosis [48,51-53].

Psychosis and its Association with Non-Neurological Autoimmune Disorders

The relation between psychosis and non-neurological autoimmune (NNAI) diseases has remained under investigation over the past few decades [54]. In 1950s, rheumatoid arthritis was less prevalent in general population [55,56], however, a non-neurological disorder such as systemic lupus erythematosus (SLE), celiac disease, and autoimmune thyroid diseases were more widespread in psychosis patients [57]. The existence of autoimmune disorder poses a high risk of schizophrenia by ~ 1.29 folds. On the contrary, autoimmune disorder was observed to grow by 1.53 folds as a result of schizophrenia [58]. Schizophrenia and autoimmune disorder cause the enhanced activity of complement system [59]. Multiple factors are involved in the association between the NNAI disorder and psychosis. These factors include infection, predisposing infections, shared genetic exposure, and the brain reactive antibodies [25,60]. In psychosis, the level of different inflammatory markers such as C-reactive proteins and cytokines increases. Furthermore, it also causes the increase of pro-inflammatory cells, such as T helper 17 cells [13,61]. A study showed a positive association between schizophrenia and autoimmune disorders. Furthermore, the overall relationship between the NNAI disorders and psychosis has been monitored by using meta-analytic techniques. The result indicated that NNAI disorders causes the psychiatric manifestation of the neurological auto-immune diseases. Moreover, the primary investigation showed the effect size acquired from the different studies. The overall consequence size was small and heterogeneity was determined indicating the positive relation between the designs of study and outcomes of psychosis. The study was performed separately for the NNAI resulted a positive association for different disorders like Graves' disease pemphigoid, psoriasis, celiac disease, and anemia. The negative association between the rheumatoid arthritis and ankylosing spondylitis was detected [62,63].

Psychosis and its Association with Autoimmune Disorders

The prevalence of autoimmune disease in the general population is about 4% while the prevalence of schizophrenia is around 1%

[64]. In a hospital survey, it was seen that 3.4% population with autoimmune disorders had contact with schizophrenia during their follow-up period [65]. Furthermore, an increase of 70% in bipolar disorder was detected during the 5 years after exposure to autoimmune disorder and prognosis [25]. Schizophrenia has a positive association with different autoimmune diseases such as celiac disease, pernicious anemia, grave disease, psoriasis, hypersensitivity vasculitis, and the negative relationship with the rheumatoid arthritis [27].

Psychosis and its Associations with Celiac Disease

Investigations at clinical level have found the abundance of celiac disease in 2.1-2.6% of patients having schizophrenia as compared to 0.3% to 1% population [66]. The intake of gluten causes production of transglutaminase and antigliadin antibodies by the immune system [67]. In the presence and absence of autoimmune diseases, a wide variety of neurological issues is linked with gliadin [68,69]. A recent finding indicated the presence of self-antigen tissue transglutaminase that is characteristic of celiac disease. In 1950s and 1960s, a close association between celiac diseases and schizophrenia was observed [70,71]. The epidemiologic studies indicated the increased occurrence of celiac disease in patients of schizophrenia. A study represented the amplified prevalence of schizophrenia in population who consumed more grains. Thus, the whole study concluded the valuable outcome of a gluten-free diet in the symptoms of schizophrenia having celiac disease and gluten sensitivity [72-74].

Psychosis and its Association with Rheumatoid Arthritis

Several studies showed the negative association of rheumatoid arthritis with psychosis. The disease onset for rheumatoid arthritis is less as compared to schizophrenia and bipolar disorder [75]. The incidence of rheumatoid arthritis lowers/raises the risk of bipolar disorder and schizophrenia [76,77]. Several autoimmune diseases are associated with rheumatoid arthritis that occurs due to genetic influences. Several markers in the major histocompatibility complex region are involved with psychiatric disorders [5]. A study indicated the role of interleukin 1 antagonist that causes the elevation in schizophrenia but is protective against rheumatoid arthritis [77]. In the negative association, anti-inflammatory and analgesic effect is involved. Furthermore, bipolar disorder has no association with rheumatoid arthritis [78,79]. However, the increased incidence was seen within 5 years of prognosis of rheumatoid arthritis [80].

Psychosis and its Association with Autoimmune Disorders of Thyroid Glands

Auto-immune thyrotoxicosis (Graves' disease) and autoimmune thyroiditis have an association and increases the risk of schizophrenia in the general population [27]. Furthermore, autoimmune thyroid disease has psychiatric symptoms associated with anti-thyroid antibodies [81]. In a study, positive family history

was detected between thyroiditis and autoimmune thyrotoxicosis with schizophrenia [27,82].

Psychosis and its Association with Diabetes

In diabetes type-I, the autoantibody against glutamic acid decarboxylase (GAD) causes the affinity towards GAD that is expressed in the brain [83]. GAD is complicated in development of gamma-aminobutyric acid (GABA) (a central neurotransmitter) [79,84]. GAD antibodies are linked with neurological disorders, include stiff-person syndrome. According to the survey, the occurrence of diabetes type-I is enhanced in patients of schizophrenia prior to diagnosis and later. Three different studies recommended the positive family history among diabetes type-I and schizophrenia [25].

Psychosis and its Association with Systemic Lupus Erythematosus

Almost 40% of neuropsychiatric systemic lupus erythematosus (SLE) indications developed before the SLE onset or at diagnosis time. Moreover, about 60% of manifestations occur in the 1st year of diagnosis. Current evidence showed that 14% and 75% of SLE experience symptoms of neuropsychiatry include psychosis. Brain reactive antibodies have a defined role in developing neuropsychiatric symptoms. These antibodies have an affinity towards the anti-N-methyl-D-aspartate glutamate receptor within brain and are known to be the current pathophysiological theories of psychosis. In another study, it was confirmed that SLE patients have also increased association with non-effective psychosis [13,85].

Psychosis and its Association with Multiple Sclerosis

Multiple sclerosis causes the large-scale infiltration of the immune system cells in the brain parenchyma and activate the resident inflammatory nerve damage. It is linked with the high risk of schizophrenia, bipolar disorder, and non-effective psychosis. Furthermore, the family history between the multiple sclerosis and schizophrenia with non-effective psychosis was detected [86-89].

Conclusion

Psychosis is a serious mental illness that causes the hallucination and delusions. Furthermore, it also leads to personality change. It occurs in three phases such as prodromal phase, acute phase, and recovery phase. There is a positive relationship between several auto-immune disorders and antibodies with schizophrenia. The relationship of numerous auto-immune disorders observed in the accumulation with psychosis, together with positive relationship of auto-immune thyrotoxicosis, pernicious anemia, and psoriasis, and the negative relationship with the rheumatoid arthritis. Moreover, a close association of family history and genetic factors contributes to the development of psychosis. We have highlighted genetic association of several autoimmune diseases has been explained with schizophrenia in more details in reference to abnormal level

of serum cytokines. It is therefore concluded that for the treatment of psychotic patients, medications and therapies are possible that offer their overall recovery.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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