CHAPTER 5

Results & Discussion

5. Results and Discussion

5.1. Association studies of dopamine receptor genes, tyrosine hydroxylase gene and dopamine transporter gene in delusional disorder

5.1.1. Association of DR, TH and DAT genes in delusional disorder (DD) as a whole:

The present study was undertaken to investigate the phenotype frequencies of the dopamine receptor genes, tyrosine hydroxylase gene and dopamine transporter gene in patients with delusional disorder and compared with the age and gender matched healthy controls.

The results demonstrated a significant elevation (62%) of the frequency of DRD2S (χ^2=36.4614, p<0.001) in patients with delusional disorder than to healthy controls (20%). TH1(42%) allele was found significantly elevated when compared with the controls (25%) which has been presented in Table-14.

When the frequency of the dopamine alleles was compared between the patients and the controls, several alleles like D1A (3% vs. 8%), D2 (2% vs. 6%) and D5A(6% vs. 10%) have also shown increased frequency. However, they were not significant after Bonferroni correction. The comparative account of different alleles of the patients and the controls have been represented in Fig2.

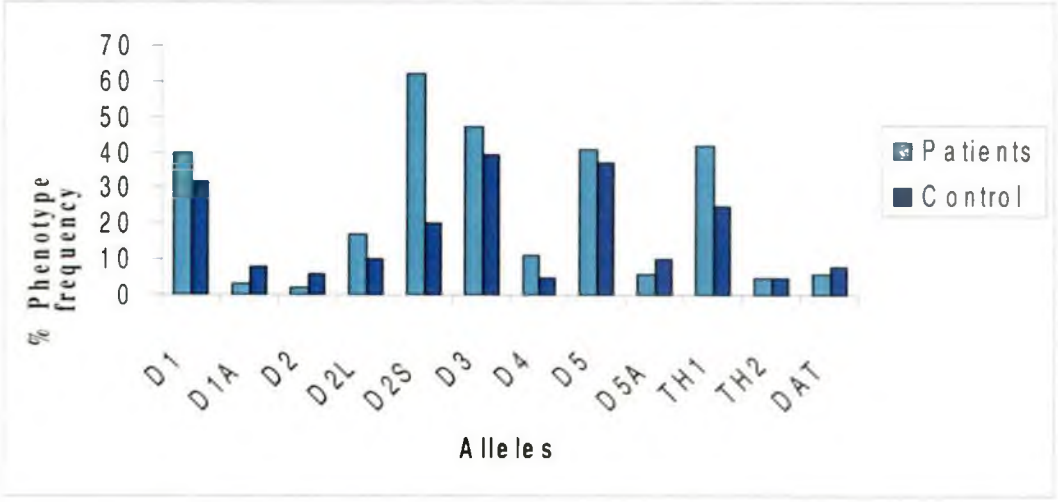


Fig2: Comparative account of % Phenotype frequency of different dopamine receptor, TH and DAT genes in patients with delusional disorder and healthy controls.

Table 14: Shows % phenotype frequency, Chi square, relative risk (RR) values and probability of dopamine receptor alleles, and alleles for tyrosine hydroxylase (TH) and dopamine transporter (DAT) genes in patients with delusional disorder and healthy controls.

Allele	*% Phenotypic frequency*		*Chi Square*	*RR*	*p*
	Patients (N=100)	*Controls (N==100)*			
D1	40	32	1.3889	1.41	NS
D1A	3	8	1.5392	0.355	NS
D2	2	6	1.1719	0.319	NS
D2L	17	10	2.0981	1.843	NS
D2S	62	20	36.4614**	6.526	Significant
D3	47	39	1.3056	1.387	NS
D4	11	5	2.4457	2.348	NS
D5	41	37	0.3363	1.183	NS
D5A	6	10	1.0870	0.574	NS
TH1	42	25	6.9328*	2.172	Significant
TH2	5	5	0.0000	0.00	NS
DAT	6	8	0.3072	0.734	NS

*$p<0.01$

**$p<0.001$; NS= Not Significant.

5.1.2. Genes of Dopaminergic system and Clinical Subtype of Delusional Disorder :

In the present investigation it was found that the onset of the disease appear to be in the middle age of the patients (mean value 42.09 ±1.29). A clear gender difference was also observed which is more frequent in females than the males (3:2). Different subtypes of 100 DD patients like 46 jealous, 22 persecutory, 18 somatic, 6 grandiose, 4 mixed, 3 erotomanic and 1 persistent type have been observed **(Fig 3).**

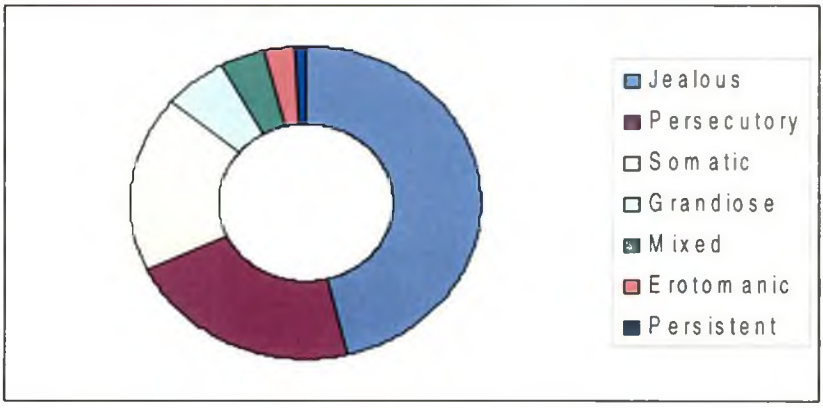


Fig 3: Comparative account of incidence of different subtypes of delusional disorder

The percentage or the pattern of distribution of TH1 and D2S alleles were analysed in different subtypes of delusional disorder **(Fig 4, 5)**. The highest frequency of both the D2S and THI alleles were found in somatic type (77.7%). The frequency of D2S allele was also high in mixed type (75%) and erotomanic type (66.6%)(Table 15). We have excluded the data of persistent type as the frequency was very low and the result could be the artifacts.

