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Review

Neurobiology of Schizophrenia

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Abstract

Schizophrenia is a complex neurological disorder characterized by continuous or relapsing episodes of psychosis that profoundly affect an individual's thoughts, emotions, and behaviors. This review looks at the epidemiology, etiology, pathophysiology, clinical symptoms, and diagnosis of schizophrenia. Epidemiologically, it affects millions globally, with onset typically in late adolescence or early adulthood, and it carries a higher risk of premature mortality. Etiologically, schizophrenia involves anomalies in brain structure and neurotransmitter activity, with a neurodevelopmental model suggesting in utero abnormalities and genetic susceptibility. The pathogenesis is associated with abnormalities in dopamine, serotonin, and glutamate systems. Positive signs of schizophrenia include hallucinations and delusions, as well as negative symptoms such as social disengagement and cognitive deficiencies. Diagnosis relies on specific criteria involving symptom duration, social/occupational dysfunction, and exclusion of other causes. Understanding these aspects is crucial for early diagnosis and effective management of this debilitating disorder.

Keywords: Schizophrenia, Psychosis, Hallucination, Positive symptoms, Dopamine hypothesis, cognitive deficiency.

INTRODUCTION

Schizophrenia is a severe complicated neurological condition characterized by recurrent or continuous episodes of psychosis that impair how a person thinks, feels, and interacts with others. Schizophrenia may appear to be disconnected from reality and may include hallucinations and delusions. It also affects your ability to recognize. It is a serious condition but is treatable. Social isolation, diminished emotional expressiveness, and indifference are among their symptoms. Symptoms often appear gradually during young adulthood and, in many cases, do not disappear. [1,2].

Epidemiology

Schizophrenia affects around 24 million individuals worldwide, or one in every 300 people (0.32%). This occurs in 1 in 222 adults (0.4%). The most typical ages for onset are late teens and early twenties, and males often experience onset sooner than females. Symptoms are more common in men in their late teens or early twenties. Women's symptoms are most likely to appear in their early to mid-thirties. Schizophrenia patients are two to three times more likely than the normal population to die early.[3–5].

Etiology

Numerous studies have shown that schizophrenia has anomalies in the way the brain's structure and functions even if the cause is unknown[6]. Abnormalities in several neurotransmitters, such as glutaminergic and GABA hypoactivity or dopaminergic, serotonergic, and alpha-adrenergic hyperactivity, have been linked to the development of schizophrenia, according to several studies. Schizophrenia is most likely caused by a combination of factors.[1,6–9].

Neurodevelopmental Model

Schizophrenia develops from an unidentified in utero abnormality. The second trimester of pregnancy is when it generally happens. The aberrant neuronal migration found in the majority of brain investigations on schizophrenia serves as proof. This "schizophrenic lesion" may cause anomalies in cell location, symmetry, connectivity, form, and size, as well as the emergence of dysfunctional brain circuits[6,10]. Studies link upper respiratory infections with a greater risk of schizophrenia, and the alterations correspond to cell migration during the second trimester[1,11].

Other studies demonstrate a connection between schizophrenia and obstetric difficulties or new-born hypoxia. Additionally, several research link low birth weight (2500 g)[7]. Psychosis doesn't show clinical signs until adolescence or early adulthood because this is when neural growth takes place. The fact that, while studies have found lower cortical thickness and increased ventricular size in the brains of many people with schizophrenia, this happens in the absence of extensive gliosis lends more credence to a developmental hypothesis.[6,12–14].

It is believed that gliosis, or the expansion of glial cells, occurs as a result of a compensatory shift in degenerative brain diseases. One theory is that genetic susceptibility, along with obstetric difficulties and hypoxia, might trigger a glutamatergic cascade, leading to greater neuronal pruning. This hereditary propensity may be linked to the genes that regulate the N-methyl D-aspartate (NMDA) receptor activation, according to a theory. Dendrite pruning happens as part of the typical neurodevelopmental process[8,15,16].

