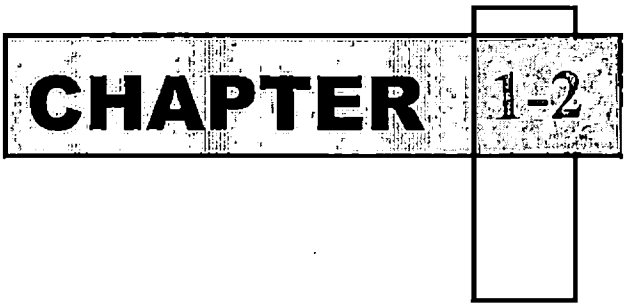

Introduction

Introduction

Delusional disorder is a psychiatric disorder in which the central feature is the presence of delusions in the absence of other symptomatology. Since the beginning of psychiatry, delusional disorder has been at the center of attention and continuing to engender controversy till today. Delusions have been regarded as the hallmark of insanity in Western cultures, long before psychiatry became a branch of medicine (Berrios,1991). In contemporary classification system of mental disorders, such as Diagnostic and statistical manual, 4th edition (DSM-IV) and International Classification of Diseases, 10th edition (ICD-10), delusions are considered as cornerstone symptoms for the diagnosis of psychotic disorders. Delusional formation is a fascinating and enigmatic psychic process, which has been the object of numerous scientific debates and theoretical models, but of surprisingly few empirical studies (Berrios 1991;Butler & Braff,1991).

Delusions has been defined as a false belief that is firmly maintained in spite of incontrovertible and obvious proof or evidence, in spite of the fact that other members of the culture do not share the belief. The delusional material may be rational, but the belief is not arrived at through normal processes of logical thinking (Rotterstol, 1986). Delusional believes may lead to great distress in patients and their relatives. Delusions vary widely in content and composition, which can be shaped by many different factors, including social and political events (Sher, 2000). Delusions involve thought contents and as such, tend to be idiosyncratic and richly varied. They are formed from and colored by the individual's background, including personal, familial, social and group experiences, educational background and cultural including religious influences (Benson& Gorman, 1996). Delusions are a common symptom of several mood and personality-related mental illnesses, including schizoaffective disorder, schizophrenia, shared psychotic disorder, major depressive disorder and bipolar disorder. There are also delusional disorders such as dementia that clearly have organic or physical causes. Systematic study of the phenomenology of delusions, however, is a relatively recent enterprise and many fundamental questions remain unanswered.

Delusional disorder, an uncommon, probably heterogeneous group of illness, has a prevalence of 0.03 % and incidence 1-3 new cases/1,00,000 population. Epidemiological data suggests that delusional disorder is a separate condition or is an atypical form of schizophrenia and mood disorders (Kendler, 1980). It is far less prevalent than schizophrenia and mood disorders. The age of onset is later than in schizophrenia although men tend to experience the illness at earlier ages than women (Hsiao *et al.*, 1999). The observed sex ratio is different from that of mood disorder, which occurs disproportionately among women.

Numerous attempts have been made to demonstrate an underlying psychological basis for delusions. Delusional thinking may have proved difficult to explain by consistent psychological mechanisms (Oltmanns & Maher, 1988) but the nature of the disorder has led to many suggested psychological explanations (Strauss, 1988). Kraepelin (1989) considered the delusions of paranoia to be the 'morbidity transformed expression of the natural emotions of human heart' and more specifically, 'a kind of psychological compensation for the disappointments of life.' However, anomalous perceptual experiences that lead to thought disorders are often suggested by others (Maher & Ross, 1984). Disturbing social experiences establishing delusional defense mechanisms has been a suggested explanation (Higgins, 1987) and reasons for an individual's vulnerability to delusional belief (Neale *et al.* 1985). Personality disorder, situational stresses (particularly recurrent), and cultural background have been proposed as significant in the formation of delusional believes (Westermeyer, 1985). Despite the many psychological approaches proposed over the years, a consistent psychological explanation for delusional believes remains elusive.