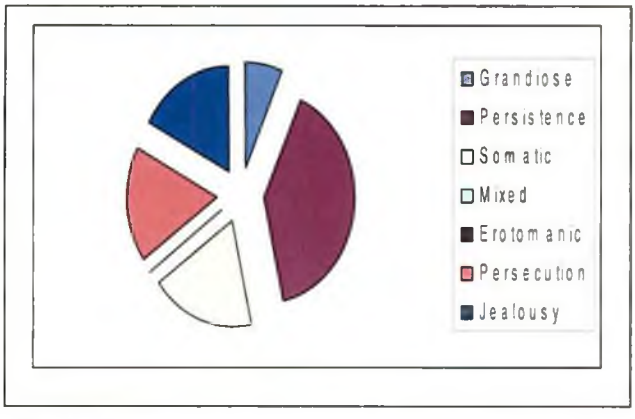


Fig 4: Distribution pattern of TH1 allele in different subtypes of delusional disorder

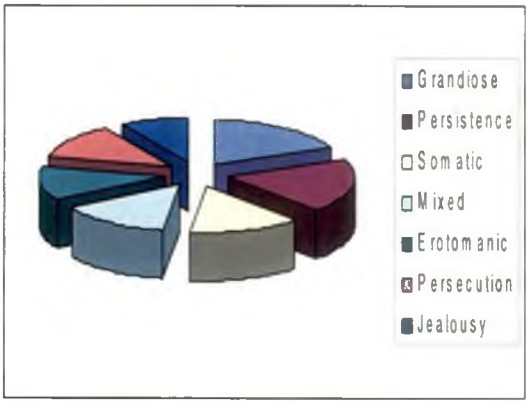


Fig 5: Distribution pattern of D2S allele in different subtypes of delusional disorder

Table 15: Allele Frequency of Dopamine D2S Receptor and TH Gene in different clinical subgroups of delusional disorder

		Allele frequency	
		D2S	TH 1
Delusional disorder	N=100	62%	42%
Jealousy	N= 46	47.8%	43.4%
Persecution	N= 22	63.6%	45.4%
Somatic	N= 18	77.7%	45.4%
Grandiose	N= 6	100%	16.6%
Mixed	N= 4	75%	0.0%
Erotomanic	N= 3	66.6%	0.0%
Persistant	N=1	100%	100%
Control	N=100	20%	25%

5.1.3. Family studies of delusional disorder :

A total number of 100 complete families were studied to estimate the incidence of the familial clustering of delusional or paranoid traits in the family members. Family members comprised the probands and the first degree biological relatives of the patients. Persons with traits like jealousy, suspiciousness, paranoid personality were grouped under the category of paranoid feature (PF). Apart from the occurrence of delusional disorder and paranoid features, the incidence of other psychiatric disorders like schizophrenia, depressions etc were also taken into the consideration. Family pedigrees of these families are represented in Annexure-II and the associated features of the relatives and the patients have been given in **Table 16.**

In the present study we have included 100 delusional disorder patients who have attained the OPD of the Psychiatry Dept. of North Bengal Medical College & Hospital, Siliguri. All the 100 patients with delusional disorder were from 100 different families who attended the OPD and reported for the first time to the psychiatrist about their mental illness were considered as probands. Upon interviewing the probands as well as their family members, the incidence of different illnesses like delusional disorder,

paranoid features, depression, dementia, schizophrenia, bipolar disorder, OCD etc were diagnosed (**Table 17**). There were a total number of 500 family members excluding the number of probands, who were either affected or unaffected. The percentage of different illnesses was calculated by considering the frequency of occurrence of a particular trait out of total 500 numbers of family members.

Table 16: Associated features of 20 probands with delusional disorder and their first degree biological relatives

Subjects	No.	Range of age (in years)	Sex (Female: Male)
Probands	100	24-90	3:2
Affected relatives			
A. Delusional disorder	110	30-69	2:1
B. Paranoid Features	85	17-58	5:3
C. Other non-paranoid disorders	45	17-85	2:1
Unaffected relatives			
A. Live members	210	10-90	23:19
B. Dead members	50	40-80	1:3
	120		

Table 17: Prevalence of delusional disorder, paranoid features (i.e. jealousy, suspiciousness, paranoid personality) and other non paranoid psychotic illnesses in the family members of the probands

Disease	No.	%
Delusional disorder	110	22%
Paranoid Features	85	17%
Other psychotic disorders		
A. Schizophrenia	10	2%
B. Bipolar disorder	5	1%
C. Dementia	5	1%
D. Depression	10	2%
E. Psychosis	10	2%
F. OCD	5	1%

5.1.4. Discussion:

Several studies have been done on the associations between the dopamine receptor genes and the schizophrenia as well as on reported associations of D2 (Seeman P, 1975,2002,2005; Jönsson *et al.*, 2003) and D3/MscI (Crocq *et al*, 1992; Donovan *et al.*,1999,2003;Ilani *et al*, 2001) with schizophrenia as a whole. Paranoid (delusional) disorders are usually thought to overlap with schizophrenic disorders, and a continuum may exist, especially with paranoid schizophrenia (Mc Guffin and Stuart 1986). The diagnostic value of delusional phenomena is still a controversial issue in psychiatry. This problem is related to the fact that the specific link between certain delusional symptoms and particular etiologies has not yet been completely clarified.

To our knowledge, the present investigation is the first report on possible association between the delusional disorder as a whole and the dopamine receptor genes along with the probable association of the tyrosine hydroxylase gene and the dopamine transporter gene. We found a significant positive association between the delusional disorder and D2S. When the strength of association was measured by cross product-ratio or the RR of developing a disease, D2S showed a high value (i.e., RR 6.5) reflecting a strong positive association. In addition, we have also observed a moderately strong association of the TH1 allele (RR 2.17) and the dopamine D4 allele (RR 2.34) with delusional disorder. However, the exact nature of the underlying mechanisms of the empirically observed associations between D2S, TH1 and D4 alleles and the delusional disorder are not fully understood.

When the incidence and strength of the association of dopamine D2S and TH1 allele in different subtypes were analysed, it revealed that the grandiose type exhibit highest percentage of D2S i.e., 100% followed by 77% somatic type, 75% mixed type, 66.6% erotomanic , 63.6% persecutory and 47.8% jealous for the D2S allele, while the persecution type and somatic type showed the highest frequency (both 45.4%) for TH1 allele. The data of persistence type was not considered for the statistical analysis

because of its very low incidence. Although the sample size from each subtype was small, yet it may suggest the phenomenon of clinical heterogeneity.

Family studies have revealed the familial clustering of the delusional disorder. About 22% of the first degree biological relatives of the probands were affected with the delusional disorder and 17% represented paranoid features. Thus upon compiling the percentage of delusional disorder and paranoid features, both of which represent a delusional prototype, familial aggregation was 39%. This is a unique finding and would definitely help to enrich the epidemiological information of the paranoid disorders. In the present study the frequencies of schizophrenia, depression and psychosis were 2% while the frequency of dementia, bipolar disorder and OCD were 1% each.

