Decoding Schizophrenia: Understanding Key Risk Factors and Insightful Approaches to Prevention

Tingzhi Wang

Troy High School, Fullerton, CA, United States
Email: cindyxinxinwangtzx@gmail.com

***Abstract*—Schizophrenia may result in a mix of hallucinations, delusions, and disorganized thinking and behavior, and it currently affects approximately 1 in 222 people worldwide. While the exact cause of schizophrenia is unknown, certain people exposed to genetic factors, drug abuse, and environmental factors are more at risk. For example, the chances of getting schizophrenia are higher if a close relative has received it and if you have been a heavy user of drugs, such as cannabis. There is no current cure for schizophrenia, but close surveillance and antipsychotic medications may act as preventive measures. I will investigate how the disease manifests through causes, risk factors, and neurotransmitter expression. Finally, I will give future perspectives on how it may be prevented.**

***Keywords*—schizophrenia, neurotransmitter, dopamine, symptoms, genetic**

I. Introduction

Schizophrenia is a mental disorder that causes delusion, mental unclarity, and hindered thoughts and actions [1]. Those who possess the disorder may lose touch with reality and see or hear nonexistent voices, thus categorizing it as a psychotic disorder [2, 3]. Schizophrenia affects 1 in 222 adults worldwide, with an alarmingly high suicide rate among patients [4]. The condition is also a common cause of disability. People with schizophrenia are often unable to navigate their daily lives and interpersonal relationships normally. Despite the medical necessity surrounding schizophrenia, its causes and cures are still unknown. While numerous hypotheses and models have been proposed, they have yet to be broadly accepted by the community. Here, I will discuss some of these potential causes and risk factors while also touching on symptoms and future outlooks in schizophrenia diagnosis and management.

II. Causes and Risk Factors

While the current causes and direct risk factors of schizophrenia are unknown, there are several hypotheses on factors leading to the disorder. Additionally, it is important to remember causation vs. correlation. Some risks might be the causation of the disorder, meaning they directly affect the possibility of getting schizophrenia. However, other risks might only be correlated to schizophrenia, where they're closely related, but they don't necessarily cause the disorder.

A. Genetics

Those with a family history of schizophrenia are more perceptive to developing the disorder. Scientists have found a correlation between genetics and the risk of developing schizophrenia [5].

The "Common Disease-Common Variant" (CD-CV) hypothesis states that for a disease to manifest, the entirety of common disease-causing variants must be present for a disease to manifest. Although the variants might be commonly found, the combination that causes the disease is rare. For CD-CV, global consortiums were created to obtain large amounts of data and establish statistical significance. One of the main findings of the consortium's data collection was a mutation in the Major Histocompatibility Complex (MHC) in chromosome 6 [6]. MHC is typically associated with fighting infections during the perinatal phase.

The "Common Disease-Rare Variant" (CD-RV) hypothesis states that for a disease to manifest, only the rare variant has to exist. However, the variant is unlikely to be found in a population. One example of this hypothesis is shown in a study by Blackwood *et al*. [7]. In this study, the translocation of chromosome 1 and chromosome 11 caused a disruption in a gene, which is in turn named *disrupted-in-schizophrenia-1* (DISC1), causing schizophrenia. DISC1 is an important protein in brain development and regulating synaptic composition.

Research has shown that both models have flaws when used to explain schizophrenia. In CD-CV, the study requires consenting schizophrenia patients and relatives to collect their genome sequence. However, this is difficult to find; thus, the lack of diversity in data can lead to false findings.

CD-RV's flaw is due to the laws of natural selection. In natural selection, the unbeneficial traits are not selected to be inherited since they do not aid the species' survival. Therefore, the rare variant that causes schizophrenia

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would be negatively selected. This contradicts the statement that schizophrenia is a genetic disorder.

