REVIEW ARTICLE

Schizophrenia: An Overview

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Abstract

Schizophrenia is still one of the most mysterious mental disorders that are characterized by delusions, hallucinations, and impaired social behavior. Symptoms of schizophrenia emerge in adolescence and early adulthood while their description is controlled by conventional criteria. The incidence of the mental disorder varies across cultures and migrant groups. Genetic vulnerability overlaps with environmental factors causing individual symptoms and course. This review article focuses on definitions, symptoms, causes, etiology, epidemiology prognosis, history, mechanisms, diagnostics, pathophysiology, possible treatment, and prevention of schizophrenia.

Key words: Dopamine, etiology, management, prognosis, schizophrenia

INTRODUCTION

Schizophrenia is a severe psychiatric disorder, a heterogeneous behavioral and cognitive syndrome that is related to the disruption of brain development caused by genetic or environmental factors.[1] According to American Psychiatric Association schizophrenia is a mental disorder that is characterized by delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms including diminished emotional expression or avolition.[2] The symptoms must be present during a 1-month period.

Sweden psychiatrist Eugen Bleuler introduced the term schizophrenia in 1908. It was composed of Greek words meaning, "splitting of the mind." The earliest medical description of schizophrenia symptoms belongs to Haslam and Pinel published in 1809. However, schizophrenia-like syndrome is considered to be rare prior 1800[3] though the description of uncontrolled behavior and psychosis was common in ancient Greek and Roman. Avicenna described some symptoms of schizophrenia. This condition was called "Junun Mufrit," or severe madness. However, other similar cases of this state are not described during the medieval ages. One of the first historical cases of schizophrenia-like syndrome belongs to Italian priest, writer and cartographer Opicinus de Canistris in the 14th century. His autobiographical work describes his mental disease characterized by mania, self-deprecation, and depression.[3] More recent case of schizophrenia-like disorder was described by German sculptor Franz Xaver Messerschmitt in the 18th century. During the Messerschmitt life, his thinking was considered as bizarre and implausible, his behavior included social isolation, loss of employment, mania, and depression. He is famous for the collection of busts called "character heads" with extreme facial expressions that may confirm mental disorder.[3] Rare cases of schizophrenia-related symptoms before 1800 confirm that this mental disease became widespread only beginning from the 19th century. Possibly, it was caused by the development of particular social conditions affecting human behavior. Scientists and psychiatrists have made a great contribution to the understanding of causes, mechanisms and treatment approaches during one century though there are many controversial thoughts related to schizophrenia.

SYMPTOMS

The symptoms of schizophrenia begin between late adolescence and the middle 30s. All the symptoms of schizophrenia are divided into three separate categories: Positive, negative, and cognitive symptoms. Classification based on negative and positive symptoms was presented

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by Tim Crow in the 1980s[4] though positive and negative symptoms were declared in the 19th century.[5] Positive symptoms are those that are not recognized normally in individuals but are present in patients with schizophrenia. The scale for the assessment of positive symptoms[6] describes five groups of positive symptoms: Delusions (persecutory delusions, delusions of guilty or sin, and religious delusions), hallucinations (voices commenting, voices conversing, and visual/olfactory hallucinations), thought disorder (incoherence, illogicality, and pressure of speech), bizarre behavior (clothing and appearance, aggressive and agitated behavior, repetitive, and stereotyped behavior), and inappropriate affect.[6] Negative symptoms can occur in patients with other neurodegenerative disorders: Parkinson's disease, Alzheimer's disease, or severe depression. These symptoms include blunted effect (reduction of spontaneous movements, scarcity of facial expressions, poor eye contact, and lack of voice modulation), a logia (poverty of speech), anhedonia (inability to experience pleasure, scarcity of recreational and leisure activities, and inability to experience closeness), Avolution (poor hygiene and reduced motivation), and asociality (absence of friends, poor relationship with other people, and reduced social interaction).[5] These symptoms are evaluated by the scale for the assessment of negative symptoms.[7] As studies show, the negative symptoms occur in 50–90% of patients at the onset[5] while treatment reduces the prevalence of negative symptoms to 35–70% of patients at the end of the follow-up. However, some patients do not possess negative symptoms or loss them after some time.[8]

Cognitive dysfunctions appear widely in patients with schizophrenia. Such cognitive impairments include different types of memory (working memory, long-term, verbal declarative, and episodic memory), attention, and learning.[9] For example, studies show that patients with schizophrenia do not show "Pollyanna" effect and remember unpleasant, neutral or pleasant words with equal frequencies while healthy persons remember more pleasant words.[9] These studies show that the patients with schizophrenia possess problems with encoding the meaning of the words and verbal memory in general. Patients with schizophrenia possess difficulties with paying attention and focusing and understanding the information. Working memory impairments are considered as one of the most distinguished features of schizophrenia. Analysis of patients[10] has demonstrated that verbal and spatial working memory dysfunction correlate with impairments of visual orientation, memory for objects, memory for faces, and executive functions. Very often, cognitive dysfunctions can be present before the appearance of schizophrenia in adolescence or early childhood.[11]

Summarizing, patients with schizophrenia may possess broad range of psychosis signs. At early stages of schizophrenia development, persons become asocial, unmotivated, emotionless, and depressive. Other most expressed symptoms are delusions, hallucinations, and disorganization of speech and behavior. In addition, patients with schizophrenia possess the absence of normal behavior and impairments with working memory. However, not all symptoms may occur in one person. Broad specter of the signs and symptoms causes difficulties in the disease diagnosis and treatment.

