



SCHIZOPHRENIA: UNRAVELING THE LABYRINTH OF ETIOLOGY AND EPIDEMIOLOGY

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ABSTRACT

Schizophrenia mental disorder is the combination of psychotic and neurotic disorder where the clinical symptoms and signs, duration and cognitive adjectives are well defined. In this, pharmacological treatments are existing successfully, even though they are likely relieving pain without dealing with the cause of the condition. The most risky constituents for schizophrenia are genetics and formational and operative abnormalities of brain. These factors are precautionable by the scientists by innovating new genetic information in the human genome and brain imaging techniques which direct inquiries the structural functionality of neurochemistry. Dopamine role does not ignore in current assumption of pathophysiology but it emphasizes the integration of neural systems in the expression of illness and symptoms generating in limbic system. Advanced observations for futuristic discovery are arising from the combination of molecular genetics and brain imaging techniques.

KEY WORDS

Schizophrenia, Pharmacological, Pathophysiology, Dopamine, Molecular Genetics, MRI.

INTRODUCTION:

Schizophrenia mental disorder is accumulation of psychotic and neurotic disorders and it is emerged by structural and utile abnormalities in brain and genome which directly reflects in thought, emotion, sentiments and thinking of people in which ideas are not logically related. The word *schizophrenia* derived from the Greek words *schizo* and *phrenos* which is significantly best translated as "shattered mind". The concept "Schizophrenia" was known in the early years of the 20th century and it was described as the disintegration among emotion, thought, and action. It is very attenuate and severe disease because it attacks 1% of individuals of all geographical area, cultural groups etc. in this psychotic disorder, we find that the aggregate

distortions of reality, retraction from social interaction, disorganization and fragmentation of perception, thought, thinking, sentiments and emotions. Schizophrenia is a continuous psychotic illness which begins in adult age and lasts a life- time. Schizophrenia affects the human's clinical characteristics, responses towards interventions and tissue response characteristics. [1,3]

History: In 1860, MOREL who was the psychiatrist of Belgium presented the description of 13 years old boy. This boy was genius in his early age but after some time he lost his interest from the study. He became taciturn and his memory level turned zero. Now he wants to kill his father. Morel named this disease "Dementia Praecox" it means – deterioration at an early age. Emil Kraepelin translated Morel's Dementia Praecox into

Dementia Praecox, a term focused on the distinguishable cognitive process (Dementia) and early onset (Praecox) of the disorder. According to, German psychiatrist Kraepelin this disorder find out in children and adolescence and commonly interlinked with hallucinations and delusions [1,14,27]. Eugen Bleuler used the term Schizophrenia, which replaced the term Dementia Praecox. He used this term to describe the proximity of schisms between thought, emotion and behavior in patients with the disorder [3,4].

The Four Aspects: Bleuler presented some basic symptoms which describes the schizophrenia effectively. These symptoms are

1. Atrocity
2. Affective Disturbances
3. Autism
4. Ambivalence [1,27]

Clinical Signs and Symptoms: In 1980, T.J. Crow presented a categorical description of schizophrenic patients into Type I and Type II, on the basis of presence and absence of productive (positive) and deficit (negative) symptoms. Positive symptoms are: delusions and hallucinations. The negative symptoms are: blunting, alogia (lack or decline in speech), or avolition (lack or decline in motivation), blocking, poor glooming, lack of motivation, anhedonia and social withdrawal [20, 21]. Type I patients have mostly positive symptoms, normal brain structures on CT scans and relatively give a positive response to treatment. Type II patients have mostly negative symptoms, abnormal brain structure on CT scans and give negative response to treatments [18]. The most commonly-used criteria for diagnosing schizophrenia are from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD). The most recent versions are ICD-10 and DSM-IV-TR [24, 25]. There are some common symptoms of schizophrenia, but none of them appears at the same time. Eight months are essential for the diagnosis of schizophrenia.

● Mental Status Examination

1. **Odd behavior:** It includes catatonic behavior, absence of personal hygiene, talking in rhymes, and lack of social interaction.