5.2. Estimation of Plasma Homovanillic Acid level in delusional disorder patients as well as in controls

5.2.1. Study of pHVA in the delusional disorder patients and the normal controls:

In the present study the pHVA concentrations in delusional disorder patients were compared with the age and gender matched healthy controls. The results demonstrated a significant elevation of the mean plasma homovanillic acid concentration in the patients (28.014ng/ml.) with the delusional disorder than in normal controls (7.437ng/ml.) and the p value was also found to be $p<0.001$. The mean value, standard deviation and coefficient of variance in both the patient groups and the normal controls have been presented in the Table18. Comparison of mean HVA concentrations (ng/ml) in the plasma of both the controls and the patients are shown in Fig 6. Again, the comparative account of HVA concentrations (ng/ml) in the plasma of both the controls and the different subtypes of the delusional disorder patients are represented in Fig7. Significant correlation has also been found between the BPRS score and amount of pHVA present in the patients (Table 19). Relationship between the pHVA and the BPRS score among the patients is presented in Fig 8.

Table18: Plasma HVA levels (ng/ml) in both the patients and the controls

Characteristics	Patients (N=100)	Controls (N=100)
Range of pHVA (ng/ml)	9-95	2-20
Mean (ng/ml)	28.014	7.437
SD	19.363	5. 091
Coefficient of variation	69.118%	68.448%

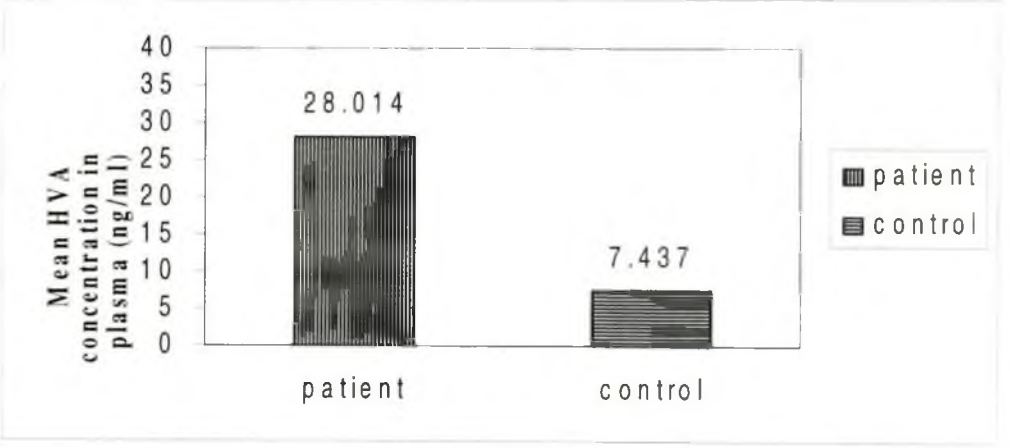


Fig 6. Comparison of mean HVA concentrations (ng/ml) in the plasma of both the controls and the patients.

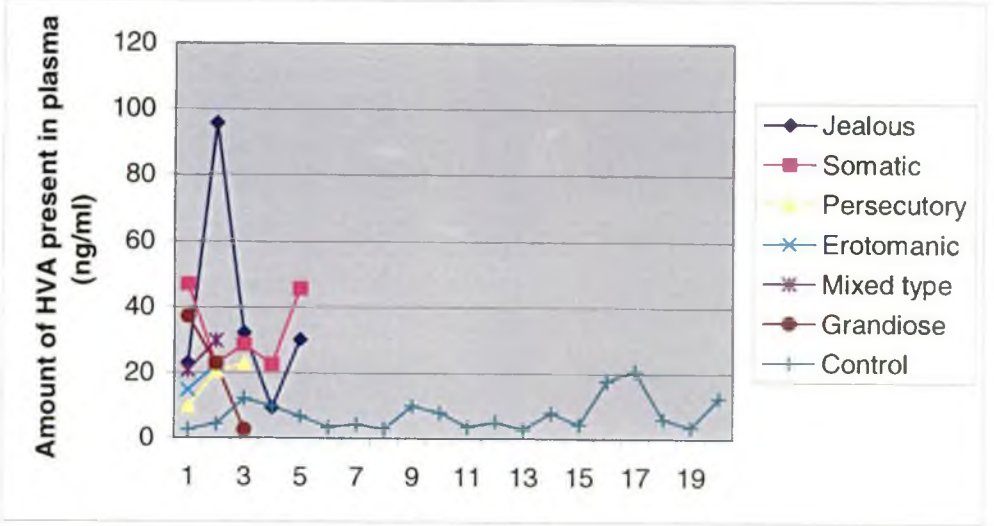


Fig 7: Comparison of HVA concentrations (ng/ml) in the plasma of both the controls and the different subtypes of delusional disorder patients.

Table 19: Comparison of pHVA level and the BPRS scoring among the patient group

Characteristics	Mean	S.D.	Variance	t value	p value
Amount of pHVA	28.014	19.363	374.92	2.3629	Significant
BPRS score	17.4	5.679	32.25		

