Review Article

Pharmacologic Advancement in Schizophrenia

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ABSTRACT:

Schizophrenia is a disorder of mental debility characterized by abnormal social behavior in which person is unable to recognize reality. The sign and symptoms are variable and heterogeneous. Due to the diverse symptoms and variable treatment response, it is challenging to treat. Recent advancements in genomic, epidemiology and neurosciences can provide the appropriate medicines and treatments for minimizing symptoms and consequences of schizophrenia. This literature review was highlights the etiology, pathophysiology, neurotransmitter system, novel treatment and management of schizophrenia.The mainstay treatment of schizophrenic patients included antipsychotic drug with psychotherapy, social rehabilitation and job training.

Keywords: Antipsychotic drug, Schizophrenia, Pathophysiology, Neurotransmitter system

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INTRODUCTION:

Schizophrenia is a chronic mental ailment which disturbs the numerous areas of brain and results in inconsistency of cognitive memory and behavior. It is a diverse disorder categorized by positive,negative and cognitive symptoms, often accompanied by signs of depression.The diagnosis of schizophrenia is purely based on clinical assessment of patient psychiatric history along with group of signs and symptoms.[2] The major signs and symptoms included hallucination (hearing voices), delusion (having false belief) and disordered thinking. Typically symptoms start gradually, usually occur in young adulthood and in many cases never resolve[3-4]. Prognosis of this diseases is unpredectible and merely 20% patient showed favourable treatment results. Many patients experience a psychotic episode along with long term symptoms and insufficient response to antipsychotic drugs [5]

METHDOLOGY:

This review explained the etiology, pathophysiology and management of schizophrenia.The past 40 years literature search was employed by searching engines of Pub MED, Science direct, MEDLINE Google and Google scholar. Key word and phrases used were schizophrenia, causes, signs and symptoms, pathophysiology and treatment of schizophrenia. A total of 50 relevant articles/book chapter were used for comprehensively writing this review.

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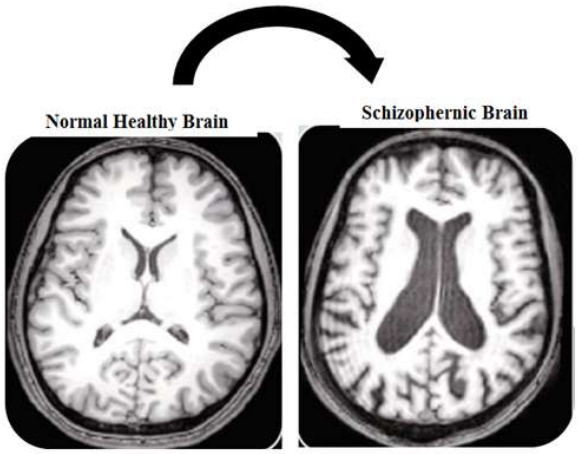
Pathophysiology of Schizophrenia:

Anatomical Defect: The researches investigated the structural variations in the brain of schizophrenic patients, such as changes in volume and modifications of various parts mainly cortical, subcortical, global and white and gray matter of the brain.[6] Numerous neuropathological investigations and brain imaging showed changes in different areas and specific regions of brain in schizophrenic patients. Researcher investigated the delicate reductions in gray matter and irregularities of white matter in brain areas and circuits.[7] Many studies validated that the progression of gray matter reduction, particularly in the region of temporal lobe is associated with anti-psychotic drug treatment during the period of illness.[8] Several studies reported no confined anatomical variations and functional anomalies specifically associated with the disorder.[9-13]

Dysfunctional Neurotransmission: The complex pathological examination indicated abnormalities in the

Fig-1: Comparsion of structural variations in Healthy versus Schizophrenic brain



release of dopamine, serotonin, glutamate and GABA neurotransmitter that is leading cause of heterogeneous symptoms.[14] A number of brain imaging and pharmacological literature verified that psychotic symptoms such as delusion and hallucination are associated with dopaminergic neurotransmission dysfunction.[15-17] However the dysfunctional dopaminergic neurotransmission is unable to explain the complete range of this disorder because most of the schizophrenic like symptoms were also observed in other psychiatric conditions.[18-21] Many other pharmacological and physiological studies of brain imaging reported that cognitive dysfunctions were due to the disturbed glutamatergic function specifically NMDA-type glutamate receptor which is responsible to cause the para albumin positive interneuron dysfunction in the region of cerebral cortex and hippocampus and dysfunction of these spiking neurons may lead to cognitive dysfunction in schizophrenia.[22] Numerous symptoms of schizophrenia are due to unusual actions of dopamine receptor,especially at D2 site. Four main dopaminergic pathways involved to initiate these symptoms are as under.[16,23]

1. The mesolimbic pathway produces excessive dopamine responsible for positive symptoms of schizophrenia
2. The mesocorticol pathway play role in initiating negative symptoms due to decrease in the level of dopamine.
3. The nigrostriatal pathway originating from substantia nigra and culminating at caudate nucleus
4. Tuberoinfendibular dopamine outcome blockage produces an elevated prolactinlevel and cause symptoms of amenorrhea, galactorrhea and decrease libido.