2. **General Descriptions:** Silent and immobile person but sometimes talkative and present bizarre postures, lack of spontaneity in speech and movement, clumsiness and stiffness in body movements.

● Mood, Feelings, and Affect

1. **Emotional Responsiveness:** it includes lack of emotional responsiveness because patients don't know how to react in extreme situations like; happiness, sadness and anxiety.

2. **Mix Feelings:** omnipotence, intimidation at the disintegration of their souls, perplexity, sense of isolation, depression etc.

3. **Inappropriate Effect:** Failure to react with appropriate sentiments towards events which is occurring in the environment.

● Perceptual Disturbances

1. **Hallucinations:** Imaginary visuals and voices telling the person what to do or giving comments on the person's behavior negatively. Some hallucinations are unfounded sensations which are occurred in bodily organs called Cenesthetic Hallucinations. It includes; burning sensation, pushing sensation and cutting sensation.

2. **Illusions:** It is based on real images and sensations. Basically illusions are distortion of real images and sensitivity.

● Thought

1. **Content of Thought:** A person believes that an outside power controls their thoughts and behavior. They have intense preoccupation with deconstructed symbolic, psychological or metaphysical thoughts.

2. **Form of Thought:** It includes dissociative behavior, incoherence, word salad, mutism and tangentiality.

3. **Incoherent Thought Process:** Illogical thinking, belief in supernatural forces, idea blocking, impaired attention, poor abstraction and abilities etc.

● Audacity, Acuteness, Self-immolation, and Maniacal

1. **Neurological Deficits:** It includes violent and impulsive behavior, delusions of dissociative tendency, previous episodes of acuteness etc.

2. **Suicide:** Suicide attempt by 50% of all schizophrenic patients and 10-15% die by suicide. They feel emptiness, escape from mental torture or imaginary voices which command them to kill themselves.

3. **Homicide:** Possible indicators of homicide activity are a history of previous violence, dangerous behavior while hospitalized and hallucinations or delusions.

● Sensorium and Discernment

1. **Orientation:** Lack of orientation regarding person, time, and place. Schizophrenic patients may give incorrect answers to question like; I m Christ.

2. **Judgment and Insight:** They have poor insight, poor compliance, inferiority complex etc are described. [15,25,29]



Figure 1. “Schizophrenic Withdrawal.” (Courtesy of Sid Bernstein, Research Facility, Orangeburg, NY.)

Epidemiology

The population who have a specific characteristic of schizophrenia in a given time period is between 0.6% and 1.9% in the US. The estimation of annual proportion of affected population in the US is 5.1 per 1,000 lives. The prevalence of disorder equal in males and females both. Males experienced this disorder in their early 20s and females experienced in their late 20s or early 30s [10, 12, 19]. Schizophrenia found in all geographical areas and all the societies. A collaborative study by the WHO (World Health Organization) in 10 countries found that the occurrence of schizophrenia in across the global assignments or geographical areas [1, 2, 6].

Subdivision of Schizophrenia

Historically, in the West schizophrenia was categorized into Simple, Catatonic, Hebephrenic, and Paranoid. Now the DSM consists of five sub-categories of schizophrenia viz.

- **Catatonic Type Schizophrenia:** - This type of schizophrenia is developed suddenly. There is two stages of catatonic type schizophrenia-

I. Stupor stage OR Withdrawn stage: - Where person become static for many hours and because of it they don't know about their bodily movements and functions

like; swelling, hunger, secretion of saliva from mouth etc,

II. Excited stage: - Where a person is excited suddenly. In this stage person talks loudly and not has clarity in his voice and do the weird things which is not a normal thing.

● Disorganized Type Schizophrenia:

Hebephrenic Schizophrenia was named in DSM-III which has change in DSM-IV as Disorganized Schizophrenia. In this type of schizophrenia some symptoms are recognized like; weird behavior, unusual smile, hallucinations, delusions (sex related, religious, punishable and hypochondriacal) etc.

