

GENOMIC IMPRINTING IN BIPOLAR AFFECTIVE DISORDER

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ABSTRACT

With recent advances in molecular genetics, a new mechanism proposed for the inheritance of Bipolar Disorder is Genomic Imprinting or Parent of Origin Affect. In this study of 79 consecutive first episode manic patients, predominantly male, we failed to establish the phenomenon of imprinting. With other proposed non-Mendelian patterns of inheritance, it may be that bipolar disorder is genetically heterogenous.

Key words : Genomic imprinting, bipolar disorder, mania

Family, twin and adoption studies have consistently indicated that the familial aggregation of major psychoses is accounted for largely by genetic factors (Petronis & Kennedy, 1995). Once it was established that the disorder had a strong genetic basis, a search for the mode of inheritance was made using pedigree analysis. However, none of the known Mendelian patterns of inheritance could be found which would fit the pattern and thus a multifactorial model was proposed. This model assumed that both genetic and environmental factors were responsible for the disorder combined into a variable termed liability, affected persons being those whose liability values exceeded the threshold. A concentrated search for genetic markers was undertaken in the form of Association and Linkage studies. However these have yielded conflicting results (Merikangas & Kupfer 1995).

With the recent advances in Molecular genetics, one of the new non-Mendelian mechanisms proposed is that of Genomic imprinting. This is also referred to as the Parent of Origin Effect and is defined as the differential expression of the genetic material at either a chromosomal or Allelic level depending on whether the genetic material has been transmitted from the paternal or the maternal side (Hall, 1990). Thus only the sex of the affected

parent influences the phenotypic characteristic of the illness in the offspring. Genomic Imprinting may accompany different transmission models and may modify their characteristics. In complex disorders, the phenotypic indicators of imprinting can be differences in the age of onset of the disorder, clinical picture, illness severity, morbidity risk in probands relatives and anticipation (successive generations having a younger age of onset or a greater morbidity) depending on whether the illness has been inherited from the maternal or the paternal side. The exact molecular mechanism of imprinting is yet not delineated. Current line of evidence suggest that methylation of DNA is involved. Non allelic changes such as trinucleotide repeat expansion had also been implicated (Flint, 1992). Imprinting has also been one of the mechanisms proposed for the inheritance of bipolar 1 disorder (McMahon et al., 1995).

This study was conducted to study the phenomenon of Genomic Imprinting in the transmission of bipolar 1 disorders. For this study the age of onset was taken as an indicator for imprinting.

MATERIAL AND METHOD

This study was conducted at Central Institute of Psychiatry, (CIP). The subjects of this study were

all consecutive patients attending the outpatient department (OPD) who had received a diagnosis of bipolar affective disorder, first episode, current episode mania as per DSM-IV (APA,1994a).

Subjects with a comorbid Axis-II diagnosis or those with any evidence of organicity were excluded from the study. However patients with a comorbid psychoactive substance abuse were included in the study

Family history was ascertained by the accompanying relative and the patient. In case of a positive family history, the diagnosis was ascribed as per DSM-IV. The age of onset of the illness was used as the imprinting indicator. The sociodemographic details, details of the family history, the age of illness onset and the presence of comorbid substance abuse was recorded in a specially designed proforma.

RESULT

The total sample size was 79. Of these

TABLE 1
DEMOGRAPHIC DETAILS

	(N=79)	Male (N=63)	Female (N=16)
Marital status	Bachelor	31	8
	Married	32	8
Age (years)	(mean)	24.90	21.62
	(S.D.)	10.57	6.61
Substance abuse	Present	23	2
	Absent	40	14
Religion	Hindu	53	12
	Moslem	9	4
	Christian	1	0

64 patients (81.01%) were male and 15 (18.99%) females. The demographic detail of the sample is shown in table 1.

Family history of mental illness was present in 42 (53.16%) patients of which 32 (76.19%) were male and 10 (23.81%) females (X^2 test, $p=N.S.$). The break up of history of mental illness in relatives and the details of the mental illness of the paternal or maternal side is shown in table 2. Statistical analysis (student's t-test) did not show any significant difference in the age of onset between those with positive or negative family history, those with inheritance of illness from the paternal or maternal side and those with an ill father or mother (Table 2).

Substance abuse was present in 25 (31.65%) cases of which 14 (56.0%) had no family history of any mental illness while 11 (44.0%) had a positive family history.

Regression analysis did not show any significant difference when studying the effect of marital status, sex and substance abuse on the age of onset.