CAUSES

Genetic and environmental factors are considered as the major factors that can stimulate the development of schizophrenia. Although schizophrenia is considered as highly heritable disease, it is likely that there are multiple genetic variations that cause the development of schizophrenia symptoms. Genetic factors include changes of the genetic material at different levels starting with gene sequence and finishing with genomic abnormalities. Several studies analyzing variations of coding regions (exome sequencing) have demonstrated that patients with schizophrenia possess *de novo* mutations in the number of putative genes including dihydropyrimidine dehydrogenase, laminin, α2, transformation/transcription domain-associated protein, and vacuolar protein sorting 39.[12] Another investigation has shown that 50 genes related to calcium channels and postsynaptic activity-regulated cytoskeleton-associated scaffold protein complex contained one or two mutations in schizophrenia patients. However, only 1% carried mutations that could have an impact on the development of schizophrenia including coiled-coil alpha-helical rod protein 1.[13] Other studies revealed that epigenetic factors could be involved into the etiology of schizophrenia. Genome sequencing of the methylated genome fraction has determine several potential genes involved in schizophrenia. These genes include family with sequence similarity 63, member B, and Reelin (*RELN*) associated with neuronal functions. Among other differentially methylated genes, nitric oxide synthase 1, v-akt murine thymoma viral oncogene homolog 1 (*AKT1*), dystrobrevin-binding protein 1 (*DTNBP1*), DNA (cytosine-5)-methyltransferase1, protein phosphatase 3, catalytic subunit, gamma isozyme, and sex determining region Y-box 10 are associated with schizophrenia. A ChiP-chip study (Chromatin immune Precipitation with DNA microarray) determined genes (*NRG1, DTNBP1, DISC1, DAO, DAOA, PDE4B,* and *COMT*) that are associated with the disease and its molecular abnormalities.[12] Other groups of scientists have shown the changes at transcriptomic, proteomic, and metabolomics levels. These altered proteins are related to mitochondrial dysfunction, oxidative stress, and abnormal functions of oligodendrocytes. For example, decreases in *RELN* and *ANK3* expression were observed in the brains of schizophrenia patients. Although hundreds of genes related to the neuronal functions are impaired in the patients with schizophrenia, it is hard to predict all the possible interactions between them. It seems that there are several genetic changes that can promote the development of schizophrenia symptoms. On the other hand, many investigations confirm that the primary causes of schizophrenia are represented by environmental factors including infectious agents. Studies demonstrated that there

is an association between the infection of *Toxoplasma gondii* and development of schizophrenia.[14] Infection in early childhood may have a direct effect on the schizophrenia symptoms.[15]

Prenatal and perinatal complications have a strong effect and increase the risk of schizophrenia from 1 in 100 to 2–4 in 100 individuals.[16] It was hypothesized that infection-associated immunological disorders during early fetal development increase the risk of neurodevelopmental impairments. Furthermore, the abnormal immune response in maternal organism correlates with the development of schizophrenia in children. For example, increased levels of interleukin-8 during pregnancy increase the risk of schizophrenia.[17] The use of drugs or other psychotropic substances correlates with the development of schizophrenia. Cannabis is one of the most potential reasons that are consistent with psychosis and schizophrenia. Meta-analysis studies have shown that use of cannabis has a deleterious effect on the prognosis of patients with late psychosis and schizophrenia. Although the estimated relative risk was relatively low, cannabis may have a direct influence on the development of psychotic symptoms and increases the risk of schizophrenia.[18] Among other factors that are believed to increase the risk of schizophrenia development are other drugs (amphetamines) that increase dopamine release, alcohol, and tobacco. However, the association between these factors and psychosis is relatively low. Studies have shown the direct correlation between urban life and psychosis risk.[19] It was confirmed that rate of schizophrenia is higher in the urban environment. It was suggested that ecological or social factors could have an effect on the development of psychosis symptoms. Furthermore, it was hypothesized that these influences can be combined with genetic factors causing changes in the brain development.[19,20] However, further investigation should be conducted to find more specific factors inside an urban environment that can cause the development of psychotic symptoms.

Summarizing, schizophrenia can be caused by a variety internal and external factors related to the development and functions of the complex neuronal cells system. "In most cases, schizophrenia is an end result of a complex interaction between thousands of genes and multiple environmental risk factors - none of which on their own causes schizophrenia," John H. Gilmore postulated.[16]

ETIOLOGY

It is widely accepted and proved that vulnerability to schizophrenia is related to genetic factors including heredity. Studies show that incidence of schizophrenia in third-degree relatives (i.e., cousins) is ~2%, in second-degree relatives (nieces/nephews) incidence varies between 2 and 6%, while the incidence of schizophrenia in first-degree relatives (parents, children) equals 6–17%. Interesting, that incidence of schizophrenia in dizygotic twins is ~17%, while in monozygotic twins with identical genomes incidence of schizophrenia equals 50%.[21]

Environmental factors including infections, stress during gestation, or childhood play an important role in the development of schizophrenia symptoms. For example, studies demonstrated that children born in winter are likely to develop schizophrenia.[22] Individuals with schizophrenia also are surrounded by socioeconomic environment, belong to urban population or represent members of the immigrant population. Males with schizophrenia are considered to have more severe manifestation of disorder, earlier onset, lower response to treatment, and less favorable outcome.[23] These features may be related to the physiological and hormonal differences in women and men. Overall, the etiology of schizophrenia is based on the genetic vulnerability and environmental factors, which interact with each other affecting development, maturation, and plasticity of the brain.

