Immunological Perspectives of the Indian Schizophrenic Patients: An Over View.

Bisu Singh [7] *& Tapas Kumar Chaudhuri* [8] *

Abstract

Schizophrenia is a complex psychiatric illness with unknown etiology. Its prevalence in India has been found to vary between 0.7/1000 to 14.2/1000. Till date enormous effort have been put to unravel its underpinnings but the success has eluded the scientific faternity till now. Moreover, number of hypothesis such as dopamine, neurodevelopment, winter birth and autoimmune hypothesis have been proposed to explain its etiology. Recently, with the advent of the modern immunological techniques the autoimmune hypothesis of schizophrenia is gaining popularity. In India good number of studies has been conducted to investigate the immune-pathological aspect of schizophrenia. Many studies, done in the western world, have reported the immunological abnormalities among the Indian patients. Contrastingly, most of these findings did not have a common consensus. The non agreement of these results may be due to the varied ethnicity of the Indian populations as well as varied psycho-social conditions which may play an important role in the etiology of this disorder. Recently, schizophrenia is designated as a heterogeneous disorder with heterogeneous etiology. Being a country with heterogeneous population, the heterogeneous nature of this disease has added to this complexity. The authors have discussed here regarding the immunological findings among the Indian patients and also the main limitations of the Indian studies in addition with the future directions.

1. Introduction

Schizophrenia is perhaps the most enigmatic, tragic and devastating amongst all the psychiatric disorders. It is a psychotic illness manifested in its acute / active phase by delusions, hallucinations, impaired social functioning, loss of drive, neglect of self-care and disturbance of other mental processes. Symptoms are generally manifested during adulthood and cause different disabilities among the patients. Schizophrenia occurs equally in male and females but it appears earlier among males. The age of

[7] Department of Zoology, School of Life Sciences, Sikkim University , Gangtok 737102, Sikkim, India.

[8] Cellular Immunology Laboratory, Department of Zoology, University of North Bengal, Siliguri 734 013, West Bengal, India.

* corresponding author

onset is between 20-28 years in case of male and between 26-32 years in case of female (*Castle et al., 1991).* Negative symptoms tend to predominate in men, whereas depressive episodes, paranoid delusions and hallucinations tend to predominate in women. Onset of the disease in childhood, middle or old age is rare (*Kumra et al., 2001; Hassett et al., 2005)*. The lifetime prevalence of schizophrenia, the proportion of individuals expected to experience the disease at any time in their lives is commonly given at 1%. However, a systematic review of many studies found a lifetime prevalence of 0.55% (*Goldner et al., 2002)*. The studies in India have reported prevalence of 0.7/1000 to 14.2/1000. These studies reported a higher prevalence of the disorder in urban slums, in those living alone, with no schooling and unemployed (Rajkumar et al., 1993). Irrespective of the common assumption that schizophrenia occurs at similar rates worldwide, its prevalence varies across the world (*Jablensky et al., 1992)*, within countries (*Kirkbride et al., 2006*) and at the local and neighborhood level (*Kirkbride et al., 2007*).

2. Basic concept and historical overview of schizophrenia

The historical evidence suggests that psychotic symptoms or the madness similar to schizophrenia was known to humans from ancient times. Many signs and symptoms of disease similar to schizophrenia have been described in ancient Egyptian, Greek, Roman, and Chinese scripts. In India the disease having the symptoms like schizophrenia was first described in Atharva Veda around 1400 BC. It was assumed in Vedic period that health resulted from a balance between 5 elements (Buthas) and 3 humours (Dosas) and that an imbalance between these various elements might result in madness (Kyziridis, 2005).