In a typical person, by the middle of puberty, roughly 35% of the dendrites that peaked at 2 years old are trimmed. A larger percentage of pruning has been seen in people with schizophrenia, according to certain research. Additionally, glutamatergic dendrites are primarily involved in synaptic pruning. There may be fewer basal neurons to start with due to hypoxia or other prenatal insults, and glutamatergic stimulation may speed up the pruning process. This is consistent with research suggesting that prenatal hypoxia is linked to schizophrenia developing earlier in life. Others have proposed that alterations in the metabolism of membrane phospholipids may trigger a chain of events that manifest as schizophrenia[8,17,18].

Numerous studies have revealed that those who subsequently develop schizophrenia exhibit cognitive impairments as young as 4 years old[1,7]. Schizophrenia has been linked to delays in achieving typical motor milestones and aberrant motions in infants as early as 8 months old. These findings give empiric evidence that schizophrenia is a neurodevelopmental condition and that impairments in brain function occur long before the beginning of psychotic symptoms[19,20]. It also accompanies with the Tardive dyskinesia due to dopamine receptor blockade, also caused by use of antipsychotics also[21–23]. However, the continuous clinical deterioration in some people suggests that this disorder may have a neurodegenerative component. This is consistent with current brain imaging studies, which shows that persons with chronic diseases typified by relapses have worsening brain abnormalities[19,24,25]. Because of this, our discipline has begun to rethink schizophrenia as having a neurodegenerative tendency based on a susceptible neurodevelopmental substrate rather than schizophrenia having a neurodevelopmental or neurodegenerative genesis. This idea has important ramifications for the early diagnosis and management of this crippling illness[26–28].

Genetical

The complicated method of inheritance for schizophrenia includes a number of genes, biological functions, and environmental influences. Genetic factors have a significant impact. It is yet unclear how numerous genes, as well as specific DNA and protein alterations, contribute to the aetiology of schizophrenia. Specific DNA variations and the role that different risk alleles play in the illness have been demonstrated in recent large-scale genomic investigations. Schizophrenia, according to genetic studies, includes hundreds or maybe thousands of distinct genetic loci, making it a highly polygenic condition. GWAS have discovered more than 100 distinct genetic loci with common alleles that have a variety of effects.[29,30].

There are shared risk variants between schizophrenia and bipolar disorder, major depressive disorder, and an autism spectrum disorder, demonstrating that the disease's genetic risk is very pleiotropic[31]. Another

genomic analysis shows that genes encode a variety of synaptic proteins, including members of the voltage-gated calcium channel family and postsynaptic density (PSD) proteins. It also has an impact on genes that encode glutamate receptors and dopamine receptor D2 (DRD2)[29].

The major histocompatibility complex (MHC) has numerous linked variations, which is a notable result from the GWAS of schizophrenia. MHC class I molecules control the creation of synapses, neurite outgrowth, and homeostatic plasticity, among other aspects of brain development. The results of GWAS studies enable us to pinpoint potential genes for individualised therapy and further investigation into the immunological systems underlying schizophrenia. So, it's uncertain how much genetics will be used to treat schizophrenia[32,33].

An alternate method for examining phenotypic diversity in the search for the genes causing schizophrenia is called "endophenotype." The pathogenesis of schizophrenia involves a significant amount of CNS activity. These include alterations to the temporal lobe, which is in charge of language comprehension, auditory perception, and episodic memory, as well as changes to the frontal lobe, which is in charge of memory and executive functions. There are several putative genetic loci that predispose to these neurological abnormalities in schizophrenia[34,35].

COMT, DISC1, RGS4, PPP3CC, ZDHHC8, AKT1, neuregulin, dysbindin, G72/G30, TRAR4, and alpha-7 nicotinic receptor genes have all been connected in promising research. These genes influence dopamine regulation, which contributes to the underlying causes of schizophrenia. Although the actual mechanism behind these genetic associations is unknown, two of these genes, dystrobrevin binding protein 1 (DTNBP1) and neuregulin 1 (NRG1), exhibit the strongest evidence of linkage. DTNBP1 and NRG1 are both expressed at CNS synapses and have an influence on glutamate neurotransmission associated to schizophrenia[36].