EPIDEMIOLOGY

It is commonly considered that schizophrenia affects <1% of the human population at certain point of their life. However, the prevalence can vary between 0.3 and 0.66% depending on several factors. For a long time, it was considered that the incidence of schizophrenia was constant all over the world. However, later studies have demonstrated that its prevalence and incidence vary in different countries and cultures of the world and even at local areas. The incidence of schizophrenia varies from 7.7 to 43/100,000 person-years.[24] The rates vary due to different diagnostic definitions of schizophrenia and its criteria. Studies show that incidence rate is higher for men than for women based on the negative symptoms and long duration of illness[25] demonstrating that schizophrenia symptoms are more severe in men than in women. In general, schizophrenia is diagnosed 1.4 times more frequently in man than in women. Furthermore, in men, the symptoms appear between 18 and 25 years of age, while in women, symptoms appearance has two peaks 25–30 years and after 40 years.[26] People with schizophrenia have higher mortality risk than healthy persons. It was demonstrated that the standardized mortality ratio is 2.6. Suicide and cardiovascular disease make the main contribution to the mortality rate.[24]

It is considered that prenatal, perinatal and complications of normal brain development have a great effect on the pathogenesis of schizophrenia. Season of birth is one of the epidemiological features of high risk of schizophrenia. It is known that individuals born in the winter or early spring period are more likely to have schizophrenia. Although the relative risk is small (7–10%), it is a significant result that is replicated many times.[27] The possible explanations are dietary deficiency or high risk of infectious disease that affects maternal organism during second trimester of pregnancy. It was demonstrated that prenatal exposure to genital and reproductive infections, influenza virus,

herpes simplex virus, and toxoplasmosis increase the risk of schizophrenia development. In the case of genital and reproductive infections it is 5 times more likely to develop schizophrenia.[24] Studies have shown that patients with schizophrenia have higher prevalence of antibodies to toxoplasma. Adult patients with toxoplasmosis may develop similar symptoms to psychotic disorders. It was also shown that toxoplasma increases dopamine synthesis and release.[27] Other studies confirm that pregnancy and birth complications also are associated with schizophrenia. These complications can be grouped into three types including complications of pregnancy (bleeding, diabetes, pre-eclampsia, and rhesus compatibility), abnormal fetal growth and development (low birth weight, congenital malformations, and reduced head circumference), and complications of delivery (uterine atony, asphyxia, and emergency cesarean section).[28] Overall risk for schizophrenia after pregnancy complication was assessed as 2.0. The data demonstrated that exogenous factors that may affect the brain development play an important role in pathogenesis of schizophrenia. Another cohort of population-based epidemiological studies demonstrates the evidence of association between paternal age and the risk of schizophrenia. Relative risk of schizophrenia is 2.96 in the group of fathers with the age >55 years. Accumulation of genetic mutations in the progenitor sperm cells is considered as the major possible explanation of this effect. Furthermore, it is known that autism is also associated with increased paternal age confirming possible negative effect of paternal age on the development of psychotic disorders.

Other factors that correlate with the development of schizophrenia are social factors including urbanization and migrations. Early studies have demonstrated that social isolation that can be found far of urban areas increases the risk schizophrenia development. However, more recent studies from Europe including Sweden and Netherlands have demonstrated that risk of schizophrenia increases with urban birth or upbringing having the most negative effect during childhood or adolescence. Explanation of this phenomenon can be related to the environmental pollutions, social exclusion or cannabis, and genetic vulnerability.[24,27] In general, there is a strong association between low social class and schizophrenia that can be explained by infectious agents, environmental conditions, unemployment, and physical stress.[27] Schizophrenia is also associated with migration. For example, Surinamese migrants in the Netherlands, African refugees in Sweden, Greek migrants to Belgium, Scandinavian migrants to Denmark, African-Caribbean's, and black Africans to Europe. These data can be explained by the absence of social support or high racial discrimination as external factors influencing the functioning of nervous system.[24]

Several studies show that there is a correlation between parental loss or separation, physical abuse in early childhood, and schizophrenia development.[24] In adulthood, stress related to the emotional life events and social isolation may increase schizophrenia risk. The abnormalities of hippocampus are caused by the elevation of dopamine system after exposure to stress or drugs. These abnormalities can be the reason for psychotic disorders.[27]

PROGNOSIS

In the past, schizophrenia was considered as a disorder with a poor prognosis. Now, with the development of drugs, medical and social support most of the patients can live independently outside the hospital with regular diagnostics. However, the disease course, its response and results of treatment are characterized by heterogeneity. One-third of schizophrenia patients remain with the same or even worse symptoms in spite of the normal and continuous treatment. On the other hand, about 20% of patients can demonstrate a positive outcome and normalization of the symptoms.[26] However, due to the heterogeneity of reasons and symptoms mostly it is impossible to predict the results.