$p<0.05$

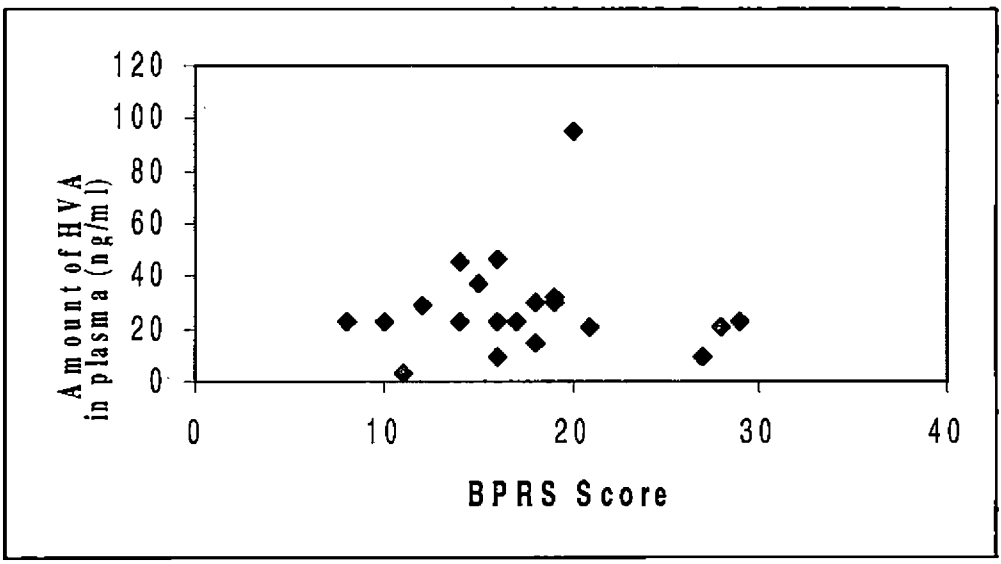


Fig 8: Relationship between the pHVA and the BPRS score among the patients

5.2.2. Discussion:

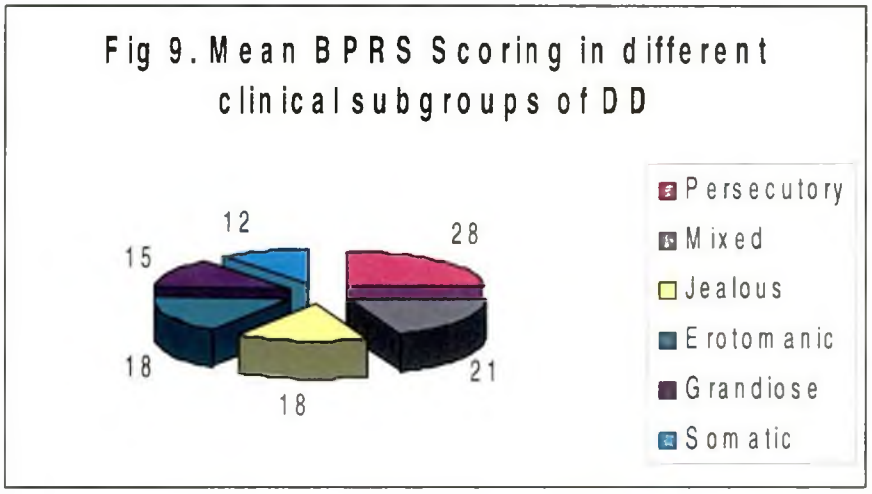
A number of previous studies have been done on the association between the pHVA and the schizophrenia, but all the studies have failed to obtain th e consistent results (Morimoto *et al.*, 2002). This inconsistency were suggested to be due to the following reasons like: (1) pHVA is correlated positively with the severity of the psychotic symptoms (Davis *et al.*, 1985; Pickar *et al.*, 1986; Davidson & Davis, 1988); (2) in case of good responders, pHVA decreases along with the neuroleptic treatment (Pickar *et al.*, 1984,1986; Chang *et al.*, 1988; Koreen et al., 1994; Nagaoka *et al.*, 1997) ; and (3) pHVA is lower in deficit-type than in non-deficit-type (Davidson & Davis, 1988; Ribeyre *et al.*, 1994; Thibaut *et al.*, 1998).

In contrast to these non-coherent results for pHVA in schizophrenia, more consistent results have been observed in delusional disorder (Morimoto *et al.*, 2002). It is suggested from the earlier studies on the pHVA levels and psychosis that the consistent results have been observed in psychoses with a good prognosis, which is unrelated to their conventional diagnosis (Bowers et al., 1984; Bowers, 1993; Garver et al., 1997; Ottong & Garver, 1997). Garver et al., in 1997 have suggested that the higher pHVA psychosis is a dopamine psychosis that may have a familial origin. Our findings on pHVA in delusional disorder have corroborated the results of Garver et al., 1997 and Morimoto *et al.*, 2002.

Therefore, the present finding suggests that the hyper function of the dopamine system may be at least partly responsible for the brain mechanisms underlying its delusional symptoms and could be used as the state marker for the delusional disorder (Bandopadhyay et al., 2009).

5.3. BPRS scoring in delusional disorder

The mean BPRS scoring of delusional disorder patients is 17.4. The highest scoring was found in persecution type which is 28. The mean BPRS scores in different clinical subgroups of delusional disorder (DD) is shown in Fig9.



5.4. Dopamine receptor Association studies in Schizophrenia

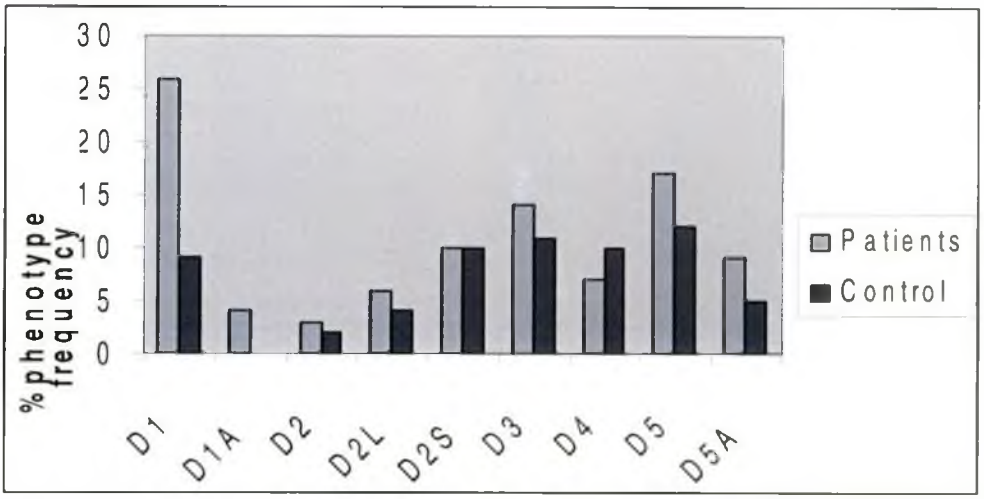
5.4.1 Study of dopamine receptor genes in schizophrenic patients as well as Controls:

The present investigation was undertaken to study the dopamine receptor gene phenotype frequencies in patients with schizophrenia as a whole and the age and sex matched healthy donors. The data presented in Table 20 are the results of molecular typing of 30 schizophrenia patients and equal number of healthy controls. It was observed that dopamine D1 allele showed very significant positive association (χ^2 =10,p<0.01) with schizophrenia. Apart from this, D1A (13% vs. 0%), D2L (56% vs. 40%) and D5A (30% vs. 16%) have also showed increased frequency though not significant statistically. The comparative account of different alleles of the patients and the controls has been presented in Fig 10.

Table 20: Shows % phenotype frequency, Chi square, values and probability of dopamine receptor alleles in patients with schizophrenia and healthy controls.