● Paranoid Type Schizophrenia:

- where delusions and hallucinations are exist but thought disorder, disorganized behaviour, and affective flattening is absent. In paranoid schizophrenia disorganization is not to so extreme as to cause the person to give up attempts to understand and deal with his

situations through delusional interaction with the all-over world.

- **Residual Type Schizophrenia:** - where positive marks and symptoms are existing at a low intensity only.

- **Undifferentiated Type Schizophrenia:** - Psychotic signs and symptoms are exist but the criteria for paranoid, disorganized, or catatonic types has not been met. It is the pre-stage of schizophrenia. [25]

Table1. DSM-IV-TR Diagnostic Criteria for Schizophrenia Subtypes (From American Psychiatric Association. Diagnostic and Statistical Manual Disorders. 4th Edition. Text rev. Washington,DC: American Psychiatric Association, copyright 2000,with permission).

<ul style="list-style-type: none"> • Paranoid type
<ul style="list-style-type: none"> • A type of schizophrenia in which the following criteria are met: Preoccupation with one or more delusions or frequent auditory hallucinations. None of the following is prominent: disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect.
<ul style="list-style-type: none"> • Disorganized type
<ul style="list-style-type: none"> • A type of schizophrenia in which the following criteria are met: All of the following are prominent: disorganized speech, disorganized behavior, flat or inappropriate affect. The criteria are not met for catatonic type.
<ul style="list-style-type: none"> • Catatonic type
<ul style="list-style-type: none"> • A type of schizophrenia in which the clinical picture is dominated by at least two of the following: motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor excessive motor activity (that is apparently urposeless and not influenced by external stimuli) extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing echolalia or echopraxia
<ul style="list-style-type: none"> • Undifferentiated type
<ul style="list-style-type: none"> • A type of schizophrenia in which symptoms that meet Criterion A are present, but the criteria are not met for the paranoid, disorganized, or catatonic type.
<ul style="list-style-type: none"> • Residual type
<ul style="list-style-type: none"> • A type of schizophrenia in which the following criteria are met: Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in Criterion A for schizophrenia, present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences

Table2. ICD-10 Diagnostic Criteria for Schizophrenia (From World Health Organization, the ICD-10 Classification of Mental and Behavioural Disorders Diagnostic Criteria for Research, Copyright, World Health Organization, Geneva, 1993)

This overall category includes the common varieties of schizophrenia, together with some less common varieties and closely related disorders.
General criteria for paranoid, hebephrenic, catatonic, and undifferentiated schizophrenia
G1. Either <i>at least one</i> of the syndromes, symptoms, and signs listed under (1) below, <i>or</i> at least two of the symptoms and signs listed under (2) should be present for most of the time during an episode of psychotic illness lasting for at least 1 month (or at some time during most of the days).
1. At least one of the following must be present: <ul style="list-style-type: none"> a. thought echo, thought insertion or withdrawal, or thought broadcasting; b. delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception; c. hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body;