A mortality risk in schizophrenia patients is 2–3 times higher than that of healthy persons. Most deaths are caused by diseases of cardiovascular and respiratory body systems, thromboembolic events, and cancer.[29] There are several possible reasons for the development of these diseases. At first, the lifestyle of people with schizophrenia can be characterized by unemployment, homeless, low social conditions, stress, poor diet, low exercise levels intake of drugs, or alcohol that may have a negative effect on the physical health. Controversial studies demonstrated that use of antipsychotics may lead to increased insulin resistance, weight gain, and lipid metabolism impairment that has direct influence on the cardiovascular functions. However, use of additional treatment and active lifestyle decrease the risk of cardiovascular diseases in patients with schizophrenia.[30] One more reason of mortality in patients with schizophrenia is suicide. This is a serious concern for doctors and family members of person with schizophrenia. Up to 40% of the deaths in persons with schizophrenia are caused by suicides.[31] The risk of suicide is 13 times higher in person with schizophrenia than that of healthy person.[32] Approximately 5% of patients with schizophrenia are at risk of suicide. Such symptoms as hallucinations, delusions, substance abuse (alcohol or drugs), and depression increase the risk of suicide. Risk factor is also higher in young males with a high level of education. The family history of suicide is also associated with the high-risk suicide. However, adequate treatment, control, and professional support may reduce the risk of suicide. Prevention of the suicide should include analysis of potential risk factors and use of additional treatment including clozapine.[32]

HISTORY

The earliest medical description of schizophrenia symptoms belongs to Haslam and Pinel published in 1809. However,

the definition "schizophrenia" appeared much later. During the 19th century, psychiatrists described more cases with the same symptoms though the definitions were different. In 1899, Emil Kraepelin improved the classification of mental disorders separating mood disorder and dementia praecox that was characterized by schizophrenia-like symptoms. In 1908, psychiatrist Eugen Bleuler introduced the definition "schizophrenia" which is translated from Greek as "splitting of the mind." He described four main symptoms related to the disease: Flattened affect, autism, impaired association of ideas, and ambivalence. Later, the psychiatrist Kurt Schneider described more detailed symptoms that distinguished schizophrenia from other disorders. They are called first-rank or Schneider's first rank symptoms including, for example, delusions, voice auditory hallucinations commenting actions or conversations, and inserted thoughts.[33]

During early century, schizophrenia was considered as highly hereditary disorder. Therefore, eugenic psychiatrists including Bleuler tried to control the incidence of the disorder sterilizing or murdering the patients with schizophrenia. In 1970, the schizophrenia concept was estimated once more. New criteria were introduced by psychiatrists Robins and Guze while Schneider's first-rank symptoms became less important. During this period, large amounts of discrepant studies from Europe and the USA were compared to unify the symptoms that helped to develop reliable diagnosis of schizophrenia. The controversies took place due to different descriptions of symptoms in the DSM-II manual in the USA and ICD-9 in Europe. It was investigated that symptoms of schizophrenia can be found in different countries and cultures suggesting great biological impact to the development of the disease. The WHO data indicated stable similar incidence rate all over the world. In 1970, more than 40 criteria of schizophrenia diagnosis were suggested that are used now.[27] In 1950, first antipsychotic named chlorpromazine introduced to treat schizophrenia.[34] This was the revolutionary discovery that started the development and investigation of new antipsychotic agents that helped to understand the molecular bases of schizophrenia and the development of dopamine hypothesis in 1960s. Psychoeducation and family therapy, as well as atypical psychotics including clozapine, were used for treatment beginning from 1970s. Cognitive-behavior therapy and cognitive remediation were introduced to treat schizophrenia starting from 2000s. Now, molecular mechanisms based on the gene-environment interaction and personalized approaches to treatment are the major directions of modern neurobiology, psychiatry, and medicine in the field of schizophrenia.[34]

MECHANISMS

Schizophrenia is a complex highly hereditable disease. The development of schizophrenia symptoms is considered to be associated with the genetic abnormalities and mutations in a range of genes. The impairment of genetic material and its interaction with external environmental factors serve as the cause of schizophrenia. These causes induce the development of pathological processes in neurons and synapses mediated by impairment of neurotransmitter systems and functional networks in brain at the molecular and cellular levels. There are several hypothesis describing these mechanisms.

The neurodevelopmental hypothesis suggests that impairment of biochemical functions and neuronal network during embryonal and fetal development cause the mental disorder later in life.[35] Imaging studies show that neurodevelopmental alterations are associated with the formation of the hippocampus, the prefrontal and superior temporal lobe as well as with ventricular enlargement, reduction of the brain volume, and cerebral asymmetry. More than 50% genes implicated in the development of schizophrenia including *AKT1*, *IL10*, *NOTCH4, RELN, TNF-alpha,* and others are regulated by hypoxia[36] that is considered as a possible cause of alterations in neuron system including apoptosis. All these factors confirm the role of developmental process in schizophrenia.