Alleles	Patients (N=30)	Controls (N=30)	Chi Square	Remarks
D1	26	9	10.0087*	Significant
D1A	4	0	2.2959	NS
D2	3	2	0.0000	NS
D2L	17	12	1.0083	NS
D2S	6	4	0.1053	NS
D3	14	11	0.4114	NS
D4	7	10	0.5786	NS
D5	10	10	0.0000	NS
D5A	9	5	1.2289	NS

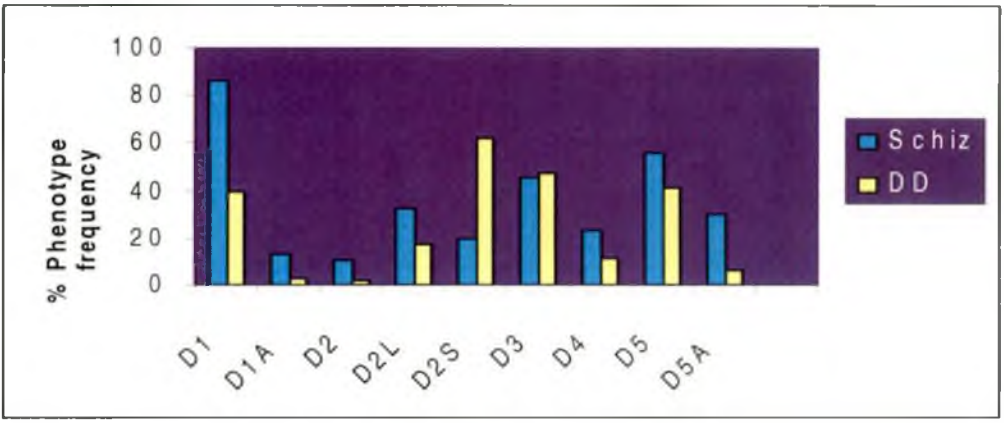
Fig 10. Comparative account of % Phenotype frequency of different dopamine receptor genes in patients with schizophrenia and healthy controls



5.4.2. Study of dopamine receptor genes in delusional disorder patients as well as in the schizophrenic patients:

When the frequency of different alleles of dopamine receptor genes were compared between the schizophrenia and the delusional disorder (Fig 11), the results demonstrate a marked elevation of D1 (86% vs.40%), D2L (56%vs. 17%) and D5A (30% vs. 6%) alleles. While decreased frequency of D2S allele was observed (20% vs. 62%) in case of schizophrenia.

Fig 11. Comparative account of % Phenotype frequency of different dopamine receptor genes in patients with schizophrenia and delusional disorder



5.4.1. Discussion:

The etiology of schizophrenia is not perfectly understood, but family and twin studies have demonstrated that both the genetic and the environmental factors may be involved. Several attempts have been made to identify the genetic markers associated with the schizophrenia and much effort has been given to understand the dopamine hypothesis of schizophrenia and in this respect the association study of the dopamine receptor genes with the disease has been extensively done.

Most of the previous studies on the involvement of the dopamine receptor genes in schizophrenia yielded inconsistent results mainly due to the heterogeneous nature of the disease. Studies have reported the association between the D2L and the schizophrenia (Tallerico *et al.*, 2001). However, a number of studies have failed to find any association of D2 receptor with the schizophrenia (Moises *et al.*, 1991; Grassi *et al.*,1996). Moreover, D3 has been shown to be elevated in schizophrenia in other studies (Crocq *et al.*, 1992; Ilani et *al.*, 2001; Donovan *et al.*, 2003).

In this investigation, we observed strong positive association between the schizophrenia and the D1 receptor allele. When the strength of association was measured by cross product ratio or relative risk of developing a disease, the allele D1 showed very high value (RR=15.16). Our findings on D1 receptor gene in schizophrenia supports the view of Kojima *et al.*,1999.

We also observed the moderately strong association of dopamine D2L allele with the schizophrenia which coincided with the previous findings of Tallerico *et al.*, 2001; however we did not find any association between the dopamine D3 allele in our patients as previously reported by some other studies.

It has been found that D1 receptors are responsible for the cognitive-enhancing effects of dopamine (Heijtz *et al*, 2007) in the periaqueductal gray, in which dopamine D1 receptor activation attenuates pain presumably via activation of neurons involved in descending inhibition (Wood,2008). In addition, D1 receptor activation in the insular

cortex appears to attenuate subsequent pain-related behaviour. The degree of forward locomotion is primarily controlled by the ventral striatum through activation of D1. The D1 like receptors appear to modulate intracellular calcium levels by a variety of mechanisms. Workers have suggested that the dopamine acts through the D1 receptor on the Na^{+}-K^{+}- ATPase activity (Laitinen, 1993). As there is a great disturbance in the locomotor activity and speech in the patients with schizophrenia, it may be explained on the basis of the D1 receptor activity.

5.5. Comprehensive Discussion

Many studies explored the possibility of relating delusional disorder with other disorders like schizophrenia and affective disorders. However, there exists huge controversy and also not supported biologically. Paranoid (delusional) disorders are usually thought to overlap with schizophrenic disorders, and a continuum may exist as both the diseases have delusion as the major clinical symptom. The diagnostic value of delusional phenomena is still a controversial issue in psychiatry. This problem is related to the fact that the specific link between certain delusional symptoms and particular etiologies have not yet been completely clarified. The present investigation is designed with the objective to investigate the biological basis as well as the etiological mechanism(s) of the formation of delusion in delusional disorder.

Chronic diseases of the central nervous system are suspected of having genetic etiology with a polygenic mode of inheritance by many investigators (Prasad *et al.*, 2002). Our study represents the only first reported attempt to study the possible associations between the delusional disorder as a whole and the genes of the dopamine receptors (DR) and their synthesizing enzyme tyrosine hydroxylase (TH). In the present investigation, a robust and significant association was found between delusional disorder and D2S. Since the Ser 311Cys mutation associated with D2S allele has been shown to cause functional alteration of D2 *in vitro*, such as receptor internalization (Itokawa *et al*, 1996) and inhibition of cAMP synthesis (Cravchik *et al.*, 1996), dopamine signal transmission may be increased in delusional disorder patients with this allele.

Dopamine plays a very important and critical role in controlling neurotransmission and signal transduction of important pathways of the brain. It 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. We can hypothesize from this study that polygene of both the pre- and post-synaptic

mechanisms of dopamine systems may be involved in the genetic etiology of delusional disorder. In addition, the present study provides suggestive but not conclusive evidence for an association between the delusional disorder and D2S among the Indian Bengali population.