In modern times schizophrenia has been described scientifically and elaborately since the seventeenth century. Falvet in 1851 first described cyclical madness termed as 'Folie Circulaire'. Later, Hecker termed it as 'Hebephrenia', or a silly, undisciplined mind after Hebe, goddess of youth and frivolity. In 1874, Kahlbaum used the term catatonia to describe a movement disorder characterized by a mannequin-like muscle stiffness associated with unusual postures and a pervading fear. Then, in 1878, Emil Kraepelin pointed out the difference between manic-depressive psychosis and schizophrenia, which he called "dementia praecox". Later in 1908, Eugen Bleuler criticized the use of the term dementia praecox and he suggested the term ‘schizophrenia’ for this disorder. He described four characteristic features of schizophrenia such as blunted affect (diminished emotional response to stimuli), loosening of associations (by which he meant a disordered pattern of thought, inferring a cognitive deficit), ambivalence (an apparent inability to make decisions, again suggesting a deficit of the integration and processing of incident and retrieved

information) and autism (a loss of awareness of external events, and a preoccupation with the self and one's own thoughts).

The decade of 1950s and 1960s saw vast improvement in the field of psychiatry and Bleuler's ideas became more refined. During this time concepts like "latent schizophrenia" and "pseudoneurotic schizophrenia" came into existence (Black and Bofelli, 1989). These concepts were included by American Psychiatric Association in its first editions of "Diagnostic and Statistical Manual of Mental Disorders". The first edition (American Psychiatric Association, 1952) emphasized intrapsychic mechanisms rather than classes of disease, whereas the second edition (American Psychiatric Association, 1968) shifted the emphasis to classification, but without listing specific criteria.

In 1960 major conceptual and theoretical differences were observed between diagnostic systems followed in various countries. It was observed that in United States/United Kingdom the prevalence of schizophrenia was greater in New York than London; while the reverse was true for manic depressive illness (Cooper et al., 1972). Investigators suggested that this type of discrepancy may occur due to the fact that the same patients received different diagnoses in different countries. These findings emphasized the necessity for more reliable diagnostic criteria which further led to the development of structured interviews such as the Present State Examination (Wing et al., 1967) and operational diagnostic criteria such as the St. Louis Criteria (Feighner et al., 1972).The Present State Examination reintroduced the concepts of Kurt Schneider (1887-1967) and his emphasis on "first-rank symptoms".

These developments further led to the reassessment of how schizophrenia and other mental disorders were diagnosed, culminating in the third edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-III) (American Psychiatric Association, 1980), which enumerated specific criteria for all recognized psychiatric disorders. DSM-III and its revision (DSM-III-R) (American Psychiatric Association, 1987) represented an accumulation various points of view such as the Kraepelinian diagnostic criteria like emphasis on the symptoms to be present for at least at least 6 months, Schneider's criteria like emphasis on specific delusions and hallucinations, and Bleulerian criteria such as thought disorder in the form of associative loosening or incoherence and affective blunting.

The decade of 1980s saw much development in the field of molecular genetics, brain imaging, and further with the introduction of neuroleptics, a careful and precise definition of schizophrenia was again reemphasized. It was realized that DSM-III and DSM-III-R definitions of schizophrenia are too narrow to diagnose the subclinical cases of schizophrenia in the family pedigrees. The geneticists emphasized the need to expand the diagnostic criteria for schizophrenia and advocated the inclusion of the

nonpsychotic forms such as simple and latent schizophrenia and "schizotaxia" as originally stressed by Bleuler (Tsuang et al., 2000). Further, psychopharmacological studies suggested that florid psychotic symptoms are probably not the core defining features for schizophrenia because negative or deficit symptoms persist in many of the cases. These criteria were addressed in DSM-IV (American Psychiatric Association, 1994) and DSM-IV-TR (American Psychiatric Association, 2000). Research conducted in 1980s, as well as field trials conducted specifically for the Task Force on DSM-IV, showed that deficit symptoms can be reliably defined and should be considered as core features of the disorder (Cosgrove and Krimsky, 2012). Recently in May 18, 2013 American Psychiatric Association published DSM V. The major changes in DSM V are the symptom threshold for schizophrenia was increased to at least two unlike DSM IV. Additionally, the diagnostic criteria no longer identify the subtypes.