Despite the fact that 0.6% to 1.9% of people in the general population are at risk of having schizophrenia, this risk rises to 10% in first-degree relatives and to 3% in second-degree relatives. The likelihood of having schizophrenic kids increases to about 40% if both parents have the disorder. According to twin studies with dizygotic twins, there is a 12% to 14% chance that the other twin will also develop schizophrenia if the first twin does. However, the risk rises to 48% in monozygotic twins[37]. Numerous research on adoption have shown that the biological parents carry the majority of the risk for schizophrenia, and that changes in the child's environment during developmental stages do not affect this. Siblings with schizophrenia often experience the start of the illness at the same age, reducing the likelihood of an environmental trigger[7,37,38].

It has been challenging to identify a genetic connection in schizophrenia, and any genetic causes are probably varied yet show comparable manifestations. There are potential loci found on chromosomes 6, 8, 13, and 22[37]. The focus of research on the genetics of schizophrenia has shifted more and more towards molecular mechanisms, going beyond conventional family and twin association studies[6,37].Recent research has demonstrated that variability in the catecholamine-o methyl transferase gene's VAL/MET alleles may account for part of the frontal lobe functional abnormalities in schizophrenia patients. Several genes that code for neurodevelopment and trophic factors have been shown to have anomalies, according to other recent investigations[37,39–41].

Pathogenesis

Brain Structural Changes

The Computer Axial Tomography and Magnetic Resonance Imaging shown that there was increase in third and lateral ventricles size. Recent studies shows a decrease in size of brain with decrease in corticol and increase un ventricular size in left temporal zone along with changes in hippocampal volume, shows an impairment in neurological testing where first generation anti psychotics don’t produce enough action. There will be no decrease in number of neurons in affected region but will be a lack of connection between axonal, dendritic communication[6,11,24,37,42].

The clinical state that we refer to as schizophrenia certainly has several etiologies since it is a complicated illness. It is unwise to believe that any etiology now being considered can fully explain the origins of this complicated disease considering the facts we currently possess. It is possible to detect the biological problems connected to schizophrenia through molecular studies including genetically determined subtle alterations in G proteins, protein metabolism, and other subcellular processes. Based on that, 3 hypotheses were familiar. They are Dopamine hypothesis, Serotonin hypothesis and Glutaminergic hypothesis[6,19,42].

Schizophrenia can include secondary abnormalities in various neurotransmitters, with modifications in the dopaminergic, glutamatergic, or serotonergic systems constituting the major pathophysiologic aberration. Examples of primary defects that might cause postsynaptic DA receptor hypersensitivity include aberrant presynaptic release of dopamine from the cell and inadequate feedback mechanisms. Another strategy that can result in dysregulation across neurotransmitter systems is the NMDA hypofunction concept[6,7,19,42,43].

The Tracts(Dopaminergic Tracts) in Brain

The Nigrostriatal tract begins in the Substantia nigra (A9 region), innervates the Caudate nucleus Putamen, and performs extrapyramidal system and movement tasks. The Mesolimbic tract arises from the ventral tegmentum of the midbrain (A10) and innervates Limbic regions (e.g., amygdala, olfactory tubercle, septal nuclei), the cingulate gyrus, and performs activities such as arousal, memory, stimuli processing, and motivational behaviour. The Mesocortical tract arises from the ventral tegmentum of the midbrain (A10) and innervates the

frontal and prefrontal lobe cortex, performing duties such as cognition, communication, social function, and stress response. The hypothalamic tuberoinfundibular tract innervates the pituitary gland and performs activities such as regulating prolactin secretion[19,44].

Dopamine Hypothesis

Growing evidence suggests the existence of a defect in dopamine (DA) receptors in individuals with schizophrenia. Several investigations using positron emission tomography (PET) have found abnormalities in various areas of the brain. Among these are increased glucose metabolism in the caudate nucleus, decreased blood flow, and decreased glucose metabolism in the frontal and left temporal lobes. These findings point to increased dopaminergic activity in the caudate nucleus's head and decreased dopaminergic function in the frontotemporal regions[6,7].