<p>d. persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g., being able to control the weather, or being in communication with aliens from another world).</p> <p>2. Or at least two of the following:</p> <p>a. persistent hallucinations in any modality, when occurring every day for at least 1 month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent overvalued ideas;</p> <p>b. neologisms, breaks, or interpolations in the train of thought, resulting in incoherence or irrelevant speech;</p> <p>c. catatonic behavior, such as excitement, posturing or waxy flexibility, negativism, mutism, and stupor;</p> <p>d. “negative” symptoms, such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).</p>
<p>G2. Most commonly used exclusion clauses</p> <p>1. If the patient also meets criteria for manic episode or depressive episode, the criteria listed under G1(1) and G1(2) above must have been met <i>before</i> the disturbance of mood developed.</p> <p>2. The disorder is not attributable to organic brain disease or to alcohol- or drug-related intoxication, dependence, or withdrawal.</p>
<p>Comments</p> <p>In evaluating the presence of these abnormal subjective experiences and behavior, special care should be taken to avoid false-positive assessments, especially where culturally or subculturally influenced modes of expression and behavior or a subnormal level of intelligence are involved.</p>
<p>Pattern of course</p> <p>In view of the considerable variation of the course of schizophrenic disorders it may be desirable (especially for research) to specify the pattern <i>of course</i> by using a fifth character. Course should not usually be coded unless there has been a period of observation of at least 1 year.</p>
<p>Continuous</p> <p>No remission of psychotic symptoms throughout the period of observation.</p>
<p>Episodic with progressive deficit</p> <p>Progressive development of cognitive symptoms in the intervals between psychotic episodes.</p>
<p>Episodic with stable deficit</p> <p>Persistent but nonprogressive “negative” symptoms in the intervals between psychotic episodes.</p>
<p>Episodic remittent</p> <p>Complete or virtually complete remissions between psychotic episodes.</p>
<p>Incomplete remission Complete remission Other Course uncertain, period of observation too short Paranoid schizophrenia</p> <p>A. The general criteria for schizophrenia must be met.</p> <p>B. Delusions or hallucinations must be prominent (such as delusions of persecution, reference, exalted birth, special mission, bodily change, or jealousy; threatening or commanding voices, hallucinations of smell or taste, sexual or other bodily sensations).</p> <p>C. Flattening or incongruity of affect, catatonic symptoms, or incoherent speech must not dominate the clinical picture, although they may be present to a mild degree.</p>
<p>Hebephrenic schizophrenia</p> <p>A. The general criteria for schizophrenia must be met.</p> <p>B. Either of the following must be present:</p> <p>1. definite and sustained flattening or shallowness of affect;</p> <p>2. definite and sustained incongruity or inappropriateness of affect.</p> <p>C. Either of the following must be present:</p>

<ol style="list-style-type: none"> 1. behavior that is aimless and disjointed rather than goal-directed; 2. definite thought disorder, manifesting as speech that is disjointed, rambling, or incoherent. <p>D. Hallucinations or delusions must not dominate the clinical picture, although they may be present to a mild degree.</p>
<p>Catatonic schizophrenia</p> <p>A. The general criteria for schizophrenia must eventually be met, although this may not be possible initially if the patient is uncommunicative.</p> <p>B. For a period of at least 2 weeks one or more of the following catatonic behaviors must be prominent:</p> <ol style="list-style-type: none"> 1. stupor (marked decrease in reactivity to the environment and reduction of spontaneous movements and activity) or mutism; 2. excitement (apparently purposeless motor activity, not influenced by external stimuli); 3. posturing (voluntary assumption and maintenance of inappropriate or bizarre postures); 4. negativism (an apparently motiveless resistance to all instructions or attempts to be moved, or movement in the opposite direction); 5. rigidity (maintenance of a rigid posture against efforts to be moved); 6. waxy flexibility (maintenance of limbs and body in externally imposed positions); 7. command automatism (automatic compliance with instruction).
<p>Undifferentiated schizophrenia</p> <p>A. The general criteria for schizophrenia must be met. Either of the following must apply:</p> <ol style="list-style-type: none"> 1. insufficient symptoms to meet the criteria for any of the subtypes 2. so many symptoms that the criteria for more than one of the subtypes listed above are met.
<p>Postschizophrenic depression</p> <p>A. The general criteria for schizophrenia must have been met within the past 12 months but are not met at the present time.</p> <p>B. One of the conditions in Criterion G1(2) a, b, c, or d for general schizophrenia must still be present.</p> <p>C. The depressive symptoms must be sufficiently prolonged, severe, and extensive to meet criteria for at least a mild depressive episode.</p>
<p>Residual schizophrenia</p> <p>A. The general criteria for schizophrenia must have been met at some time in the past but are not met at the present time.</p> <p>B. At least four of the following “negative” symptoms have been present throughout the previous 12 months:</p> <ol style="list-style-type: none"> 1. psychomotor slowing or underactivity; 2. definite blunting of affect; 3. passivity and lack of initiative; 4. poverty of either the quantity or the content of speech; 5. poor nonverbal communication by facial expression, eye contact, voice modulation, or posture; 6. poor social performance or self-care.
<p>Simple schizophrenia</p> <p>A. There is slow but progressive development, over a period of at least 1 year, of all three of the following:</p> <ol style="list-style-type: none"> 1. a significant and consistent change in the overall quality of some aspects of personal behavior, manifest as loss of drive and interests, aimlessness, idleness, a self-absorbed attitude, and social withdrawal; 2. gradual appearance and deepening of “negative” symptoms such as marked apathy, paucity of speech, underactivity, blunting of affect, passivity and lack of initiative, and poor nonverbal communication (by facial expression, eye contact, voice modulation, and posture); 3. marked decline in social, scholastic, or occupational performance. <p>B. At no time are there any of the symptoms referred to in criterion G1 for general schizophrenia, nor are there hallucinations or well-formed delusions of any kind; i.e., the individual must never have met the criteria for any other type of schizophrenia or for any other psychotic disorder.</p> <p>C. There is no evidence of dementia or any other organic mental disorder.</p>
<p>Other Schizophrenia, unspecified Schizophrenia</p>