DISCUSSION

Age of onset is a frequently used indicator by authors who have examined imprinting in affective disorders (Serbanescu-grigoriu *et al.*, 1995, 1997; Engstrom, 1995). Engstrom (1995) has used the episode requiring hospitalisation or treatment as the first episode. However, this may lead to an error in the true age of onset, as previous episodes may not be

TABLE 2
t - TEST FOR THE AGE OF ONSET

Mental illness	Family side	Age of onset in years mean (S.D.)	t-value	p	n		
					M	F	Total *
Present		22.59 (8.23)	-1.58	0.12	32	10	42
		26.10 (11.41)			31	6	37
Absent	Any	17.87 (3.13)	-1.34	0.19	5	3	8
		22.9 (10.19)			8	3	11
Affective	Father's side	21.89 (7.42)	0.2	0.84	14	5	19
	Mother's side	21.33 (9.26)			11	4	15
	Father's side	19.27 (4.4)			6	5	11
	Mother's side	19.44 (6.06)			5	4	9

* Chi-square test was not significant

GENOMIC IMPRINTING IN BIPOLAR AFFECTIVE DISORDER

of sufficient severity so as to need treatment leading to a potential bias. Serbanescu-grigroiu et al. (1995,1997) have used the age at which first symptoms were experienced as the age of onset. However, the mean duration of illness of their sample was fifteen years, thus there may have been a recall bias for the age at which the first symptoms might have appeared as prior episodes of lesser severity might have been overlooked. We used first episode manics as our probands, hence there would be no recall bias and no missing of prior episodes.

We found a younger age of onset in patients inheriting the disorder from the paternal side when compared to those inheriting the disorder from the maternal side, however, the results failed to reach statistical significance. Hence we were unable to replicate the findings of Serbanescu-grigroiu et al. (1995,1997) who had found a significant effect of the sex of the transmitting parent on the age of onset, morbid risk and anticipation. Those inheriting the disease from the paternal side were found to be more at risk. They did not find any difference in disease severity. However, their sample had an average illness duration of 15 years and a mean episode number of 14, may be resulting in a recall bias. Thus their sample may be a subgroup of more severely ill patients. The natural course of untreated bipolar disorder is that the first few episodes are long apart and the interepisode period generally stabilises to 9-12 months after the fifth episode with an average of four episodes occurring in the first ten years (APA, 1994b).

So far imprinting has been consistently shown to occur in diseases with a known Mendelian pattern of inheritance or those with chromosomal aberrations e.g. Prader-Willi and Angelman's syndrome (chromosome 15), Turner's syndrome (45 XO), Huntington's disease (chromosome 4) and Fragile X syndrome (X linked recessive). In diseases with multifactorial inheritance like the psychiatric disorders, it has not yet been proved. Anticipation has been well reported in schizophrenia (Basset & Horner, 1994; Asherson et al.,1994; Thibaut et al.,1995).

However, no evidence could be found for imprinting (Sharma et al., 1993; Basset & Horner, 1994; Asherson et al.,1994, Thibaut et al.,1995). In unipolar affective disorders, Engstrom et al. (1995) found anticipation but could not establish imprinting. Anticipation has also been reported in bipolar disorders (Nylander et al.,1994; McInnis et al.,1993). These authors do not mention about imprinting. In an Indian study on anticipation, Saleem et al. (1998) found that the alleles of the SCA 3 locus associated with the Machado Joseph disease in a group of unrelated young age of onset psychotics. They concluded that modest expansions may have a role in the susceptibility to develop psychosis.

With other proposed mechanisms for non Mendelian patterns of inheritance such as Epistasis (Craddock et al.,1995), Allelic heterogeneity (Sandkuyil & Ott,1989), Dynamic mutations (McInnis et al., 1993) and Mitochondrial Gene Inheritance (McMahon et al., 1995), it may very well be that Bipolar Affective Disorder may be a genetically heterogeneous group with different patients having a different mode of transmission.

Our study sample was small and perhaps with a larger sample the younger age of onset from the paternal side could have reached statistical significance. Further our study sample had a paucity of females which was consistent with other Indian studies (Chatterjee & Kulhara, 1989; Khanna et al.,1992; Khess et al.,1997). In this study we only focused on one indicator of imprinting which was a major limitation of this study.

We used mental illness in either the paternal side or maternal side as family history of mental illness as we could establish bipolar disorders with certainty in 27 out of 42 patients. Symptoms in second and third degree relatives were difficult to slot in a diagnostic group. They were clearly psychosis but whether affective or schizoaffective was difficult to categorise. However, many authors have found that mood disorders and schizophrenic disorders are opposite ends of a continuum (Crow,1990; Kendall & Gourlay,1970; Kendall & Brockington,

1980). Thus we could analyse the data both with pure forms and mixed forms. As mentioned earlier, no significant difference was found in either case.

Even though our preliminary data does not find any evidence for imprinting, prospective studies following up first episode manics with a family study of all first, second and third degree relatives with a large data base is needed in which all the indicators are examined to finally resolve the issue.

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GENOMIC IMPRINTING IN BIPOLAR AFFECTIVE DISORDER

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