In most of the psychiatric conditions, there is no evidence of localized brain pathology to correlate with clinical psychopathology in patients with delusional disorder (Manschreck, 2000). On the contrary, delusions can be a feature of a number of biological conditions (many disorders virtually all brain disorders), suggesting possibly biologic underpinnings for the disorder (Kaplan & Sadock, 1998). Most commonly, neurological lesions associated with temporal lobe, limbic system and basal ganglia are

implicated in delusional syndromes. However, other studies reveal that the patients seldom die early and show no consistent abnormalities on neurological examinations. Certain disorders produce delusions at rates greater than that expected in general population, for example epilepsy (especially of the temporal lobe), degenerative dementias (dementia of the Alzheimer's type and vascular dementia), cerebrovascular disease, extra pyramidal disorders, and traumatic brain injury (Cummings, 1992).

There is no document available regarding the systematic research on delusional disorder. Etiologic explanations range from theories based on the individual life history factors on the one side (Gabriel, 1987) to biological theories based on organic brain factors on the other (Munro, 1988; Gross *et al*, 1997). Precipitating factors, especially related social isolation, conflicts of conscience, and immigration are more closely associated to delusional disorder. These characteristics support Kraeplin's view that environmental factors may play an important etiological role. For much of the past century psychodynamic causal explanations held sway in psychiatric practice. Over the past 20-30 years the biological contribution to mental illness has been rediscovered and biological approaches to treatment and research have enjoyed hegemony over other paradigms (Jones & Kent, 2001).

It has long been suspected that genetics may play an important role in the disease processes. In psychiatry, a genetic contribution to common disorders, cognition and personality traits are well established and susceptibility loci have been identified for schizophrenia, bipolar affective disorders autism and Alzheimer's disease. The common neuropsychiatric disorders have a complex genetic etiology, probably involving interaction between genome and environment (Corvin & Gill, 2003). This understanding has largely been based on the classic approach of a high concordance rate for diseases such as schizophrenia, depression and bipolar disorder in monozygotic versus dizygotic twins (Tsuang, 2000). However, such systematic study has not yet been carried out for the delusional disorder. Although, familial aggregation of the delusional disorder along with other psychiatric disorders has been proposed by many investigators, the exact role of the hereditary factors in the etiology of delusional disorder remains controversial

(Kendler & Hays, 1981; Schanda *et al*, 1983; Kendler *et al*, 1985;Winokur, 1986). So, there is an urgent need for the study of extended case series utilizing modern neurophysiological and neuropsychological investigative methods in delusional disorder.

Chronic diseases of the central nervous system are suspected by many investigators of having genetic etiology with a polygenic mode of inheritance (Prasad *et al.*, 2002). Candidate genes identified on the basis of biochemical and pharmacological evidence are being tested for linkage and association studies in schizophrenia. Current choice of candidate genes evolved from the popular neurochemical model of schizophrenia. Actions of antipsychotic and psychomimetic agents led to the dopamine hypothesis of schizophrenia. Dysregulation of dopaminergic neurotransmission has also been implicated in the etiology of major psychoses including bipolar disorder, obsessive compulsive disorder (OCD), ADHD, etc (Monika Dmitrzak-Weglarz *et al.*,2006) as well as some neuropsychiatric disorders like Perkinson's disease, Alzheimer's disease (Holmes *et al.*,2001) etc. Therefore, the dopaminergic system holds promise of great insights in the understanding of complex psychiatric disorders.

Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain, where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation. This catecholamine also plays multiple roles in the periphery as a modulator of cardiovascular function, catecholamine release, hormone secretion, vascular tone, renal function and gastrointestinal motility. The dopaminergic systems have been the focus of much research over the past 30 years, mainly because several pathological conditions such as Parkinson's disease, Schizophrenia, Tourette's syndrome, and hyperprolactinemia have been linked to a dysregulation of dopaminergic transmission. High doses of DA can cause psychosis (Missale *et al*, 1998). A new impetus to the search in the DA field came from the application of gene cloning procedure to receptor biology 50 years ago, which revealed a higher degree of complexity within DA receptors and its major contribution in the etiology of many psychiatric diseases.

Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation. DA is present in most parts of the central nervous system (CNS) but in particular in the nigrostriatal pathway comprising the neurons of the substantia nigra and projecting to neurons of the neostriatum and the mesocorticolimbic pathway composed of neurons of the ventral tegmental area connecting with those of the limbic cortex and other limbic structures. The involvement of the dopaminergic nigrostriatal pathway in extrapyramidal dysfunctions was shown by the discovery that degeneration of this pathway occurs in the brains of patients afflicted with Parkinson's disease (Missels et al., 2005). The hypothesis that dopamine is involved in the pathogenesis of psychosis comes from the observation that the mesocorticolimbic pathway has been implicated as the principal dopaminergic pathway involved in the etiology of psychoses. The blockade of the dopaminergic system, desired for reducing psychoses, induces extrapyramidal dysfunctions and vice versa.

DA also plays multiple roles in the periphery as a modulator of cardiovascular function, catecholamine release, hormone secretion, vascular tone, renal function and gastrointestinal motility. These diverse physiological actions of dopamine are mediated by at least five distinct G protein coupled receptor subtypes. Two D1 like receptor subtypes viz,D1 and D5 and other D2 like subfamily viz.,D2,D3, and D4.

There are no vivid reports available on the role of dopamine receptor genes in the delusional disorder although some of the work has been done with regard to schizophrenia and other psychiatric disorders. Many investigators have reported the positive association of dopamine receptor genes such as DRD2, DRD3 and DRD5 with schizophrenia, DRD4 with Obsessive Compulsive Disorder (OCD) (Camarena *et al.*, 2007), DRD1, DRD2, DRD4 with Bipolar disorder (Li *et al.,* 1999; Weglarz *et al.*, 2006; Muglia *et al.*, 2002). To our knowledge till to date only one study by Morimoto et al., 2002 is available to show the association of DRD2 receptor gene with only two of the subtypes of DD. This study has been carried out in the Japanese population. On the contrary to our knowledge there no such type of study either in Caucasian or in the Indian

populations. Therefore there is an urgent need for the intensive study to determine the exact etiological underpinnings of this enigmatic disorder. Therefore the present study has been undertaken to investigate the association of dopamine receptor genes in delusional disorder patients of the Indian subcontinent.

There are several factors contributing to the regulation of dopamine. The dopamine transporter (DAT), for example, regulates the uptake of dopamine into neurons. Dopamine is thought to bind to DAT via a separate binding domain that is constructed of multiple amino acid residues. These amino acid residues are not present in the primary structure of DAT, but are thought to have interactions with the protein in its tertiary form (Chen & Reith, 2000).

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the synthesis of dopamine and norepinephrine. It may be involved in the pathophysiology of psychiatric disorders and positive associations have been reported for TH gene markers in a number of neuropsychiatric diseases including mood disorders (Serretti *et al.*, 1998), Schizophrenia (Jacewicz *et al*, 2008), Progressive Supranuclear Palsy (Dumas *et al*, 1996), Personality traits (Giegling *et al.*,2009). As the rate-limiting enzyme in the synthesis of catecholamines, tyrosine hydroxylase has a key role in the physiology of adrenergic neurons. It is regularly used as a marker for dopaminergic neurons and serves as one of the etiologic candidate gene for high level of pHVA (Morimoto et al., 2002), which is particularly relevant for research into neuropsychiatric diseases.