It has been reported previously that the polymorphism of TH gene is related to transcription *in vitro* (Meloni *et al.*,1998) and to the catecholamine turnover *in vivo* (Wei *et al.*,1997). Consistent with these results, our findings in the delusional disorder patients demonstrated that high pHVA level is significantly correlated with THI allele, suggesting that the TH polymorphism may be another etiologic candidate gene for high the pHVA level.

Plasma homovanillic acid (pHVA), a major dopamine metabolite, is an indicator of central dopamine turnover (Amin *et al*, 1992; Amin and Friedhoff 1997). Garver *et al.*, 1997 suggested that the higher pHVA psychosis is a dopamine psychosis that may have a familial origin. Our results are in good agreement with Garver, showing familial clustering of the disease as well as higher incidence of D2S allele. The finding suggests that pHVA could well be used as the state marker for the disease (Bandopadhyay *et al.*, 2009).

The BPRS scoring was higher in the patients having D2S and TH1 positive alleles and found to be strongly correlated with high pHVA level. The result is suggestive to the role of D2S and TH1 genes in the psychopathology of DD.

At this moment we are not in a position to propose the singularly powerful constellation of D2S gene being responsible for the pathogenesis of delusional disorder. The result is preliminary and so far not correlated with the birth status, drug efficacy etc. for both D2S positive and D2S negative patients. However, this significant association might contribute to the disease risk or there may be a separate susceptibility gene in strong linkage disequilibrium with D2S gene. Taking into account that there is only one previous report of the involvement of dopamine receptor gene with only 2 subtypes of

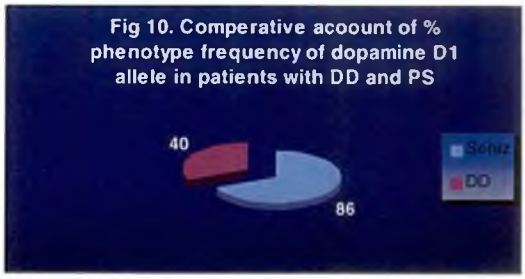
delusional disorder (Morimoto *et al.*,2002), large pool of data involving different ethnic groups will be needed to conclude strongly the direct involvement of D2S with the DD.

Delusional disorder is a condition which occurs and complicates a large number of psychiatric disorders including schizophrenia but there are meager amount of works have been done to solve the enigma of this disorder. Perhaps the most striking evidence implicating genetic factors in the etiology of delusional disorder is the existence of multiple cases within a family. It has been recorded from our socio-demographic data that the prevalence of delusional traits in the form of suspiciousness, jealousness etc was about 15% in the biological relatives of probands with delusional disorder, which is a very high significant value. These observations have provided us the initial impetus that the delusional disorder may have genetical underpinnings.

Advances in molecular genetics culminating in recent work to sequence the entire human genome offers hope to identify the genes conferring susceptibility to a range of complex psychiatric diseases (Jurewicz *et al.*, 2001). 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.

Results of the present study revealed an interesting fact that irrespective of age of onset and type of schizophrenia, the association of dopamine D1 gene is consistent in all the patients. This suggests that the formation and persistence of psychotic feature i.e. delusion in schizophrenia as a whole do not have resemblance with delusional disorder.

The presence of delusion in such conditions might be the results of some other underlying mechanism(s). The distribution pattern of D1 allele in different groups of patientsis shown in Fig 10.



From the above mentioned discussion, it can be concluded that though the delusion is present in a variety of psychiatric as well as medical conditions, the etiopathological mechanism of formation of delusion is not identical.

Mapping disease loci that predispose to mental disorders is difficult because of the several obstacles, including non-Mendelian inheritance, phenotype definition and gene and allele heterogeneity. This can only be solved by incorporating a single extended pedigree. The largest hurdle of this study remains the low prevalence of delusional disorder and diagnosis of genuine cases requires good expertization and recurrent follow up for extended period of time. Family studies for all the patients could not be done because of low attendance of such patients as well as their relatives to the OPD and unwillingness of the relatives to participate in the study.

During the five year period, we had been able to enroll only 150 patients of which 50 patients were discarded from the study as during the follow up study they turned out to be some other cases like paranoid schizophrenia, dementia, substance abuse disorder etc.

Despite these limitations, there are several strengths in the methodology of this study. Firstly, clinical assessment was rigorously conducted. The best estimate procedure was used to assign diagnoses with high reliability. Secondly,the assessment of psychotic symptoms was performed on the basis of interviews and supplementary data from family information as well as data from medical records. To evaluate the significance of the results, the calculations were corrected for the fact that we performed multiple tests.

The findings which have been reported in this study should be regarded as preliminary since they are based on only a small number of individuals, though for an illness like delusional disorder whose prevalence is only 0.03% per 1,00,000 population, the size was quite appreciably high. The mechanism of association remains unknown, however, several others including environmental factors (i.e., nature-nurture basis of the disorder) may be correlated with the association of the disease.

5.6. Study of C-reactive protein in delusional disorder patients

Fifty-one patients were enrolled in this study. 47 subjects were in the normal CRP group (CRP≤0.6mg/dl) and four subjects were in the elevated CRP group (CRP≥0.6mg/dl) with a serum level of 0.60mg/dl as the cut off value.

There were no significant differences between the normal/elevated CRP groups regarding age, gender, age of onset of the disease, age of severity of the disease and some other demographic variables as presented in Table 21. But, when compared the average age of the patients between elevated CRP and normal CRP group, gender biasness was observed (Fig 1). The average age of the females were found to be high in case of the normal CRP group of patients, whereas the average age of the males were higher than the female patients in elevated CRP group of patients. When the average age of onset of the disease is considered, the average age of onset of the disease in males were found to be higher in elevated CRP group of patients (Fig 2). In case of average age of severity also it was higher in males than in females in elevated CRP group of patients (Fig 3). Average disease duration was found to be higher in case of males with elevated CRP group (Fig 4). However, significant difference has been found between the normal and the elevated CRP group when compared for disease duration ($t=3.097$; $p<0.0065$), drug naïve status ($z= -3.756$; $p <0.001$) and sib position ($t=4.284$; $p<0.001$).

Table 21: Comparison of demographic and clinical characteristics between the normal/elevated CRP groups.