Dopamine hypothesis is the major hypothesis describing the mechanisms of schizophrenia development. It postulates that most of the schizophrenia symptoms and pathological changes in the brain structure are caused by excess dopaminergic neurotransmission. For example, it is confirmed that increased activation of dopamine neurotransmission in mesolimbic and striatal brain regions is responsible for the development of negative symptoms. Up-regulation of D-2 dopamine receptor including increased levels of its expression and higher density in the synapse is associated with poorer performance on cognitive tasks.[36] These data correlate with the positive effect of antipsychotics that are antagonists or partial agonists of dopamine D2 receptors. Several proteins and signaling systems associated with dopaminergic transmission are considered to have an influence on the development of schizophrenia at the molecular level. Studies demonstrate increased synthesis, accumulation and release of dopamine during the psychotic symptoms of schizophrenia.[37] Brain-derived neurotrophic factor (BDNF) plays an important role in the development of mesolimbic dopaminergic systems regulating the expression of dopamine D-3 receptors. This protein was suggested to be associated with the schizophrenia development. In addition, polymorphism (C270T) in the BDNF gene is associated with schizophrenia.[36]

Other hypothesis postulates the role of glutamatergic system dysfunction in schizophrenia. Reduced activity of glutamatergic neurotransmission in corticostriatal projections causes an opening effect in the thalamocortical loop resulting in an exaggerated sensory flooding and alteration of dopamine concentration. In addition, decreased glutamate function correlates with poor performance on tests requiring activity of frontal lobe and hippocampus. One type of glutamate receptors called N-methyl d-aspartate-receptors (NMDAR) work as ion channels that produce a depolarising

excitatory post-synaptic current after glutamate binding and activation. These receptors are related to excitotoxicity and further neuroinflammation and apoptosis. Studies demonstrated that NMDAR antagonists including ketamine activate dopamine release and cause psychotic symptoms. Deficit and low density of the vesicular glutamate transporter in striatus and hippocampus of schizophrenia patients confirms the hypothesis of glutamatergic transmission hypofunction.[36] A selective agonist of metabotropic glutamate 2/3 receptors improves positive and negative symptoms and do not cause the extrapyramidal impairment or weight gain in schizophrenia patients. This confirms possible treatment of schizophrenia using glutamate receptors agonists that increase altered glutamatergic transmission. Several studies demonstrate the role of neurogelin (*NRG1*) in the development of schizophrenia. Reduced expression of *NRG1* gene was shown to be associated with schizophrenia. This gene is involved in the neuronal cells signaling, axon guidance, synaptogenesis, myelination, neurotransmission, and glial differentiation suggesting its possible role in the neuronal pathologies including schizophrenia.[38] Furthermore, NRG1 activation promotes internalization of NMDAR by a clathrin-dependent endocytosis in prefrontal pyramidal neurons. In addition, to decreased expression levels of *NRG1* genetic variation of *NRG1* gene promoter were identified. These mutations correlate with decreased activation of frontal and temporal lobe areas and psychotic symptoms.[36] Dysbindin (*DTNBP1*) is another potential gene involved in the development of schizophrenia symptoms. It plays an important role in cognitive processes. Concentration of DTNBP1 is reduced in brains of schizophrenia patients. Reduced expression of DTNBP1 was shown to be associated with increased glutamate release.[38]

Molecular mechanisms of the development of schizophrenia can be studied using a mouse model. For instance, overexpression of dopamine D-2 receptor, or knockout of dopamine transporter cause behavioral abnormalities and cognitive changes in mice. Deletion of the calcineurin gene induces abnormal locomotion, reduced social interaction, and cognitive alterations.[37] At the cellular level, schizophrenia can be characterized by "reduced neuropil hypothesis." Neuropil consists of axons, dendrites, pre- and post-synaptic terminals. Studies demonstrate an increased neuronal density (up to 15–20%) in frontal and occipital cortices of schizophrenia brains, decreased dendritic spine density and length of pyramidal neurons, reduced level of presynaptic markers including synaptophysin in the prefrontal cortex. In addition, it was demonstrated that schizophrenia is characterized by reduction (4–9%) of neuron volume in the prefrontal cortex and increased levels of apoptosis markers.[39]

DIAGNOSTICS

Diagnostic of schizophrenia is tightly linked to the symptoms. However, these symptoms can be present in other neurological disorders. Therefore, correct diagnostics is an important issue in schizophrenia characterization and treatment. There are two main international documents that determine the diagnosis of schizophrenia: (1) American psychiatric association's diagnostic and statistical manual of mental disorders (DSM-V) and (2) the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (the ICD-10).[25] According to DSM-V,[40] diagnostic criteria for schizophrenia include two or more of the following positive or negative symptoms with the duration of 1 month: (1) Delusions, (2) hallucinations, (3) disorganized speech, (4) disorganized or catatonic behavior, and (5) negative symptoms. Other criteria include decreased level of functioning as work, self-care or interpersonal relations, and continuous signs of disturbance (at least 6 months) that is not attributable to medical substances. At last, schizoaffective disorder and depressive or bipolar disorders must be excluded.