In recent studies, researchers have found that both CD-CV and CD-RV seem to contribute to schizophrenia. For example, researchers found protein truncation inhibition was found to be common amongst cohorts of genome-wide sequencing data, alluding to a possible combination of common variants and rare variants [8]. Typically, proteins found in the body undergo a process of folding and regulation. However, when protein misfolding occurs, proteins become tagged for degradation to maintain homeostasis. In schizophrenia models, this protein degradation is inhibited, leading to an accumulation of misfolded proteins, potentially pointing to a cause for the disease.

Recent advancements in Genome-Wide Association Studies (GWAS) have also shed new light on how both common and rare genetic variants might jointly contribute to schizophrenia. For instance, researchers have identified specific loci in the human genome that are implicated in neural development, suggesting a multifactorial genetic architecture [9]. Despite this, the controversy remains about the precise weight of rare versus common variants in schizophrenia risk. While some studies suggest that rare, de novo mutations may play a larger role in certain cases [10], others argue that common variants, due to their population-wide occurrence, should not be underestimated [11].

B. Drugs & Neurotransmitters

Drugs, specifically cannabis, cocaine, LSD, or amphetamines, are suspected to increase the likelihood of developing schizophrenia or to cause a relapse after recovery due to increased levels of neurotransmitter production. Many scientists have noted that excessive neurotransmitter dopamine levels could be a possible root cause.

It can be summarized that, to date, the mechanism of every effective antipsychotic medication in schizophrenia involves dopamine and its interaction with other neurochemical pathways, such as those of glutamate, GABA, serotonin, and acetylcholine [12].

However, it must be noted that there still exist flaws in the dopamine hypothesis. Simple changes in sleep and eating patterns will also affect neurotransmitter production, and most of the research is done on rodents, not people. This makes the hypothesis harder to confirm as true.

Drug use is correlated with an increased risk of schizophrenia. For example, using cannabis before symptoms have occurred causes them to appear earlier: heavy users were four times as likely, while regular users were two times as likely to develop psychosis. Not only does cannabis have an association with schizophrenia, but so does cocaine, nicotine, and alcohol.

Patients are more likely to use substances if they have schizophrenia. As data stated, those with psychotic disorders use drugs more frequently than the average human being [12]. This could be due to the fact that the disorder causes a dysfunction in the reward circuit, disrupting neurotransmitters that regulate dopamine. Patients seek to satisfy their hypersensitive dopamine system, thus making them more susceptible to substance abuse.

Overactive dopamine neurotransmitters are associated with causing the positive symptoms of schizophrenia. Drastic changes in dopamine have been observed in the prefrontal cortex of schizophrenia patients, and the hippocampus appears to be overactive [13, 14]. However, neurotransmitters additional to dopamine are involved in the causation of schizophrenia.

For example, deviations in glutamate caused by N-methyl-D-aspartate receptors in the prefrontal cortex and hippocampus contribute to the negative symptoms of schizophrenia. Excessive levels of glutamate also cause excitotoxic neuronal death [15]. Furthermore, abnormal amounts of serotonin are associated with both positive and negative symptoms.

C. Birth Factors

Mothers aged above 30 are more likely than any other age range to birth children with schizophrenia. Multiparity—having two or more children at birth—and children born in small sizes also reflected risks. Maternal bleeding during birth and birth in late winter seemed to impact the likelihood of schizophrenia [16].

D. Childhood

Having childhood trauma or motor impairments, living in urban or densely populated areas, and having minority status are all described as risks of schizophrenia [17].

III. Symptoms of Schizophrenia

Schizophrenia symptoms look different for everyone, and as time progresses, symptoms will change. During schizophrenia, patients experience both positive and negative symptoms. Positive symptoms are defined as the emergence of new functions that add to someone's normal functions, such as delusions or hallucinations. Negative symptoms are defined as the loss of normal functions, such as when patients isolate themselves from their connections.