Characteristics	Normal CRP group (n=47)			Elevated CRP group (n=47)			Analysis *p*	
	Range	Mean	S.D	Range	Mean	S.D		
Age(years)	19-92	42.511	14.769	32-66	42	16.145	0.9476	
Age of onset (years)	17-90	32.830	16.970	30-60	39.75	13.720	0.432	
Age of severity (years)	19-92	37.979	15.417	32-60	41	12.832	0.706	
Disease duration(years)	1-38	8.340	9.215	1-6	3	2.160	0.0065*	
Education(years)	0-18	6.277	6.053	0-15	9	6.377	0.393	
Position in Sib-ship line	1-9	2.979	2.172	1-2	1.25	0.50	0.0005*	
	N		%	N		%	*Z*	*P*
Drug naïve cases	8		17.02	4		100	-3.756	-0.001*
Substance abuse	23		48.94	3		75	-1.0009	0.3125
Stress markers present	31		65.96	4		100	-1.409	0.1585

Note: *P<0.01

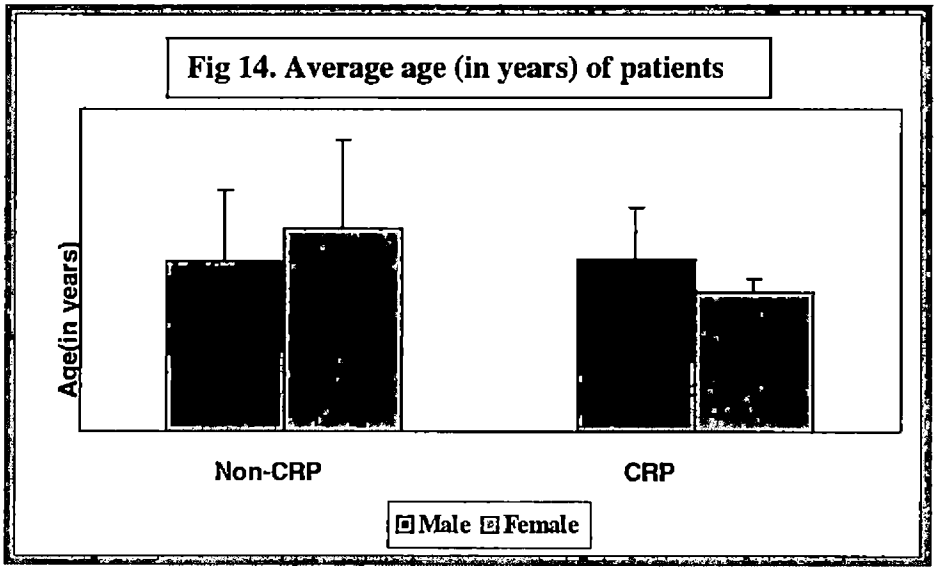


Fig 14. Average age (in years) of patients
Age(in years)
Non-CRP
CRP
Male
Female

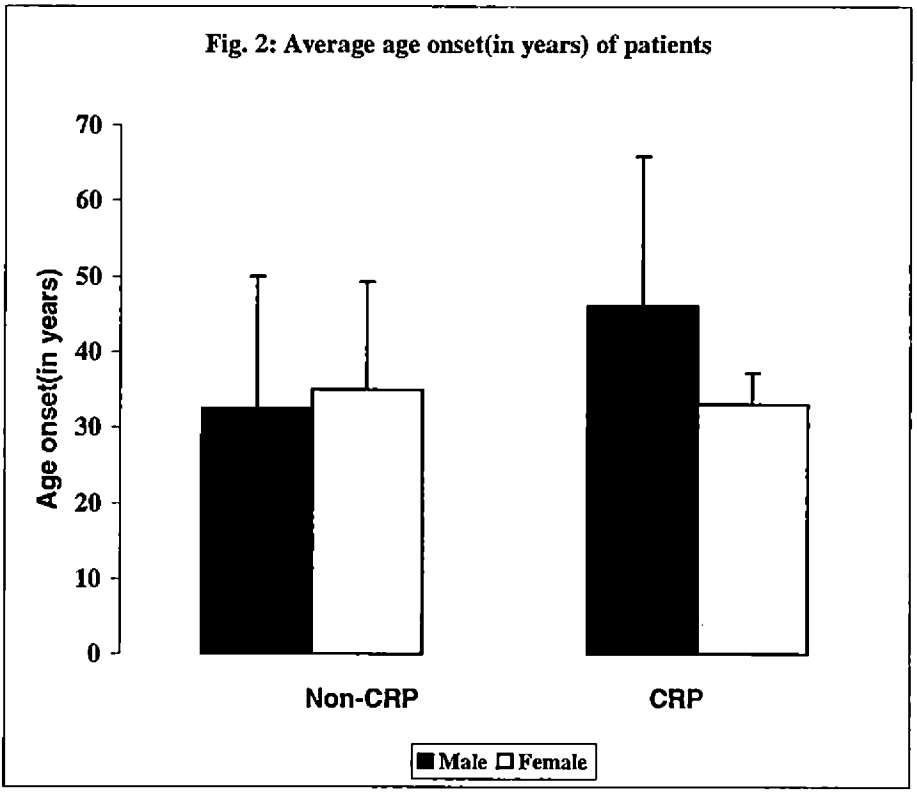


Fig. 2: Average age onset(in years) of patients
70
60
50
40
30
20
10
0
Age onset(in years)
Non-CRP
CRP
Male
Female