3. Problems associated with schizophrenia

Schizophrenia is ranked as the ninth leading cause of disability among the people of age group between 15-44 years worldwide and fourth in developed countries (Murray and Lopez, 1996). Schizophrenia paralyses the normal life and hinders general activities such as attending school, working, having children etc. Apart from its effect on individuals and families, schizophrenia creates a huge economic burden for the society. In India, there is an estimated four million people affected with schizophrenia, with different degrees of impact on some 25 million family members (Gupta and Bala, 2013). Most of these patients are from poor families and can not avail the medical treatment due to their poor economic condition. Very often they live in remote villages with limited facility for transportation. Schizophrenia is yet to receive sufficient recognition as a major health concern to initiate the necessary research support for investigating its causes, treatments and prevention despite of its tremendous impact on patients, families and society. It has been found that the chances of improvement were significantly higher in Indian patients with the shorter duration of illness (less than one year), with no family history of mental illness, with acute onset and younger age (Ray and Kapur, 1963) though the medical facilities in India for schizophrenic patients are not as par with the western countries. Further, many studies have also been documented the better outcome among Indian schizophrenic patients (Cohen et al., 2007; Isaac et al., 2007). It may be because of the social support that the Indian society provides to the family members and also there is less competition in the society. Unlike the developed nations it has been found that in India 90% of people with mental illness live with their families. This may be due to the strong social bonding of the Indian society and deep love for their dear ones.

4. Possible etiology

Till date the exact etiological factor that may trigger schizophrenia has not yet been pinpointed. In fact schizophrenia is now considered as a multifactorial disorder. Now it is considered that schizophrenia is a heterogeneous disorder and same causative factor(s) may not be operating in different individuals. Several hypothesis and risk factors have been proposed to explain its causation which is discussed below.

4.1 Genetic

Twin, family and adoption studies have suggested that schizophrenia runs in the families and the genes play a major role in the transmission of schizophrenia. Irwing Gottesman in a review suggested that the person sharing the greater number of genes with schizophrenic patients have an increased risk of developing schizophrenia. Further, Gottesman and Shields found the concordance rates for schizophrenia in monozygotic twins (MZ) were 35-58% compared with dizygotic (DZ) twin which was 9-26% (Gottesman and Shields, 1976). They also found a concordance rate in MZ twins of 75-91% when the sample was restricted to the most severe form of schizophrenia (Gottesman and Shields, 1982). The milder forms of schizophrenia had concordance rates of 17-33% which suggests that there may be greater genetic loading with severe forms of schizophrenia. The absence of 100% concordance rate in MZ twins suggested that the external environmental risk factors may be involved in schizophrenia along with the genetic factors. In 1994, an investigation was conducted to study the incidence of schizophrenia in the biological and adoptive relatives of schizophrenic adoptees and compared this to a demographically matched group of control adoptees (Kety et al., 1994). In the samples of adoptees with chronic schizophrenia, the disorder was found exclusively in their biological relatives and not their adoptive relatives. The prevalence of the disorder was 10 times higher in the biological relatives of the schizophrenic adoptees than in the biological relatives of the control group. This study further strengthens the concept of involvement of genes in schizophrenia.

4.2. Neurodevelopment

It has been hypothesized that impairment of normal neurodevelopment process during fetal life may lead to schizophrenia. The two main factors which may lead to neurodevelopment abnormalities are genetic and environmental factors. It has been suggested that the neurodevelopment abnormalities starts in uterus as early as late first or early second trimester. It has been further suggested that the brain abnormalities along with some environmental factors (viz., severe stress) may trigger the disease in the adulthood. A model was proposed by Keshavan which is called ‘‘2-hit’’ model to explain the role of neurodevelopment in schizophrenia (Keshavan 1999; Keshavan 1999). It proposes that mal development during two critical time

points (early brain development and adolescence) combines to produce the symptoms associated with schizophrenia. According to this model, early developmental insults may lead to dysfunction of specific neural networks that would account for pre morbid signs and symptoms observed in individuals that later develop schizophrenia. At adolescence, excessive elimination of synapses and loss of plasticity may account for the emergence of symptoms (Keshavan 1999; Keshavan and Hogarty, 1999).

