

Factors That Are Responsible in the Onset of Schizophrenia

transcribed plenary speech of

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Schizophrenia is a neuropsychiatric disorder which is affecting at least 1.5% of total population of Pakistan. There are several causes of Schizophrenia and in Pakistani hospitals; the drugs are prescribed based on the symptoms. However, genotyping for specific mutations, gene interactions and interaction of genes with environmental factors have not been investigated up to date. In this research, they have produced a data base on factors that could lead to Schizophrenia in Pakistani population. Schizophrenia is previously misdiagnosed due to lack of awareness in Pakistan. Schizophrenia is also a hereditary disorder which is transmitted from one generation to the next. Therefore, the object of this study was to identify the Factors that are responsible in the onset of schizophrenia.

The main problem in the treatment of schizophrenia is the lack of awareness and the side effects of the drugs used. Since there is no mutation based drugs and the drugs that are responsible for specific types of symptoms, multiple complex of drugs are given to patients leading to severe side effects in them. These drugs are not receptor specific. In the schizophrenia, dopamine concentration becomes high. It is the reduced activation of D1 dopamine receptors, over stimulation of D2 dopamine receptors and less activation of GABAergic receptors. The drugs mainly used in the treatment of schizophrenia are haloperidol and chlorpromazine which are neuroleptics which tend to decrease the dopamine levels in the brain. These drugs do not bind only to D1 and D2 receptors but also bind to D3, D4 Dopamine receptors and simultaneously they are binding to serotonin and histamine receptors leading to severe side effects. So, this study will assess in the broader context of enhancing the contribution of science and technology to human development both locally and globally.

Main symptoms of schizophrenia are delusions, hallucinations, lack of social environment and mood disorders. It affects 1% of world population including 0.34% Indian and 1.5 % Pakistani population. Since it is a hereditary disease, parents transmit the disease to children; first cousins are also at a higher risk of developing schizophrenia.

There are several types of schizophrenia such as paranoid, hebephrenic, catatonic, residual, schizoaffective and undifferentiated. The common symptoms of schizophrenia are positive symptoms, negative symptoms and cognitive symptoms. Positive symptoms include delusions, hallucinations, and abnormal movements whereas negative symptoms involve social withdrawal, lack of affect and reduced motivation. In cognitive symptoms, working memory is disturbed. It is believed that positive symptoms are related to over stimulation of D2 receptors and negative symptoms are related to reduced activation of D1 receptors. Cognitive symptoms are related to reduced activation of GABAergic receptors and excitatory neurotransmitter glutamatergic input in the prefrontal cortex involved in working memory. In Pakistan, criteria for diagnosis of schizophrenia are ICD – 10 and DSM – IV. Interaction between genetic predisposition and environmental factors influences the disruption in the neurodevelopment processes leading first to pre-morbid symptoms and to the onset and progression of schizophrenia. The causes of schizophrenia include heredity, environment and the changes in brain structure.

There are 40 genes responsible for schizophrenia. They have identified the SNP mutation in NRG1 (Neuregulin 1), AKT1 and COMT gene. It is also found that environmental factors such as metals, drug abuse, marital status, salary background, education play important role in the onset of schizophrenia. Changes in brain structure include large ventricles, reduced regional cerebral volumes and reduced activities of temporal lobe.

Neuregulin 1 are trophic factors which act through their erbB receptors, mainly erbB3 and erbB 4 receptors. Neuregulin has been shown to be involved in the myelination of central nervous system (CNS) axons, neuron glia communication.

In schizophrenic patients it is seen that NRG1 m RNA expression is increased but its receptor erbB3 expression is decreased.

A paper published in 2015 stated that NRG1 through its erbB4 receptors involved in the uptake of glutamate

excitatory amino acid carrier proteins. When the carrier proteins are increased dopamine will be removed from the synaptic cleft more efficiently. If it remains at the synaptic cleft it will lead to excitotoxicity and causes the desensitization of the receptors, which leads to failures in its function.

AKT1 gene belongs to serine/threonine-protein kinase family. It is an enzyme which is involved in neuronal excitability, synaptic plasticity and regulation of GABA-A receptor mediated synaptic inhibition. In schizophrenia, it is seen that the lower AKT1 gene expression. If there is a mutation or less of AKT1 protein, the efficiency of this gene is disturbed.

COMT (Catechol-O-methyltransferase) is an enzyme involved in the metabolism of catecholamine neurotransmitters. Mutated COMT gene contains Met in the place of Val at codon 158, producing less activity of the enzyme, lowering the breakdown of dopamine.

Schizophrenia is a disease which occurs in men and women without age limit. Postpartum depression due to the fluctuation in estrogen levels in women leads to severe psychotic problems. Single men, drug addicts and married women are significantly associated with schizophrenia.

In this study they have used inductively coupled plasma and mass optical emission spectrometry to detect the effect of trace metals in the blood of schizophrenic patients. However, in Pakistan, there was no significant effect of metals in the onset of schizophrenia.

In order to detect the mutation in NRG1, AKT1 AND COMT genes SNP1, SNP2 and SNP8 markers are used since the symptoms are different from one another. The mutations are detected by isolating DNA from the blood of schizophrenic patients, digesting them with specific restriction enzymes and sequencing them. According to this method, they have identified SNP1 by using *mun 1* and SNP2 by a specially designed enzyme and also found that the homozygous mutation in all patients.

In conclusion, postpartum depression, financial status and cannabis, tobacco are associated with schizophrenia. However, heavy metals do not play a significant role in the onset of schizophrenia in the Pakistani population. Only genetic variants of NRG1 and SNP8 have shown a strong correlation with schizophrenia and AKT1 gene is not involved in the onset of schizophrenia in the Pakistani population. COMTVAL58MET is strongly associated with schizophrenia and this mutation can be triggered by tobacco.