The differential diagnosis should be used to exclude other possible types of psychosis with the same symptoms including bipolar disorder, post-traumatic stress disorder, autism spectrum disorder, and schizoaffective disorder. Very often, the main difference between schizophrenia and other psychotic disorder is related to the duration of the symptoms. For example, delusions and hallucinations caused by brief psychotic disorder last at least 1 day but <1 month. However, more complex analysis of symptoms is required. Patients should be observed during an extended time with additional analysis of history provided by family members.[26] Patients that are characterized by long duration, bizarre delusions and negative symptoms are considered as schizophrenic. However, patients that possess several negative symptoms, high levels of depression and mania are diagnosed with bipolar disorder or psychotic depression.[25]

However, even when all detailed criteria are used in diagnosis there are some differences between patients with disorders. That is why it is important to develop new methods of diagnostics. Now, it is known that schizophrenia disorder is related to the abnormalities with dopamine and glutamate transmission. Functional magnetic resonance imaging (fMRI) can be used to measure regional cerebral blood flow that shows abnormal activation in some brain areas (cortex, hippocampus, striatum, thalamus, and cerebellum) in schizophrenia patients.[41] However, these abnormalities are not observed in all patients. Positron emission tomography (PET) and single-photon emission tomography (SPET) use radioactive ligands to visualize distribution, synthesis, and release of neurotransmitters while magnetic resonance spectroscopy (MRS) can be used to measure the concentration of molecules within the brain. These methods demonstrate that pre-synaptic striatal dopamine synthesis and released are increased. SPET investigations have shown reduced NMDAR binding in the hippocampus while MRS analysis has shown increased glutamine in the medial frontal cortex confirming glutamate release in the patients with schizophrenia. In spite

of the perspective use of neuroimaging in schizophrenia diagnostics, unfortunately, these methods possess several limitations including variations in symptom profiles and molecular abnormalities, limited availability, and the high cost of this diagnostics.[41]

PATHOPHYSIOLOGY

Pathophysiological changes can be easily observed using modern neuroimaging techniques. These studies have shown a decrease in gray matter, enlargement of ventricles, and focal alteration of white matter tracts.[25] Schizophrenia brain is characterized by reduced volume of temporal cortex that is associated with schizophrenia psychopathology. Medial temporal regions such as amygdala and hippocampal complex and frontal region of cortex have also reduced volume. Some nuclei in the thalamus including pulvinar and medial dorsal nuclei that are associated with respective cortical regions are reduced. The thalamus plays an important role in the integration between the cortex, the cerebellum, and incoming sensory information.[42] Other brain structures, including corpus callosum, cerebellum, and striatum, also demonstrate abnormalities in schizophrenia brain. Impairment of several regions in the brain that forms a functional network, cause the psychopathological difficulties in schizophrenia patients. These suggestions are supported by fMRI studies that demonstrate, for example, the association between working memory deficits, impairments, and low activation of prefrontal cortex, superior temporal area, and striatum.[43] Diffusion tensor imaging investigations show disorganization of white matter in several brain regions including prefrontal and temporal white matter, corpus callosum, and uncinate fasciculus.[37] PET scanning demonstrates decreased levels of blood flow in the left par-hippocampal region, reduced glucose metabolism in the thalamus, and frontal cortex. These techniques also show an association between delusions and hallucinations and decreased blood flow in the cingulate, left frontal, and temporal areas. In contrast, patients with active auditory hallucinations are characterized by increased blood flow in thalamus, hippocampus, striatum, orbitofrontal, and cingulate areas.[44]

Many studies based on the immunohistochemical analysis demonstrate deficits in synaptic transmission in schizophrenia. For example, connectivity between the mediodorsal thalamic nucleus and dorsal prefrontal cortex is impaired due to decreased neurons size and number, reduced amounts of dendritic spines, axon terminals, and axon density.[37] Previous pharmacological studies and observations suggested the "dopamine hypothesis" for schizophrenia development. The action of antipsychotics helped to identify that D2-dopamine receptors blockade has a positive effect on the symptoms. Furthermore, such drugs as amphetamine that stimulates the action of dopamine cause psychotic symptoms in normal individuals. Further, studies have confirmed that dopamine modulates cognitive function in the prefrontal cortex that is in line with the schizophrenia disorder.[37] Neurochemical imaging with the use of radioligands ^{18}F-dopa and ^{11}C-raclopride have demonstrated increase synthesis, accumulation, and release of dopamine during the psychotic symptoms of schizophrenia. Functional MRI has shown abnormalities in the brain structures and hyperactivity or hypoactivity of their functions. It was shown that in patients with schizophrenia possess a reduced brain response to new stimuli while the response to repeated stimuli cannot be suppressed and is highly activated.

Other studies demonstrate the role of glutamate in schizophrenia. Some agonists of glutamatergic NMDAR including ketamine can cause psychotic symptoms and cognitive abnormalities. Furthermore, it was noticed that patients with schizophrenia are highly sensitive to psychotomimetic drugs. It was suggested that hypo-activity of NMDAR may be another reason for pathophysiology of schizophrenia. It is confirmed by the fact that substances (D-serine and sarcosine) that modulate NMDAR have positive effect on the reduction of negative symptoms.[45] Reduce activity of NMDAR may cause the cortical atrophy and loss of dendritic spines observed in schizophrenia. Some other neuropathological studies demonstrate that gamma-aminobutyric acid (GABA) may have a potential role in the pathogenesis of schizophrenia. Reduced BDNF signaling or decreased NMDAR activity may reduce levels of GABA interneurons. These abnormalities can cause abnormalities in the dorsolateral prefrontal cortex affecting cognitive functions including working memory in schizophrenia patients.[43]