Paranoid type

A type of schizophrenia in which the following criteria are met: Preoccupation with one or more delusions or frequent auditory hallucinations. None of the following is prominent: disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect.

Disorganized type

A type of schizophrenia in which the following criteria are met: All of the following are prominent: disorganized speech, disorganized behavior, flat or inappropriate affect. The criteria are not met for catatonic type.

Catatonic type

A type of schizophrenia in which the clinical picture is dominated by at least two of the following: motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor excessive motor activity (that is apparently purposeless and not influenced by external stimuli) extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent

Undifferentiated type

A type of schizophrenia in which symptoms that meet Criterion A are present, but the criteria are not met for the paranoid, disorganized, or catatonic type.

Residual type

A type of schizophrenia in which the following criteria are met: Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in Criterion A for schizophrenia, present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences)

Etiology

Schizophrenia is considered as a single disease, but its diagnostic category involves an association of disorders with heterogeneous causes but with somewhat similar behavioral symptoms.

Stress- Diathesis Model

According to this model, the interlinkage of biological, psychosocial and environmental factors, a person's specific diathesis, when acted on by the stressful influence, it allows the symptoms of schizophrenia to develop. [13]

NEURODEVELOPMENTAL HYPOTHESES

1. Heritability of Schizophrenia: - Schizophrenia has heterogeneous etiologies which are emerged by the interaction between multiple genes and multiple environmental factors. Studies of schizophrenia upon twins described that it is occurred 45% in MZ twins and 14% in dizygotic twins. A current Meta analytic study has shown 81% heritability for schizophrenia. Adoption study shows a lifetime rate is 9.4% in the adopted away offspring of schizophrenia parents vs. 1.2% in control adoptees.

2. Drug dependence and the growth of Schizophrenia:

- Drug abusive habit is one of the most markable cause of the development of schizophrenia. Administration of D-Amphetamine (which is acts upon dopaminergic) to healthy people it produces a psychotic symptom. Heavy uses of cannabis, lysergic acid diethylamide or psilocylin or ketamine also develop psychotic symptoms.

3. Pyramidal Cell Abnormalities: - According to the neurodevelopment theory of schizophrenia there are various neuroanatomical deficiencies in the brain develop the schizophrenia disorder. Glantz and Lewis studied that pyramidal cells which is exist in layer III of the DLPFC subjects with schizophrenic shown a 23% decrease in spine density when compared with normal controls. There are various factors which may create neurodevelopmental dysfunction i.e.; reduced anisotropy of the white matter or altered hippocampal volume and shape these changes may evolve in pyramidal cells.