PET studies using D2-specific ligands have revealed an increase in D2 receptor density in the head of the caudate nucleus and a reduction in density in the prefrontal cortex. This hypofrontality might be linked to a lack of will, which is one of the main negative symptoms noticed in people with schizophrenia. It's important to highlight that it's unclear if these alterations are the fundamental cause or secondary to other physiological anomalies in schizophrenia[6,7].

Given the variety of clinical manifestations of schizophrenia, some researchers have proposed that the DA theory may be more applicable to a subgroup of patients dubbed "neuroleptic-responsive psychosis," with many etiological variables likely contributing to schizophrenia[45]. Attempts have been attempted to establish links between these aberrant results and the behavioural symptoms seen by those suffering from schizophrenia. Positive symptoms tend to be more strongly connected with DA-receptor hyperactivity in the mesocaudate, whereas negative symptoms appear to be more strongly associated with DA-receptor hypofunction in the prefrontal cortex[26,42,45].

Furthermore, presynaptic D1 receptors in the prefrontal cortex are thought to have a role in controlling glutamatergic activity, which might be important in understanding working memory problems in people with schizophrenia[42].

Serotonin Hypothesis

Serotoninergic receptors are found on dopaminergic axons, and when these receptors are stimulated, it's known to reduce the release of dopamine (DA), particularly in the striatum[19,44]. Although the distribution of serotonergic neurons is somewhat more widespread, It is comparable to dopaminergic neurons in that both neurotransmitter systems innervate overlapping brain areas. Serotonin2 (5-hydroxytryptamine2 or 5-HT2) receptors and D4 receptors have been discovered in the same locations of the brain, indicating possible connections between the two systems[6,19,46].

In individuals with schizophrenia who exhibit abnormal brain scans, there is evidence of higher concentrations of serotonin (5-HT) in their whole blood, and these concentrations have been associated with increased ventricular size, a common finding in such patients. Interestingly, atypical antipsychotic medications that have potent 5-HT2 receptor antagonist effects have been shown to reverse the worsening of symptoms induced by 5-HT agonists in individuals with schizophrenia. This suggests that modulating the serotonin system, particularly the 5-HT2 receptors, can have a beneficial impact on the symptoms of this psychiatric disorder[43,47,48].

Additionally, it's important to highlight that the interaction between the serotonin and dopamine systems in schizophrenia is an area of active research. Understanding these interactions could potentially lead to the development of more effective treatments for the disorder[6,19,42,43].

Glutamine Hypothesis

The glutamatergic system is one of the most common excitatory neurotransmitter networks in the brain. Any variations in its operation, whether in the form of decreased activity (hypoactivity) or increased activity (hyperactivity), might cause detrimental effects in neurons[6,7,42,49].

Dopaminergic nerve pathways originating from the ventral striatum have the effect of diminishing the inhibitory activity of the limbic system, possibly through the involvement of γ-aminobutyric acid (GABA) interneurons. Consequently, stimulation of the dopaminergic system results in heightened arousal. In contrast, the corticostriatal glutamate pathways limit dopaminergic activity originating in the ventral striatum. Because of this inhibition, the limbic system might demonstrate enhanced inhibitory activity. Furthermore, descending glutamatergic pathways interact with dopaminergic tracts both directly and indirectly via GABA interneurons[42,50].

Notably, deficiencies in the glutamatergic system can produce symptoms akin to those stemming from excessive dopaminergic activity, and possibly those observed in individuals with schizophrenia.[50] The finding that phencyclidine, a strong psychotomimetic drug, acts as a non-competitive antagonist at the NMDA receptor, a prominent glutamate receptor, lends weight to this notion. It is hypothesised that schizophrenia is caused by an unexplained prenatal trauma that causes a developmental deficit in NMDA receptor activity, known as NMDA hypofunction. This issue is expected to be clinically inactive, with cognitive impairments associated with NMDA hypofunction appearing only in late adolescence or early adulthood[42,51,52].

Furthermore, studies show that overstimulating D2 receptors might impair NMDA transmission across GABAergic neurons. As a result, antipsychotic drugs have the potential to increase glutamatergic transmission[42,53,54].