Further, according to the neuro-developmental model both genetic and non genetic risk factors contribute to developing the brain during prenatal and perinatal life. Genetic factors may contribute by wrong genetic program for the normal formation of synapses and migration of neurons in the developing brain. These risk factors may have the final common effect on nerve growth factors reduction resulting in structural abnormalities, selection of wrong neurons to survive in the foetal brain, neuron migration to the wrong places, neuron enervation of wrong targets or mix-up of the nurturing signals. Indeed abnormal cell clusters have been found more frequently in the left hemisphere of schizophrenic patients, but these abnormalities are not extensive (Bogerts, 1993).

4.3. Brain Asymmetry

Studies of cerebral asymmetry are also used to investigate the etiology of schizophrenia. The normal brain possesses a structural asymmetry such as larger right frontal and temporal lobes. Investigations involving CT and MRI studies found the enlargement of left temporal horn and left ventricle in schizophrenic patients (Bogerts,1993; Crow, 1989). Further, meta-analysis of MRI studies in 2006 found that whole brain and hippocampal volume are reduced and the ventricular volume is increased in schizophrenic patients with a first psychotic episode relative to healthy controls. The average volumetric changes in this study are however close to the limit of detection by MRI methods.

A 2009 meta-analysis of diffusion tensor imaging studies identified two consistent locations of fractional anisotropy reduction in schizophrenia. One region, in the left frontal lobe, traversed by white matter tracts interconnecting the frontal lobe, thalamus and cingulate gyrus. The second region in the temporal lobe, traversed by white matter tracts interconnecting the frontal lobe, insula, hippocampus–amygdala, temporal and occipital lobe. It is suggested that two networks of white matter tracts may be affected in schizophrenia, with the potential for "disconnection" of the gray matter regions which they link (Ellison and Bullmore, 2009). During MRI studies, greater connectivity in the brain's default network and task-positive network have been observed in schizophrenic patients and may reflect excessive orientation of attention to introspection and to extrospection respectively. The greater anti-

correlation between the two networks suggested excessive rivalry between the networks (Broyd et al., 2008).

These results put forth a major question whether schizophrenia is a neurodegenerative process that begins at about the time of symptom onset, or whether it is better characterized as a neurodevelopmental process that produces abnormal brain volumes at an early age (Steen et al., 2006).

4.4 Obstetric complications

Many epidemiological studies have found a correlation between the obstetric complications during intrauterine life and schizophrenia. Dalman (1999) studied sets of risk factors representing three different etiological mechanisms that could lead to schizophrenia. These were (i) malnutrition during fetal life, (ii) extreme prematurity and (iii) hypoxia and ischemia. Malnutrition during fetal life could lead to a reduction in the supply of nutrients, such as oxygen, iodine, glucose and iron, which could impair development of the central nervous system (CNS). This may contribute to the development of schizophrenia. The study supports the theory of an association between the obstetric complications and the schizophrenia. There was evidence of increased risk associated with all three etiological mechanisms. Pre-eclampsia was the strongest individual risk factor. Some of the factors that were looked at may not have been good indicators of the conditions they were defined as representing (i.e. small for gestational age to indicate malnutrition) therefore further studies need to be undertaken to address this issue.

Studies have also been focused on the relationship between the obstetric complications and the adult ventricular size. It has been found that obstetric complications appear to be predictive of increased ventricular size in adults, particularly in schizophrenia (Dalman, 1999). Further studies have reported earlier onset of schizophrenia in patients with a history of obstetric complications (Verdoux, 1997).

Obstetric complications alone do not explain the brain abnormalities observed in schizophrenia. Several variables probably interact in order for obstetric insults to lead to schizophrenia. These would include the site of any lesions, the timing of the injury and the presence of any genetic predisposition to schizophrenia.