4. Reelin and GABA Signaling Systems: - Basically Reelin helps in normality of the brain during embryogenesis and it affects synaptic plasticity in adult age. Reduction in Reelin mRNA and protein in cerebellar, hippocampal and frontal cortices shown in the schizophrenic patients. Reelin reduction was associated with decrease in GAD67-K Da. GABA stands for γ -aminobutyric acid. It is the inhibitory amino acid neurotransmitter. Schizophrenic patients lost their GABAergic neurons in

the hippocampus which develop the hyperactivity.
[34,37]

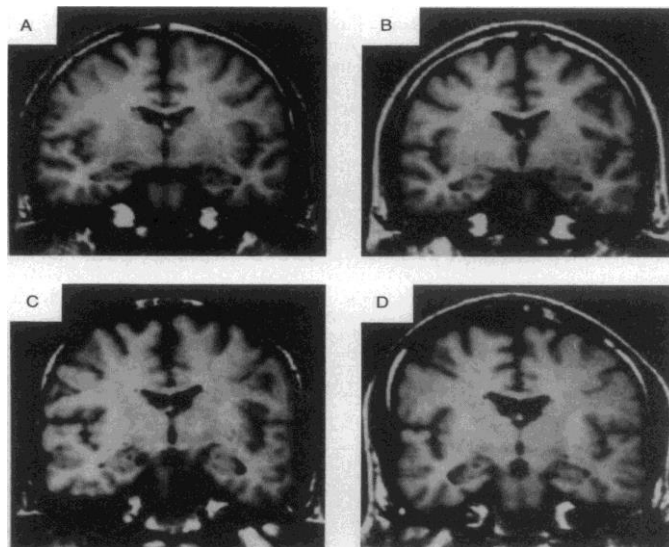


Figure 2: MRI Coronal views from two sets of monozygotic twins discordant for schizophrenia show subtle enlargement of the lateral ventricles in the affected twins (panels B and D) compared with the unaffected twins (panels A and C), even when the affected twin has small ventricles. (Reprinted with permission from Suddath RL, Christison GW, Tirrey EF, Casanova MF, Weinberger DR, Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. N Engl J Med. 1990; 322:789.)

Dopamine Hypotheses

This hypothesis developed by the results of too much dopaminergic activity. There are two observations: First, the dopamine receptor antagonists are co-extensive with their ability to acts as D2 receptor of dopamine. Second, amphetamine drug increase the dopaminergic activity. The major role of dopamine is in the pathophysiology of schizophrenia. It is correlated with the studies which measured the plasma concentrations of dopamine metabolite, homovamillie acid and it reflects in CNS. Thus, this hypothesis explains the manifestation of schizophrenia. A half century ago studies find that the antipsychotic drugs block the dopamine receptors in brain and reduce psychotic symptoms of dopaminergic system which causes schizophrenia. [1, 2]

Neurobiology

A neurobiology etiology has shown a various researches which indicated a pathophysiological role in certain areas of brain like; the limbic system, the frontal cortex, cerebellum and the basal ganglia.

1. Limbic System: - Limbic system controls the emotions. Pathophysiology of schizophrenia includes postmortem tissue studies and animal model

experiments. This finding reviewed by Harrison et al. and by this several guiding formulations emerges:

- (i) Schizophrenia continuously affects the limbic system.
- (ii) Various chemical systems like; monoamines and dopamine affected in schizophrenia. [11,22]

2. Basal Ganglia and Cerebellum: - The basal ganglia and cerebellum have been associated in schizophrenia by the two reasons: First, schizophrenic patients have shown odd movements, tardive dyskinesia, since the cerebellum and basal ganglia involved in movement control. Second, the cerebellum and basal ganglia are connected to the frontal lobes and its dysfunction seen in brain imaging studies. [5,36,38]

Genetic Architectural Hypotheses

DNA sequence variation arises the genetic risks for schizophrenia. The risk factors are Single Nucleotide Polymorphisms (SNPs) and Copy Number Variants (CNVs).

I. SNPs:- Genome Wide Association Studies (GWAS) and meta-analysis involving about 21,000 cases and 38,000 controls by the Psychiatric Genetics Consortium (PGC), 22 loci were founded in SNPs which is sufficient for schizophrenia. One or more genes at the locus and one

or more variances within the gene may increase risk of schizophrenia.

II.CNVs: - CNVs are length of DNA. It is too small to see but we can see it by using karyotyping methods. Microarray and other technologies present that CNVs are a common characteristic of genome but also it affects some specific genomic regions which are interlinked with an increased risk of schizophrenia.