Clinical manifestation

Schizophrenia is a common functional psychosis but not mean split personality, have a significant disturbance in interpersonal relationships and ability to function in society daily. During acute psychotic episodes, individuals with schizophrenia experience a profound detachment from reality. In a way, their minds construct a false reality to replace the actual one. This results in a range of acute psychotic symptoms, including hallucinations, with auditory hallucinations especially hearing voices being a common manifestation. Delusions, which are fixed false beliefs, and ideas of influence, where patients believe external forces control their actions, are also prevalent. Thought processes become fragmented, leading to disjointed thinking (loose associations), making it challenging to engage in logical conversations (alogia). Simultaneously, contradictory thoughts may arise (ambivalence)[1,50,55,56].

Emotional expression, can be noticeably flat (displaying no emotional expression) or inappropriate and unstable. Patients often withdraw from social interactions and become introverted (autism). Due to their distorted perception of reality, they might exhibit uncooperativeness, hostility, and even verbal or physical aggression. Self-care abilities decline, resulting in poor personal hygiene. Sleep patterns and appetite are frequently disrupted during these episodes[1,50,57,58].

When the acute psychotic episode subsides, residual symptoms typically persist, setting schizophrenia apart from other psychotic disorders. These lingering symptoms can manifest as difficulties in managing anxiety, heightened suspiciousness, and a lack of volition, motivation, insight, and judgment. Consequently, individuals with schizophrenia often struggle to live independently within the community. Their social withdrawal, coupled with impaired self-care skills, makes it challenging for them to maintain employment and form close relationships[1,17,50,59,60].

Furthermore, people suffering from schizophrenia frequently lack historical perspective, making it harder for them to learn from prior experiences. They may make the same social blunders again and over again, failing to recognise the need of therapy, including medication, in preserving their capacity to function in society. This frequently results in the withdrawal of drugs and other therapies, which raises the risk of relapse and rehospitalization[1,44,50,61,62].

Schizophrenia has a diverse path, but the long-term prognosis is dismal for many people. The condition is distinguished by intermittent acute psychotic episodes and reduced psychosocial functioning between these episodes, with the greatest deterioration in psychosocial functioning often happening within five years after the first psychotic episode[63]. Later in life, individuals may look "burned out," with the termination of acute psychotic episodes but the persistence of residual symptoms. Surprisingly, functional abilities may increase in comparison to previous phases of the illness. However, in a minority of individuals, around 5% to 15%, psychotic symptoms are almost constant, and they respond poorly to standard antipsychotic drugs[61,62,64].

The DSM-V-TR (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision) emphasises the chronic character of schizophrenia as well as the occurrence of negative symptoms. It states that for a schizophrenia diagnosis, the dysfunction must have lasted at least six months. Individuals with schizophrenia seldom regain the same level of adaptive functioning they had before to the start of the condition, showing the illness's chronicity[1,64–66].

Positive and negative symptoms are generally divided into two groups in the DSM-V-TR categorization of schizophrenia symptoms. However, current focus has shifted to a third category: cognitive impairment. Individuals with schizophrenia show impairments in areas such as attention, working memory, and executive function within this cognitive domain[67]. Positive symptoms, including hallucinations and delusions, have traditionally received the greatest attention and are the major targets of conventional antipsychotic drugs. However, it is critical to recognize that unpleasant symptoms and cognitive impairment are inextricably related to poor psychosocial functioning, emphasizing the importance of these factors when evaluating pharmaceutical therapy alternatives[1,64,66–69].

Various studies have attempted to identify subgroups of schizophrenia, with the hypothesis that symptom patterns may correspond with prognosis, cognitive ability, structural brain abnormalities, and reactions to antipsychotic medicines. Negative symptoms and cognitive deficiencies tend to be more strongly associated to prefrontal lobe dysfunction, whilst positive symptoms appear to be more directly linked to temporolimbic abnormalities. Many people with schizophrenia display a mix of positive and negative symptoms. Those with strong negative symptoms are more likely to have a history of poor adjustment before to disease start, poorer educational achievement, and a less favorable long-term prognosis. Understanding these symptom categories and their consequences can help guide treatment strategies and actions for those suffering from schizophrenia[1,15,61,64,70,71].