4.5 Viral infection

It has been suggested that schizophrenia may be caused by some infectious agent who hampers the normal neurodevelopmental process leading to schizophrenia. It has been observed that individuals born during the winter months appear to have a higher risk of developing schizophrenia. This is speculated to be due to exposure to some viruses during development. This hypothesis got further boost when

epidemiological studies found the high rates of schizophrenia among people whose mothers were exposed to the influenza virus during pregnancy (Kirch, 1993). During gestation the crucial period for the development central nervous system (CNS) is second trimester. It has been hypothesized that infection to the mother during this period may lead to disruption of brain development leading to major structural deficits that are found in the schizophrenic brain. However, the underpinnings of this mechanism are yet to be understood.

4.6. Neurotransmitter abnormalities

The dysfunction of several neurotransmitter systems like dopamine, 5-hydroxytryptamine (5-HT) and glutamate are thought to play a part in schizophrenia.

4.6.1 Dopamine

The possible role of dopamine in schizophrenia came from the accidental finding that a drug group which blocks dopamine function, known as the phenothiazines, could reduce psychotic symptoms. It is also supported by the fact that amphetamines which trigger the release of dopamine may exacerbate the psychotic symptoms in schizophrenia (Laruelle et al., 1996). Therefore, special focus has been placed upon the function of dopamine in the mesolimbic pathway of the brain. It resulted in the formulation of the 'Dopamine hypotheses'. According to this hypothesis excess activation of D2 receptors can cause the positive symptoms of schizophrenia. The PET and SPET imaging studies provided supporting evidence for this hypothesis. Now a days this hypothesis is thought to be too simplistic as a complete explanation, partly because newer antipsychotic medication (called atypical antipsychotic medication) can be equally effective as older medication (called typical antipsychotic medication), but also affects serotonin function and may have slightly less of a dopamine blocking effect (Jones and Pilowsky, 2002).

4.6.2 5-hydroxytryptamine

It has been observed that hallucinogen LSD is a 5-hydroxytryptamine (5-HT) agonist. Therefore 5-HT is thought to be involved in schizophrenia. It has been found that in schizophrenic brain, there is a reduced number of 5-HT2A receptors and an increase in the number of 5-HT1A receptors in the frontal cortex (Harrison, 1999). Both of these changes were seen in the post-mortems of un-medicated patients. However, these changes were not seen in PET scans of younger un-medicated patients suggesting that these abnormalities may emerge during the course of the illness. Several hypothesis have been offered in order to explain the involvement of 5-HT in schizophrenia including alterations in the atrophic role of 5-HT in neurodevelopment and impaired interactions between 5-HT and dopamine.

4.6.3 Glutamate

The discovery that the glutamate blocking drugs such as phencyclidine and ketamine which can mimic the symptoms and cognitive problems associated with the schizophrenic condition has shifted the focus of the researchers on glutamate in order to find the etiological factor for schizophrenia (Lahti et al., 2001). The reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function and that glutamate can affect dopamine function. This observation has suggested an important mediating (and possibly causal) role of glutamate pathways in schizophrenia (Coyle et al., 2003). However other studies have observed that glutamatergic medication failed to reduce the positive symptoms of schizophrenia (Tuominen et al., 2005).

Clinically, schizophrenia is heterogeneous and the findings until now points to its heterogeneous etiology. It seems that genetics, neurodevelopmental problems, neurochemistry and psychosocial stressors probably all contribute to the development of schizophrenia. While the reliability of the diagnosis introduces difficulties in measuring the relative effect of genes and environment, evidence suggests that genetic and environmental factors can act in combination for the causation of schizophrenia (Harrison and Owen, 2003).

5. Treatment and management of schizophrenia

The main focus of schizophrenia treatment is to reduce the severity and frequency of active episodes and to maximize healthy functioning between episodes. The treatment and management of schizophrenia depends largely on medications and on psychosocial interventions. No single approach is widely considered effective for all patients. A recovery model that emphasizes hope, empowerment and social inclusion is often promoted.