A. Positive Symptoms

(1) Delusions

Patients might strongly believe they're being threatened and cannot distinguish between fictional and the non-fiction world. They might also experience an impending sense of doom that a major disaster is about to occur when there is no evidence to indicate so.

(2) Hallucinations

Most hallucinations involve hearing voices that others do not observe, but they can also impact one's sight, smell, and taste. Hallucinations make it difficult for patients to separate real events from fake.

(3) Disorganized motor behavior

The symptom makes it difficult for the patient to form coherent thoughts or sentences. Their behavior could be erratic or bizarre, acting inappropriately for their social situation. It may also result in childlike behaviors or being upset for irrational reasons.

B. Negative Symptoms

Individuals might be less inclined to tend to their hygiene and lose their will or motivation. They might also become distant from social settings and lack emotions. In general, they will lose interest and the ability to perform certain behaviors.

In Fig. 1, it can be seen that negative symptoms are more severe in a patient's life for most instances, except during the phases of first-episode psychosis and relapse, where positive symptoms are more prominent [18].

Altered synaptogenesis can result in different formations of synapses, and altered synaptic pruning involves the process of stopping synapse growth. Failure in both can impact the amount of neurotransmitters signaled and gray matter loss. Gray matter loss, which means losing neurons, is irreversible and can lead to severe brain impairment.