Symptoms are classified into three categories in the context of schizophrenia symptomatology: positive, negative, and cognitive. Suspiciousness, strange thinking content (delusions), hallucinations, and conceptual

disorganization are all positive symptoms that are characterized by the existence of anomalous experiences or ideas. Affective flattening (limited emotional expression), alogia (poverty of speech), anhedonia (loss of interest or pleasure), and avolition (lack of desire or goal-directed behavior) are examples of negative symptoms that indicate deficiencies in emotional expression and motivation. Finally, the cognitive domain is characterized by reduced attention, working memory, and executive function, emphasizing disruptions in cognitive processes such as focus, information retention, and decision-making. Understanding these various symptom categories is critical for diagnosing and managing schizophrenia because they can influence treatment methods and interventions customized to the specific requirements of people suffering from this complicated condition[1,12,56,64,65,72,73].

Diagnoisis

Schizophrenia is diagnosed based on specific criteria

1. **Characteristic Symptoms:** The presence of two or more of the following symptoms, each lasting at least one month, such as Delusions, Hallucinations, Negative symptoms include disorganised speech, grossly disorganised or catatonic conduct, and grossly disorganised or catatonic behaviour. (If the delusions are odd or the hallucinations entail hearing voices offering a running commentary on the person's behaviour or several voices speaking, just one of these symptoms is required to fulfil this requirement.)
2. **Social/Occupational Dysfunction:** One or more key components of functioning, such as job, interpersonal connections, or self-care, must be significantly below the level seen prior to the commencement of the condition for a significant portion of the period since the onset of the disorder.
3. **Duration:** For a minimum of six months, there should be no evidence of the disease. Unless the symptoms have responded adequately to therapy, this time must include at least one month of symptoms matching criteria A. This six-month period may contain both prodromal (early warning indications) and lingering symptoms.
4. **Exclusion of Schizoaffective or Mood Disorder:** The fundamental cause of the symptoms must be ruled out as schizoaffective disease or a mood condition.
5. **Absence of Medical Disorder or Substance Use:** The aetiology of the problem should not be due to a medical issue or substance abuse.
6. **Pervasive Developmental Disorder:** If there is a history of a pervasive developmental problem, signs of hallucinations or delusions must be present for at least one month.

These criteria are used to diagnose schizophrenia, with physicians searching for a mix of particular symptoms, functional impairment, duration of symptoms, and the elimination of alternative possible explanations of the observed symptoms. Imaging methods are not extensively utilised for diagnosis, but they are useful for ruling out other illnesses, doing research, and planning therapy. Magnetic resonance imaging and computed tomography are two of these imaging methods.[1,73–75].

CONCLUSION

Schizophrenia remains a significant challenge in the field of mental health, affecting millions worldwide with its complex and debilitating nature. Its epidemiology highlights the need for increased awareness and resources for early detection and intervention, as its onset often occurs during the crucial transition to adulthood. Etiological research has shed light on the involvement of various genetic and neurodevelopmental factors, emphasizing the multifaceted nature of this disorder. The pathogenesis of schizophrenia is intricately linked to abnormalities in neurotransmitter systems, notably dopamine, serotonin, and glutamate, which underpins the array of clinical manifestations observed in affected individuals. Understanding these underlying mechanisms is crucial for the development of targeted treatments. Clinically, schizophrenia is characterized by a range of symptoms, including positive manifestations like hallucinations and delusions, negative symptoms that impact social functioning, and cognitive deficits that significantly affect daily life. Recognizing and addressing these diverse symptoms is essential for comprehensive patient care. Diagnosis relies on specific criteria, including symptom duration and functional impairment, necessitating a careful and thorough assessment to exclude other potential causes of psychotic symptoms. Early detection and intervention hold promise for improving outcomes and reducing the burden of this disorder. In conclusion, schizophrenia remains a complex and challenging mental health condition, but ongoing research and clinical advancements offer hope for improved diagnosis, treatment, and support for individuals and their families. Efforts to destigmatize the condition and increase awareness are critical steps towards a more compassionate and effective approach to managing schizophrenia in our communities.

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