Loss of neurons in prefrontal cortex, anterior cingulate cortex, and hippocampus, as well as reduced number of glial cells and decreased neuronal density, can be associated with the active apoptotic processes in the schizophrenia brain. Studies show that levels of anti-apoptotic protein Bcl-2 are reduced by approximately 25% in the middle temporal cortex in patients with schizophrenia.[39] Another process that increases apoptotic processes is oxidative stress. Reduced blood markers of antioxidant enzymes and increased turnover of phospholipids demonstrate increased levels of oxidative stress in schizophrenia patients.[46] Reduced activity of NMDAR, high calcium levels, mitochondrial impairments, oxidative stress, and glutamate excitotoxicity stimulate apoptosis of neuronal and glial cells that are widely observed in patients with schizophrenia.[39]

TREATMENT

Patients with diagnosed with schizophrenia should be directed immediately for specialized treatment. Not all patients should be hospitalized though it is important to oversee the patient due to a possible danger to themselves.[26] The effective treatment of schizophrenia includes complex and systematic approach consisting of pharmacologic, psychological and social treatment, and support. The

main goal of the treatment is to reach the periods without symptoms during the period of 6 months. Pharmacologic treatment includes the use of medical drugs that reduce the expression of major symptoms of schizophrenia. The first-line treatment agents are antipsychotic agents. There are over 60 antipsychotic drugs that have been developed to use in schizophrenia treatment for reducing the positive symptoms expression. These drugs are classified into two groups name first- and second-generation agents. The World Health Organization considers three of the first-generation agents as essential medications. These agents include chlorpromazine, fluphenazine, and haloperidol. All the antipsychotics are characterized by the ability to block the dopamine D-2 receptors.[34] The first-generation agents are effective in reducing the psychotic symptoms though they can lead to motor side effects. The second-generation agents including olanzapine, risperidone, and quetiapine mostly do not cause the development of motor side effects.[25] Studies demonstrate that antipsychotic drugs are more effective than placebo in reducing the positive symptoms during the treatment of schizophrenia.[34] Patients show better quality of life within a few days or several weeks reducing positive symptoms and preventing relapse. However, patients may have different response on the use of antipsychotics, and it can take several months to achieve the maximal effect.[26] Studies show that most of antipsychotic drugs have no difference in their effectiveness of blocking D-2 dopamine receptors. The drugs differ in adverse effects or their cost. All the drugs show common adverse effects including elevated prolactin level, extrapyramidal symptoms, drowsiness, anxiety, headache, insomnia, and other side effects. It is considered that antipsychotic medications can cause further serious adverse effects including cardiovascular, metabolic, and endocrine disorders.[26] For example, second-generation antipsychotics are associated with the development of metabolic disorders including weight gain, hyperglycemia, insulin resistance, and abnormalities in lipid exchange. These changes may lead to serious physical problems impairing overall outcome.[34]

Untreated schizophrenia symptoms are associated with higher mortality risk, poor social life, and low overall quality of life. However, controversial studies demonstrate the different effect of prolonged treatment using antipsychotics including positive and no effect on the mortality risk.[34] Therefore, use of these drugs require their combining and personalized approaches to reach the best result in treatment. Antipsychotic drugs are less effective in the reducing of negative or cognitive symptoms.[5] Additional therapeutic drugs include anticonvulsants, antidepressants, benzodiazepines, and lithium. For example, anticonvulsants valproic acid, carbamazepine, and lamotrigine are effective in reducing the aggression and impulsivity. Depression and anxiety are controlled by adjunctive antidepressants, while insomnia and agitations are treated using benzodiazepines.[34]

The date demonstrates that heterogeneity of schizophrenia symptoms require the complex use of drugs that can reduce the symptoms of schizophrenia and increase the life level of the patients.

In the past years, such approach as electroconvulsive therapy (ECT) is used to stimulate antipsychotic effects or to treat catatonic syndromes in patients with schizophrenia while repetitive transcranial magnetic stimulation demonstrates effectiveness in the treatment of negative symptoms.[34] Adjunctive treatments including cognitive behavior therapy (CBT), family intervention and social skills training play an important role in the overall treatment of schizophrenia. Investigations demonstrate that psychoeducational interventions including patients and more effectively family members help to reduce relapse and re-hospitalization rates. CBT is widely used in medical practice in the treatment of schizophrenia. Several studies demonstrate that this approach help to reduce positive symptoms and prevent relapse. However, other studies including meta-analysis show that CBT is ineffective in treatment of negative symptoms while further studies are needed to analyze its effect. Cognitive remediation approaches including strategies to organize and remember information have demonstrated positive effects on the improvements of cognitive and psychosocial functioning. Social skills training are used to improve social competence including self-care, vocational skills, and recreation.[34] Other psychosocial approaches include assertive community treatment and supported employment.