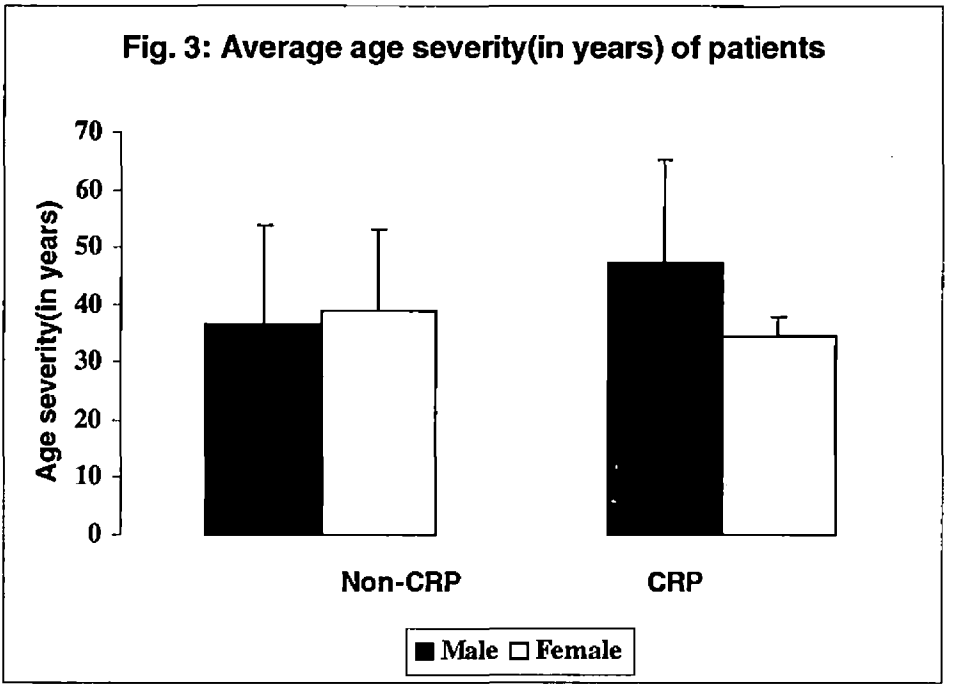


Fig. 3: Average age severity(in years) of patients
Age severity(in years)
70
60
50
40
30
20
10
0
Non-CRP
CRP
Male
Female

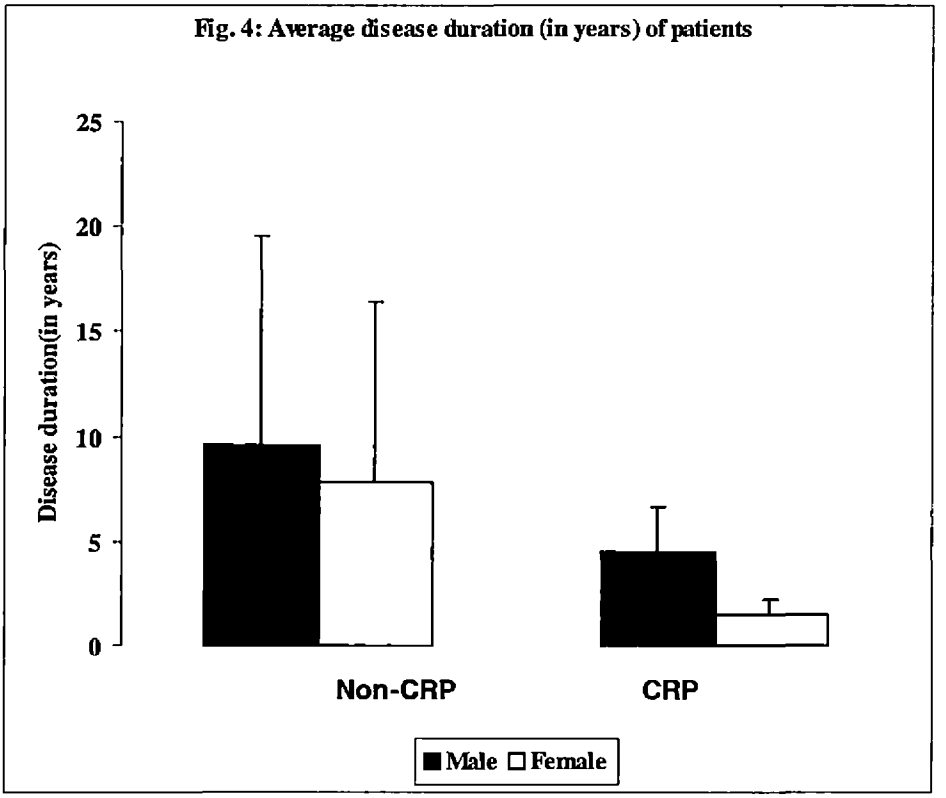


Fig. 4: Average disease duration (in years) of patients
Disease duration(in years)
25
20
15
10
5
0
Non-CRP
CRP
Male
Female

5.6.2. Discussion

The present study found that the elevated serum levels of CRP were associated with the medication status of the patients with delusional disorder. The drug naïve patients showed higher value.

Several studies have already been done on the association of CRP and the schizophrenia. Paranoid (delusional) disorders are usually thought to overlap with schizophrenic disorders, and a continuum may exist (Munro,1988). In one study, the level of CRP was found to be higher in the patient who was experiencing psychotic symptoms. In the non-psychotic state, the level of CRP was found to be normal(Ohaeri *et al.*, 1993).In other studies Fan *et al.*, 2007& Singh *et al.*, 2008 have shown that the elevated level of C-reactive protein is associated with the more severe psychopathology of the patients with schizophrenia. In this respect the present study suggests that the anti-psychotic drug may down regulate the inflammatory process, which in turn brings the CRP level to the normal state.

Thus, these findings further suggest that the inflammation may be another possible mechanism in the etiopathology of the delusional disorder. It is, however, not clearly understood whether the elevation of the level of CRP is the by-product of the pathophysiology of delusional disorder or directly contributes to the clinical manifestations of the disorder as it has been observed in schizophrenia (Fan et al.,2007).

Till todate the mechanism of the inflammation in delusional disorder is not clearly understood. It is suggested in schizophrenia that the vascular-structural brain abnormalities may be one of the etiologies behind the CRP elevation in the disorder (Howard et al.,2001; Bachneff, 1996; Shinba, 2004). It is proposed that the chronic inflammation might damage the micro-vascular system in the brain and disrupt the regulation of the blood-brain barrier and cerebral blood flow. These alterations in homeostatic mechanisms of the brain might lead to the development of the psychotic symptoms (Hanson, 2005). Further, scientific evidence suggests that an increase in the

stress hormone like norepinephrine may activate the inflammatory arm of the immune system and triggers the expression of genes that cause chronic, low-grade inflammation. This inflammation is characterized by the degree of the levels of CRP (Boyle *et al.*,2007).

This is possibly the first reported study of the association between the CRP and the delusional disorder. Findings from our study provide further evidence that some kind of inflammation may play a role in the etiopathology of the delusional disorder. The study further reveals the immunomodulatory effect of the antipsychotic drugs in the patients (Bandopadhyay et al., 2009).

There are some limitations of the present study. Firstly, the psychopathology measures were not considered for the patients. Secondly, because of the cross-sectional design and small sample size in this study, a causal relationship between the serum CRP levels and the severity of the psychopathology remains uncertain. It is unclear whether the inflammation is a byproduct of the pathophysiology of the delusional disorder or directly contributes to the clinical manifestations of the delusional disorder. Further extensive study is needed in the large sample size to further strengthen the present hypothesis.