Population based study estimated that 5% of cases of schizophrenia due to CNVs causal effect. More than half of all chromosomes have been extensively associated with the schizophrenia according to the various studies, but the long arms of chromosomes 5, 11 and 18 and short arm of chromosome 19 and the x chromosome commonly implicated. [27,32,33,35].

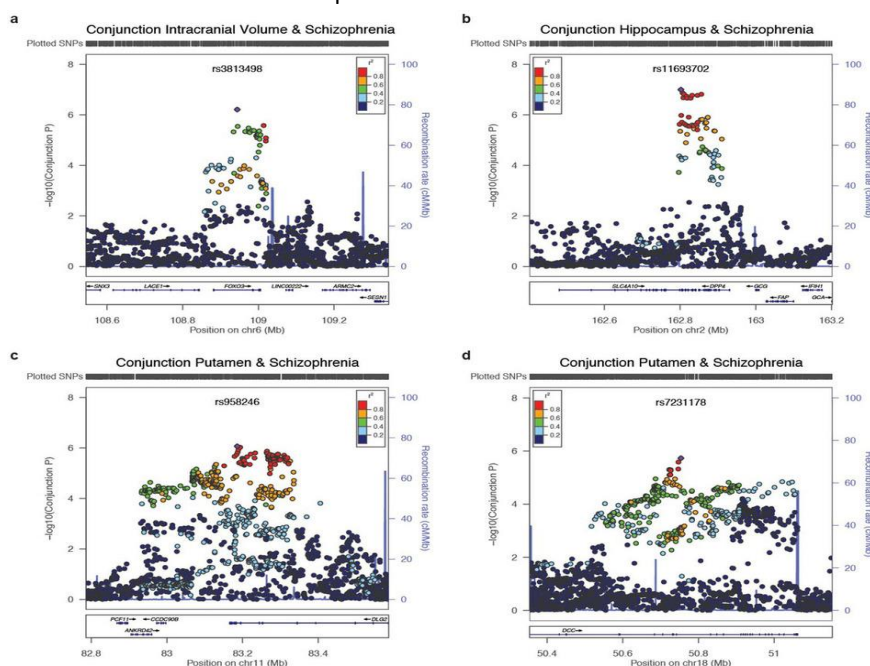


Figure3. “Regional Plots of Genetic Loci” (courtesy of Abbott A.)

Psycho-neuroimmunology: There are various immunological abnormalities have been associated with schizophrenic patients. These abnormalities include decreased T-cell interleukin-2 production, reduced number and responsiveness of peripheral lymphocytes, humoral reactivity to neurons, abnormal cellular, antibrain antibodies. Several epidemics of the disorder are neurotoxic viral infections, increased number of physical anomalies at birth and pregnancy, geographical clusters etc. [16,31,38].

Course and Prognosis

Course: The symptoms of schizophrenia usually recognized only retrospectively. The symptoms are beginning in the adolescence age with the growth of prodromal symptoms which evolve in days to a few months. Many types of changes like; a social and environmental change, completion of college, relative's death and other disturbing element may develop the psychotic symptoms. Patients usually relapse, however,

the illness during the first 5 years which indicated patients course after diagnosis. [1,27]

Prognosis: Various studies conducted over the 5 to 10 years after the hospitalization of schizophrenia, only 10 to 20% of patients have shown the good outcome and 50% of patients have shown the poor outcome with the repetition of hospitalization, psychotic symptoms, critical symptoms of mood disorder and attempts to hurt himself or herself. Schizophrenia sometimes described good prognosis like; late onset, actual onset, hereditary history, good supportive signs etc [17]. Recorded remission rate is floating in between 10 to 60% and the estimation is 20 to 30% of all schizophrenic who are able to live a normal life. Approximate 20 to 30% patients experienced an average symptom and 10 to 60% of patients remain disorganized by the disorder for their entire life. [1,9]