Attempts to determine whether dopamine receptor (DR) co-segregate with the disease have been investigated and dopamine D2 receptor (DRD2) has been found to be associated with some of the psychiatric diseases like alcoholism, substance abuse, addictive disorders, post-traumatic stress disorder, movement disorders, migraine and Schizophrenia. Other dopamine receptors are also found to be associated with the psychiatric disorders such as Obsessive Compulsive Disorder (OCD) and DRD4(Camarena *et al.*, 2007), Bipolar disorder and DRD1, DRD2, DRD4(Li *et al.*, 1999; Weglarz *et al.*, 2006; Muglia *et al.*, 2002), Alzheimer's disease and DRD1, DRD3 (Sweet *et al.*, 2002), delusional symptomatology in mood disorders and DRD4, DRD1

(Serretti *et al.*, 1998; Suhara *et al.*, 1992) cervical dystonia and DRD5(Placzek *et al.*, 2001), myoclonic dystonia , essential myoclonus and DRD2(Dürr *et al.*, 2001), blepharospasm and DRD5 (Misbahuddin *et al.*, 2002) migraine and DRD2, DRD4 (Graeme *et al.*, 2002; Mochi *et al.*, 2003).

There are no comprehensive reports available on the role of dopaminergic system as well as dysfunction in the dopamine regulation and dopamine receptors in delusional disorder as a whole and should be the subject of intensive research. This study, however, undertakes to investigate the role of dopaminergic system in the sporadic patients with delusional disorder and also in schizophrenia, a closely related thought disorder which show delusion as one of the predominant symptoms.

Chronic diseases of the central nervous system including schizophrenia are suspected by many investigators of having genetic, immunological and viral etiology. Immunogenetic studies considering HLA system has been carried out for a long time for a number of psychiatric disorders like Schizophrenia, bipolar disorders, delusional disorder etc. The relation of HLA with some of the psychiatric diseases like Delusional disorder and A*03 (Debnath *et al*, 2005), Schizophrenia and A9 (Mercier *et al*,1977, McGuffin& Stuart,1986), A28, CW4 (Ivanyi *et al*,1978), A1, (McGuffin *et al*, 1981, Lahdelma *et al*, 1998), A2 (Luchins *et al*, 1980), DRB1*04 (Wright *et al*, 1998), DRB1*0101 (Sasaki *et al*, 1999), Manic depressive disorders and HLA antigens B7, Bw16 (Shapiro *et al*, 1977, Lowell *et al*, 1981) have been established suggesting a possible association of immune dysfunction in these disorders.

The roles of immune dysfunction and inflammation in schizophrenia have long been described by the scientists. Several studies have showed that the elevated level of C-reactive protein is associated with the more severe psychopathology of the patients with schizophrenia (Fan *et al.*, 2007; Singh *et al.*, 2008).

There are also no reports available on the role of CRP in delusional disorder. In the present investigation, it was speculated that like schizophrenia- a closely related thought disorder, delusional disorder may also involve immune dysfunction and inflammation and for this purpose of C-reactive protein (CRP) was estimated in the patients.

Therefore, in the present investigation, mainly two etiological approaches were considered for studying the formation of delusion in delusional disorder as well as in schizophrenia. Firstly, association of genes of dopaminergic system, including the gene for its main metabolizing enzyme tyrosine hydroxylase was studied to understand the neurogenetic etiology of delusion in delusional. Secondly, pHVA was considered to find whether abnormality in the level of pHVA correlates with mental illness and mount to an association by studying the following objectives:

- To study the incidence of different alleles of dopamine receptor genes (D1, D2, D3, D4 and D5) and to analyze the specific allelic association (positive and /or negative) of dopamine receptor genes with delusional disorder.

- To investigate the polymorphism of the gene for tyrosine hydroxylase to understand the dysfunction of dopamine system.

- To estimate the plasma homovanillic acid levels in the patients as well as in the normal healthy controls to understand the brain dopamine dysfunction.

- To evaluate the role of dopamine receptor genes in disease susceptibility of delusional disorder.

- To evaluate the role of dopamine gene as a trait marker and plasma homovanillic acid as a state marker in the etiopathology of delusional disorder.