MEDICATION

Antipsychotic medication is major psychiatric strategy of schizophrenia treatment through these substances possess limitations in the effectiveness of treatment in individual patients and is associated with adverse side effects. Antipsychotics are considered to take approximately 7–14 days to reach their major effect. These medications reduce the positive symptoms though they have no effect on the negative symptoms. All these medications inhibit the activity of postsynaptic dopamine D-2 receptors. Chlorpromazine was the first antipsychotic to treat schizophrenia. However, modern medication has a wider spectrum of target neurotransmitter systems including serotonin, norepinephrine, acetylcholine, histamine, and glutamate. For example, clozapine that is considered as atypical antipsychotic possesses affinities to different neuroreceptors (dopamine, 5-HT serotonin, and noradrenergic receptors) and serves as a multi-neuroreceptor antagonist. Clozapine reduces suicide risk and is considered as the most effective antipsychotic for patients that are resistant to other antipsychotics.[47] Atypical antipsychotics are recommended to be used as first-line treatment in patients with schizophrenia through the medication intake should be optimized for certain individual patient.[23] Additional therapeutic drugs include anticonvulsants, antidepressants, benzodiazepines, and lithium. They should be used to reduce negative symptoms that are not sensitive to antipsychotics.[34]

Typical antipsychotics possess several adverse effects and complication. Controversial studies demonstrate that the use of these medications cause extrapyramidal symptoms including pseudo-parkinsonism, akathisia, and dystonia. However, other medications including lorazepam, propranolol, and amantadine, can be used to reduce extrapyramidal disorders.[48] Second-generation, or atypical antipsychotic also possess some negative effects. For instance, clozapine intake is associated with increased level of white blood cells, agranulocytosis, and myocarditis. Other atypical antipsychotics cause metabolic changes including weight gain, insulin resistance, and hyperglycemia.[26] Therefore, patients must be examined during treatment with second-generation antipsychotics as well as with typical first-generation antipsychotics to predict complication and physiological impairments.

PREVENTION

Prevention of schizophrenia is difficult due to heterogeneity of symptoms and causes of the disorder. Psychotic disorders occur in young people disrupting educational and social contacts that is why it is important to prevent the development of schizophrenia. Several studies have demonstrated that early interventions may help to improve the symptoms. However, these benefits can be lost in the next 5 years.[25] Several studies demonstrate that mild psychotic symptoms including hallucinations and delusional thinking might precede the diagnosis of schizophrenia.[25] It is important to detect individuals with high risk of the mental disorders development. Such groups should undergo cognitive-behavioral therapy and pharmacological treatment to reduce further impairment of brain structure at molecular and cellular level. However, therapeutic interventions are effective during critical periods of the illness considering neuroplasticity in the pathogenesis.[34] Identification of risk factors is crucial for the disease prevention though causes of schizophrenia are considered currently as a complex of genetic-environmental interactions.

It is important to prevent the transition from the prodromal syndrome that precedes schizophrenia to complex psychosis. Meta-analysis demonstrates that this transition can be preventable using psychological, psychosocial, and pharmacological interventions such as CBT and additional nutritional supplements including antipsychotics and antidepressants omega-3 fatty acids.[34] The intervention of the current prodromal phase is necessary to reduce the risk of the disorder development. However, in some cases, such preventive approaches can be unnecessary due to the false-positive results of the diagnosis.

Considering the possible causes of schizophrenia, it is important to avoid factors that increase the risk of schizophrenia development. These factors include cannabis, cocaine, and amphetamine. Furthermore, much attention should be paid for potential patients in families with schizophrenia history due to the high heredity of the disorder. Number of studies indicates that maternal infections including influenza, herpes simplex virus Type 2 toxoplasmosis and genital infections during pregnancy correlates with the development of schizophrenia in offspring.[49] That is why it is important to prevent these infections and to avoid possible complications to reduce the risk of future mental disorders. The population attributable risk for the mentioned infection is approximately 30% indicating that prevention of the infectious diseases may reduce the risk of schizophrenia development by about one-third.[49] For example, prevention of *Toxoplasma* infection is related to the control of the sources of the parasite including infectious water and soil. However, prevention of schizophrenia basing only on the risk factor or symptoms alone is not enough to predict the development of the disorder.[50] Duration of the untreated psychosis is associated with delayed remission of the symptoms, higher risk of relapse, increased depression periods and suicide risk, high drugs abuse, uncontrolled behavior, and increased costs of treatment. These investigations confirm the importance of early prediction and treatment of psychosis development especially based on the personalization.[51]

CONCLUSIONS

Schizophrenia is a severe psychiatric disorder that is related to the disruption of brain development caused by genetic or environmental factors. Schizophrenia appears during adolescence or middle 30s and can be supported with periods of remission throughout the lifespan. The prevalence of schizophrenia is approximately 1% of human population. Without an appropriate treatment patients with schizophrenia are unable to have normal social contacts and possibilities. Management of the disorder includes medications, social training, cognitive behavioral therapy, and other approaches. There are approximately 60 different antipsychotic medications that inhibit positive, negative, and cognitive symptoms though most of them are characterized by additional negative effects and complications. Modern methods of investigation including neurochemical imaging provide the data about structural and functional changes of schizophrenia brain. It is widely accepted that impairment of dopaminergic neurotransmission is the major mechanism of neurological changes through other neurotransmitters systems (glutamate, GABA, and serotonin) are considered to have a great effect. Although in the 100 years scientists have described possible causes, mechanisms and treatment strategies of schizophrenia, most of the patients remain chronic ill requiring additional social help, physical support, and understanding.

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