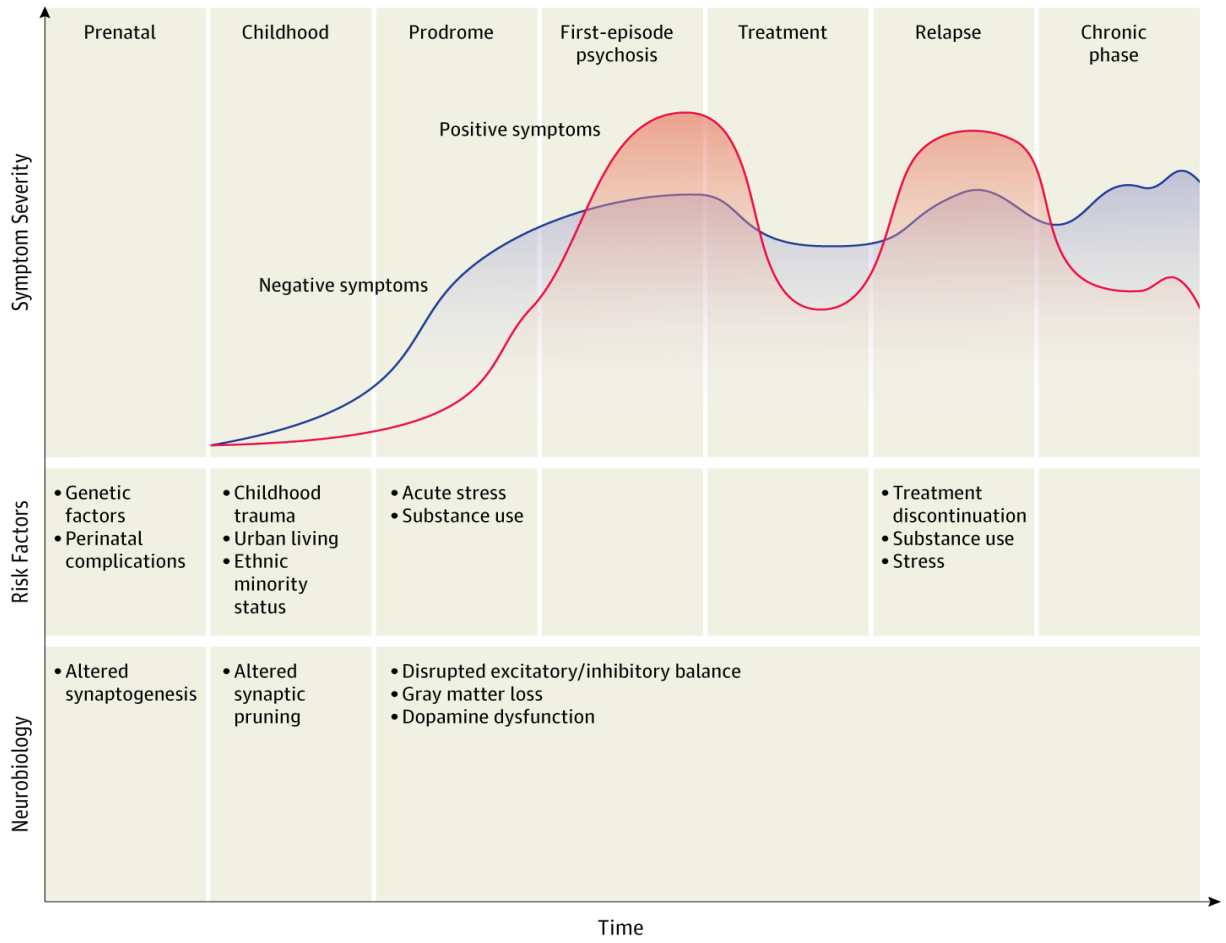

Fig. 1. The timeline of schizophrenia symptoms. Timeline shows the development of positive and negative symptoms from prenatal (before birth), childhood, prodrome (early symptoms of disorder), first-episode psychosis, treatment, relapse, to chronic phase. Adapted from McCutcheon *et al.* [19].

IV. Potential Preventative Measures

Schizophrenia, a genetic disorder, puts individuals with schizophrenic relatives at high risk for the disorder, as well. These individuals should be monitored closely for early symptoms to provide a solution as quickly as possible. Since maternal bleeding is a risk factor, mothers with a family history of schizophrenia should ensure proper maternal care. Intaking oxytocin and iron will provide adequate nutrition and help prevent maternal hemorrhage [19]. An innovative preventive strategy might involve the use of artificial intelligence to predict schizophrenia risk by analyzing an individual's genetic data and environmental history.

Patients who are already diagnosed with schizophrenia should be provided with a proper support network to prevent withdrawal and social distancing. We can use digital health tools, such as telemedicine platforms and mental health apps, to provide real-time support for individuals showing early symptoms. Furthermore, we know that patients are more likely to use drugs if they have schizophrenia. Thus, they should be placed in research-based programs that prevent drug abuse. Lastly, medications that prevent excessive dopamine and antipsychotic drugs, such as Clozaril, Risperdal, Sulpride, and Zyprexa can aid the treatment process [20, 21]. Personalized medicine, where treatment is tailored based on one's genetic and neurotransmitter profile, could further optimize outcomes and reduce the burden of this disorder.

Finally, psychotherapy and cognitive behavioral therapy can both help the patient identify troubling behaviors and manage psychotic symptoms [22, 23].

V. Conclusion

Schizophrenia remains a complex mental disorder with both genetic and environmental influences contributing to its manifestation. While genetic factors, such as familial history and certain chromosomal variations, play a significant role, environmental triggers, like drug abuse and birth complications, also heighten the risk. The interplay of neurotransmitters, particularly dopamine, further complicates the disorder's pathology, influencing both the positive and negative symptoms experienced by patients. Although the exact causes of schizophrenia are not fully understood, advances in genetic research, neurotransmitter studies, and drug therapies offer hope for more targeted treatments.

Preventive strategies are crucial, especially for individuals with a genetic predisposition. Early monitoring, drug abuse prevention, and ensuring proper maternal care can reduce the likelihood of developing the disorder. Psychotherapeutic interventions, along with antipsychotic medications, provide a lifeline for those already diagnosed, helping to manage symptoms and improve their quality of life. As research continues to evolve, integrating both genetic and environmental insights may lead to more effective interventions, offering hope for better outcomes and possibly reducing the prevalence of this debilitating disorder in the future.

Conflict of Interest

The author declares no conflict of interest.

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