5.1 Medication

The mainstay of psychiatric treatment for schizophrenia is an antipsychotic medication. These can reduce the "positive" symptoms of psychosis. Most antipsychotics take around 7–14 days to have their main effect. Some of the psychotrophic medication that is used to treat schizophrenia are olanzapine, clozapine, olanzapine, risperidone, quetiapine etc. Although effective in treating the positive symptoms these drugs have common side effects like weight gain, tardive dyskinesia, reduction of white blood cell etc.

5.2 Psychosocial intervention

Psychotherapy is also widely recommended and used in the treatment of schizophrenia. Some of the psychotherapic methods are cognitive behavioral therapy used to target specific symptoms and improve related issues such as self-esteem,

social functioning and insight, cognitive remediation therapy, a technique aimed at remediating the neurocognitive deficits, methacognitive training aims at sharpening the awareness of patients for a variety of cognitive biases (e.g. jumping to conclusions, attributional biases, over-confidence in errors), which are implicated in the formation and maintenance of schizophrenia positive symptoms (especially delusions), and to ultimately replace these biases with functional cognitive strategies.

5.3 Other therapies

Electroconvulsive therapy is not considered a first line treatment but may be prescribed in cases where other treatments have failed. It is more effective where symptoms of catatonia are present, and is recommended for use under proper guidelines.

6. Immunological research in schizophrenia: Indian scenario

From the last decade India has come a long way and contributed immensely to the knowledge of schizophrenia. By large research on schizophrenia in India has followed the trends in the West. Many of the pioneering work from India are in the field of epidemiology, course and outcomes and phenomenology (Avasthi and Singh, 2004). Along with it the Indian researchers has also contributed immensely to biological research. With the advent of the modern technology the immune dysregulation and autoimmune hypothesis of schizophrenia has become the focal point of research. Indian researchers are also stimulated by some of the pioneering findings from their counterparts from the west to investigate the immunological basis of schizophrenia. Some of the findings of the Indian researchers are hereby discussed.

In agreement with the findings from the west in India too various kind of immune abnormalities such as lymphocyte abnormalities were documented in schizophrenia patients and their family members (Sethi *et al*. 1973). Abnormalities were also recorded for various components in the bodies of patients such as creatine phosphokinase (CPK) (Kondaiah *et al*.1981), Vanilmandelic Acid (VMA)(Ghosh *et al*.1981), CSF 5-hydroxy indole acetic acid (5 HIAA) (Pandey *et al*.,1987), serum and cerebrospinal fluid immunoglobulins (Tiwari *et al*., 1984), antioxidant enzymes (Dadheech *et al*., 2008). On the contrary, other studies did not find any changes in immunoglobulins (Rao *et al*., 1985), Platelet monoamine oxidase, serum prolactin levels (Gupta et al., 1985). In another study serum prolactin levels were found to be raised in drug naïve patients but no correlation was found with severity of psychopathology or prognosis (Shrivastava and Tamhane, 2000). Studies have also found change in T-suppressor cell counts correlated significantly with improvement in psychosis. This finding suggests a correlation between neuronal and immune system and thus strengthens the autoimmune hypothesis of schizophrenia (Agarwal

et al.1992). On the other hand our study did not find any correlation between CD4+ and CD8+ cell subsets with schizophrenia (Singh et al., 2011). After the advent of the 'dopamine hypothesis' dopamine have become focal points of research in schizophrenia. Thus, one of the main metabolite of Dopamine, Plasma Homovanillic acid was extensively studied and it was found to have positive correlation with the neuroleptic free patients (Gong *et al*., 1993). In another study significant negative correlation was found between cerebrospinal fluid Homovanillic acid and Psychosis dimension (Anand *et al*., 2002). On the contrary some studies did not find any correlation between Homovanillic acid and medicating patients (Pradhan *et al*. 1992) which proves the plasticity of the dopaminergic system to neuroleptics.