Treatment: The clinicians have to focused on the treatment of the schizophrenia by three observations- First, it is based on the analysis of two elements like;

how the patient has been affected by the disorder and how will be the patient cured by the medication and therapies. Second, 50% rate for the augmentation of schizophrenia by the contribution of environmental and psychological factors. Pharmacological agents are used to handle chemical imbalance. Third, the complexity of schizophrenia depends upon the multifactor approaches. [2,28]

1. Hospitalization: - The aim of hospitalization is to safe patients against the idea of self-harm, to harm others and to take care of their substantial needs. The primary goal is to develop mutual concern and relationship between patients and community support system. Hospitalization decreases stress, maladjustment and build rehabilitation. Research studies shows that short stay of 4 to 6 weeks more effective as compare to long term hospitalization.

2. Biological Therapies

(I)Pharmacotherapy: - Antipsychotic drugs are introduced in the early 1950s. Antipsychotic medicines include two major classes: Dopamine receptor and SDAs.

(i)Dopamine Receptor Antagonists: - The dopamine receptor antagonists specifically effective treatment of the positive symptoms of schizophrenia. There are two disadvantages of this- First, only approximately 25% patients are recovered with schizophrenia. Second, dopamine receptor antagonists are associated with annoying and critical adverse effects.

(ii)Serotonin-Dopamine Antagonists: - The SDAs produce no extrapyramidal symptoms. It is interacting with serotonin and glutamate receptors. SDAs include **clozapine, risperidone, olanzapine, sertindole, quetiapine and ziprasidone**. These drugs replaced the dopamine receptor antagonist. [26,30]

(II)Electroconvulsive Therapy: - It may be indicated catatonic patients. If the patient responds towards this therapy then he has been ill less than 1 year. This therapy applied on those patients who are non-responsive to pharmacological therapies. [1,9]

3. Psychosocial Therapies: - Psychosocial therapies goal is to decrease the maladjustive behavior of patients towards vocational and social environment. This therapy carried out at many sites like; hospitals, clinics, home, social clubs, health centres, etc.

(I)Social Skill Training: - It is blended with the behavioral skill therapy. This training involves various tools and

methods like; role playing, videotapes of the patients, spontaneous practices, homework assignments, etc.

(II)Assertive Community Treatment: - ACT program eventually developed by researchers Madison and Wisconsin in the 1970. In this, patients are ascribed one community or team which includes case manager, general physicians, nurse, and psychiatrist who serves patients 24*7.

(III)Group Therapy: - Group therapy focuses on the real-life problems and relationships which are faced by the patients in their day to day life, it reduces seclusion, increase cohesion and build a realistic environment.

(IV)Cognitive Behavioral Therapy: - Cognitive behavioral therapy improve cognitive deterioration, distractibility and judgment. By this therapy patients develop their cognitive insight. [1,7,8]

4. Vocational Therapy: - Vocational therapy includes shelter home or workshops, job clubs, transitional employment programs. [30]

Five Recently Developed Antipsychotics

Many companies have worked on old antipsychotics because they want to reduce the side effects of these antipsychotics which indirectly harm the patient's body. There are few antipsychotic drugs which are recently developed-

1. Rexulti(2015)
2. Latuda(2010)
3. Saphris(2009)
4. Fanapt(2009)
5. Invega(2006)[23]

CONCLUSION

The overall study of schizophrenia like their signs and symptoms, factors affecting schizophrenia, etiology, epidemiology and as well as treatment shows that this psychotic disorder has difficult to find, handle, anticipated and to treat. Schizophrenia linked with the neuroimaging studies and as well as structural and operative changes in genes. The structural and functional changes in brain are measured by MRI but it is also in under investigation, we attempt to identify those people who are at greatest risk and to learn target treatment by reduces their side effects on patients. On the other hand, genetic findings pave the way for next generation of studies. It integrates genome with other 'omics', to develop newer analytical and bioinformatics tools, to discover how genes are interact with the environment. It subsequently encourages the pharmaceutical investments. There are vast

opportunities to recover from this disorder but it depends upon the proper techniques, scales and expenses over it in a right proportion.

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