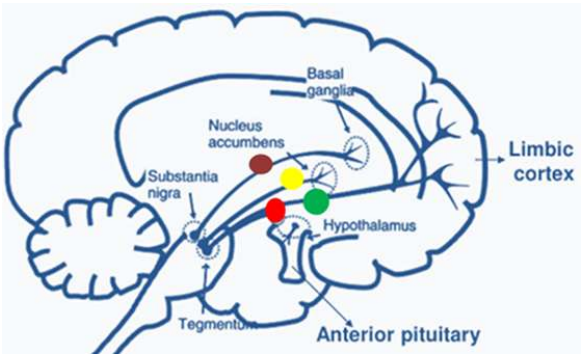
Stress related Signaling Cascade: The connectivity, maintenance and development of synapses is dependent on stress associated signaling cascade, especially oxidative stress and inflammatory processes. Microglia are responsible for synaptic preservation and destruction, particularly synaptic lopping during puberty, particularly synaptic lopping during puberty and the main histocompatibility complex I as well as the complement system involving synaptic plasticity are the examples of this. Moreover the investigation on preclinical models suggested piercing upsurge of parvalbumin interneurons, which are indicated mainly susceptible to produce oxidative stress and inturuption of arrangement in myelination.[24]

Causes of schizophrenia: Numerous studies documented several factors such as genetic, environmental and family history (20-40%) played a role in the development of schizophrenia.

1. Genetic Factors

Investigations revealed that 80% development of schizophrenia is due to the hereditary difference in gene and 6.5% risk associated with this disease in first degree relative, 40% in monozygotic twins and if one parent affected; there

Fig 2: Brain pathways involved in schizophrenia



is 13% chance and if both parents then ther is a 50% risk.[25] Many genes involved in schizophrenia showed unknown transmission and expression. Around 5% cases showed CNVs (copy number variants) specifically 22q11, 1q21and 16p11 are comorbids with autism and intellectual disabilities. Occurrence of schizophrenia increases to 20 fold in these patients 20 fold.[26-28]

2. Environmental Factors

Many studies investigated that several environmental factors were also associated in the development of schizophrenia such as living environment,drug use and maternal stress increased the risks of schizophrenia.[29-31] Maternal stress causes hypermethylation in animal model lead to reduction of GABAergic neurons along with nutritional deficiencies as well as maternal obesity is also the potential risk features of schizophrenia. In both maternal stress and infection,inflammatory protein IL-8 andTNF alters the fetal neuro development.[32,33]

Researchers investigated that in some people intestinal tract dysfunction due to non-celiac gluten sensitivity of intestinal flora and elevated level of serum biomarkers such as anti-gliadin IgG and IgA antibodies is also accountable to cause schizophrenia.[34] Additional factor that play an important role are childhood trauma, being bullied or abused, critical and hostile parents, social isolation, unemployment, cultural discrimination, poor housing condition and death of parents. These are related to the increased risk of psychosis.

3. Drug causing Factors

Approximately half of the schizophrenic patients are drug and alcohol abusers. It has been reported that amphetamine, cocaine and minor amount of alcohol use can develop transient stimulant of psychosis via kindling mechanism. Cannabis is also the contributing factor among those at risk.[35]

4. Developmental Factors

Many other considerations such as hypoxia, stress, infection, malnourished mother during fetal development may increase the risk of schizophrenia in future.[36] On the other hand socio-economic reasons,difficulty in childhood, first and second

generation immigrant credentials are also linked to schizophrenia.[37] Social pressure, such as financial sufferings may predispose person in the way of delusion, fearfuland paranoid thoughts.[38] It has been proposed that most of the schizophrenic people are born in winters or spring; as there is 5 to 8% increased risk of in utero viral exposure during these seasons. Other infection such as *Toxoplasma gondi* and *Chlamydia* during pregnancy may also increase the risk of this disease.[39]

Management and treatment of schizophrenia: Schizophrenia is managed and treated with antipsychotic medication along with the psychological session , therapies , social support and rehabilitation. According to the survey report, 20% of patients showed positive result after first episode of psychosis while 35% patient showed relapse.[40]

Pharmacological treatment: Neuroleptic drug both typical (first generation) antipsychotic drug including Chlorpromazine, Prochlorperazine, Thioridazine, Haloperidol, Fluphenazine and atypical (second generation) including Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone and Zipresidone has been used for many years for acute and long term treatment of schizophrenia.[41] The mechanism of antipsychotic drug to antagonize dopamine $D_{1\text{-}5}$ receptors, but second generation drug, particularly act on serotonin 5HT receptor to reduce neurotransmitter binding in forebrain and create feedback loop that cause the release of more dopamine after taking drug.[42] The goal of the antipsychotic drug treatment is to manage psychotic symptoms at the lowest possible dose because these medications cause less severe side effects. The second generation antipsychotic drug is preferable over first generation due to more benefits and less extrapyramidal adverse effects.[43] The physician and psychiatrist prescribe a combination of drugs with different doses to achieve best possible results. Patient willingness and cooperation is also necessary for successful treatment.[44]

Psychological intervention: Psychotherapy may help to normalize schizophrenia by individual therapy to manage this illness through thought pattern and with the help of this schizophrenic patient learn to cope with stress and early warning sign of relapse can be identified.[46]. Social skills training can improve the communication and social interaction to provide support and educate families to deal with schizophrenia.[47] Vocational rehabilitation centers help and prepare people to find jobs. However, during periods of crisis severe symptoms may require the hospitalization and elctro-convulsive therapy may be considered for patients having depression.[48-50]

CONCLUSION:

It is important to check the contributory factors in schizophrenia patient, including genetic and non-genetic since the incidence rate of this disease is rapidly increasing.Currently, many treatment options are available to treat with schizophrenia, but future modeling is required for the treatment resistant patient.Several treatment options are developing where newer drugs and their combination has revealed promising results with or without non pharmacological therapy. Further investigations are required to discover and implement advance remedies for the treatment of schizophrenia.

Author Contribution:
Hafiza Tuseef Sayyar: Perceived the idea, write-up of manuscript
Afshan Siddiq: Supervised the whole project, examined the manuscript

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