Many of the proven autoimmune disorders have shown association with Human Leukocyte Antigens (HLA). Therefore, to investigate the autoimmune pathogenesis of schizophrenia it is logical to search for its markers among HLA system. Therefore, we investigated the incidence of Human Leucocyte Antigen (HLA) Class I antigens to understand the role of HLA genes in schizophrenia and found significant increase for HLAA*03 and significant decrease in HLAA*25, A*31 and A*51 (Singh *et al*. 2008). This is first report of association of HLA among the patients of Siliguri. Along with it the abnormalities in the cytokines like IL-2 and IL-6 were also observed (Singh et al., 2009). This is one of the few studies in the world which have reported the lower level of IL-6 among the schizophrenic patients. On the other hand an elevated level of C-reactive protein was also observed in drug naïve schizophrenic patients suggesting the role of inflammatory process in schizophrenia (Singh et al., 2008). Thus our finding also adds to the autoimmune etiopathology of schizophrenia.

It is however not clearly understood weather the abnormalities of the immune system is the by-product of the pathophysiology of schizophrenia or directly contributes to the clinical manifestations of the disorder, though all these findings discussed above, points towards the immune system abnormalities in schizophrenic patients.. Nevertheless, it is too early to speculate the autoimmune etiopathology of schizophrenia based on these findings. Further studies involving the large sample size and in vitro studies may throw light in the mechanism of alteration in the immune system of schizophrenia patients of Indian subcontinent.

7. Discussion

India is a country with the heterogeneous population and each of the ethnic population with unique genetic heterogeneity. Along with the genetically unique ethnic populations India also possesses varying climatic and environmental condition which may have a very important role in the psycho-social aspect and livelihood of the population living in that particular environmental and climatic condition. It has

now been established that environmental factor also plays a very important role in the etiopathology of schizophrenia. As the environmental condition varies across India it may be possible that the same environmental etiological factor may not be playing a role in etiology of schizophrenia in the different ethnic population. Due to this, studies conducted in India need to be extra cautious and take the genetic background and environmental factors into consideration before proceeding with the investigations. The diverse ethnicity of populations may be one the reason for the lack of agreement of the present findings. Moreover, there is dearth of studies involving most of the Indian ethnic populations. This has also limited our studies for any conclusive remark. On the other hand recent findings point to the heterogeneity of schizophrenia with regard to symptomatology, severity, course and treatment response (Graver et al., 2003). Pulver (2000) makes this point by describing schizophrenia as a syndrome with 'genetic heterogeneity' having susceptibility loci at several different chromosomal regions. Kirkpatrick and Carpenter have proposed strong evidence in support of a dichotomy: 'deficit' and 'nondeficit' schizophrenia (Kirkpatrick et al., 2001). Garver et al., (1998) also delineated and subsequently replicated three distinct clusters or 'endophenotypes' within the group of patients that meet conventional criteria for the DSM-IV schizophrenia syndrome (Garver, 1999; Garver 2000). If such etiologically distinct endophenotypes exist, it should be suspected that central immune activation may be a component of one, but not all of the endophenotypes. Thus, variable observations based immunological studies possibly came out due to the heterogeneous nature of schizophrenia (Graver et al., 2003). However, a strong relationship between the immune response and the pathophysiology of schizophrenia has also been documented (Müller et al., 2000). Moreover, the inconsistent results observed in schizophrenia may be due to the fact that schizophrenia is generally treated as though it were a single disease process, instead of several etiologically distinct disorders.

8. Conclusion

The research conducted so far in India to understand etiopathology of this disease is meager despite the fact that four million people suffering are from schizophrenia. The main limitation of the Indian studies is the lack of structure and organization. Although, some the Indian researchers were able to come up with the path breaking immunological findings, but there is a lack of consensus regarding these findings among the various research groups. Therefore, the quest remains for a more comprehensive and definitive paradigmatic immunological approach to the illness. Multicentric, well-coordinated studies using modern techniques, improve research facilities and improve diagnostic criteria are need of the hour to arrive at a consensus and more meaningful research in this field (Kulhara et al., 2010).

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