Open Access Journal
International Journal of Medical Research and Pharmaceutical Sciences
Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI-10.5281/zenodo.569476 Impact Factor- 3.109

AN OBSERVATIONAL STUDY OF GENETIC ANTICIPATION AND GENOMIC IMPRINTING IN INDIAN FAMILIES WITH BIPOLAR AFFECTIVE DISORDER

Vijendra Nath Jha[*1] & Pramod Kumar Singh[2]
[*1]MD Psychiatry, Senior Resident, Department of Psychiatry, All India Institute of Medical Sciences, Patna, India.
[2]MD Psychiatry, Professor and Head, Department of Psychiatry, Patna Medical College and Hospital, Patna, India.

Keywords:
Bipolar affective disorders, Genetic Anticipation, Imprinting, Age of onset.

Abstract
Introduction – Bipolar affective disorder is known to have the strong genetic component among psychiatric disorders. Non- Mendelian patterns of inheritance like Genetic anticipation and Genomic Imprinting have been reported with this illness. This study was done to observe these two phenomena in Indian families with bipolar affective disorder.
Material and Methods – 24 families with unilineal inheritance of Bipolar affective disorder in parental-offspring pairs were selected for the study purpose and appropriate statistical measures were applied to various disease measures.
Results – A significant difference was found with an earlier age of onset of illness ($p<0.001$) and more disease severity ($p<0.001$) in the offspring generation. However, no significant difference between paternal and maternal transmission was found.
Conclusion – Our results suggest the presence of genetic anticipation in Indian families with bipolar affective disorder.

Introduction

Psychiatric disorders are seen to get clustered in families and transmitted across generations like many medical and neurological disorders, but they appear to differ in some aspects. First, they seem not to follow the simple Mendelian pattern of inheritance, but a complex multifactorial pattern of inheritance involving interplay between several genes and environmental factors. Second, the features may get modified in successive generations either in terms of disease severity and age of onset or in terms of pattern of clinical presentation. When the illness in the successive generation has an earlier age of onset and/or is more severe, this phenomenon is known as Genetic Anticipation.

Mott was the first to demonstrate the 'law of anticipation' in psychiatricillness. 1 However, Penrose rejected this concept as an artefact of ascertainment biaswith regards Myotonic dystrophy. 2 Over 40 years later, Harper in his study clearly established anticipation in Myotonic dystrophy 3 and other authors have demonstrated anticipation in various illnesses like Crohn's disease, 4 Type 2 Diabetes mellitus 5 etc. McInnis et al., 1993 were the first to demonstrate anticipation in bipolar illness. 6 Since then there have been studies on anticipation in bipolar illness, but mostly in Caucasian populations and one in Japanese population. 7-10To the best of our knowledge there has not been any such study on Indian population.

Another non-mendelian mechanism that has been proposed for bipolar illness is Genomic Imprinting.11This is also called as Parent of Origin effect and is defined as the differential expression of genetic material depending on whether it has been transmitted from the paternal or maternal side.12In our study, the age of onset of bipolar affective disorder, disease severity, were compared between parental and offspring generations to evaluate the phenomenon of genetic anticipation and genomic imprinting..

Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI-10.5281/zenodo.569476 Impact Factor- 3.109

Materials & Methods

The study was conducted at the Department of Psychiatry, Patna Medical College and Hospital, Patna, India. The study population included patients visiting the outpatient department on Mondays, Wednesdays and Fridays(as the authors had OPD on these days). All patients with diagnosis ofBipolar affective disorder (BPAD) were selected for the study after confirming the diagnosis by use of the ICD-10 Classification of Mental and Behavioural Disorders, Diagnostic Criteria for Research. [13]Subsequently their families were screened for BPAD,in consecutive generations.Regarding the occurrence of psychiatricmorbidity intheir relatives, information was obtained by means of Family Interview for Genetic Studies (FIGS).[14] Information was taken from more than one relative to eliminate any possible recall bias. The parental generation was termed G1 and the offspring generation G2.

In order to avoid the possibility of transmission of genetic material responsible for the disease fromboth parents, familieswith unilineal inheritance of mood disorders were selected exclusively. Families with other diagnoses like schizophrenia, schizoaffective disorder, and unipolar depression were excluded from the study to obtain a pure sample from which anticipation and imprinting in BPAD could be assessed.

For the purpose of this study the age of onset of BPAD was defined as the first manic/depressive episode satisfying the criteria of ICD-10. Disease severity was measured by episode frequency, which is the total number of episodes of mania and depression divided by the total duration of illness (age at the time of interview minus age at first manic/depressive episode).Total 50 families were screened for the presence of BPAD, out of which 24 fulfilled the criteria and were included in the study.Informed consent was taken from the patient and family members.

Statistics

All statistical measures were evaluated by IBM SPSS statistics data editorversion 23. Shapiro-Wilk's testwas performed to test for Normal distribution of variables in our sample and a p value >0.05 would indicate that the variables were normally distributed.[15, 16]The age of onset across the two generations and the disease severity scoreswere compared by Independent sample t-test for statistical significance. The age of onset of the mood disorders in each generation were also assessed by survival analysis with theKaplan-Meier method.To test for any possible 'cohort effect',correlation between year of birth difference and onset age difference within the parent-offspring pairs was tested by Pearson's correlation method.[17] Two tailed p values were used for all tests.

Results

Sample characteristics

A Shapiro-Wilk's test($p>0.05$) and a visual inspection of their histograms, normal Q-Q plots and box plots (Fig. 1.) showed that the age of onset scores were approximately normally distributed for both the generations G1 and G2**,** with a skewness of 0.359and a kurtosis of 0.626 for G1($p=0.495$) and skewness of 0.246 and a kurtosis of 0.403 for G2($p=0.320$). Similarly disease severity scores were also approximately normally distributed across both generationswith a skewness of 0.514 and a kurtosis of 0.681for G1($p=0.135$) and skewness of 0.002 and a kurtosis of 0.194 for G2($p=0.079$). Hence, both of our study variables were approximately normally distributed.

Anticipation

The Demographic data and clinical variables are shown in Table 1. The offspring generation had mean age of onset of BPADapproximately 10.5 years earlier than the parental generation which was statistically significant;$t(46)=4.82$, $p<0.001$. The effect size was Cohen's $d=1.39$; which was much larger than typical. The disease severity in the offspring generation was approximately 1.7 times (meandifference=0.237) the severity of the illness in the parental generation which was also statistically significant; $t(46)=3.70$, $p<0.001$. The effect size was Cohen's $d=1.03$; which was also much larger than typical. Survival analysis (Fig. 2.) showed that subjects developedmood disorders significantly earlier in theoffspring generation than in the parental generation;$\chi^2 = 21.52$, d.f.=1, $P<0.0001$(with theMantelCox method).

Imprinting

There were equal number of cases of both paternal and maternal transmission (N=12) (Table 2). The offspring generation had an earlier age of onset by an average 0.83years in offsprings inheriting the disorder from maternal

Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI-10.5281/zenodo.569476 Impact Factor- 3.109

side; however the difference was not significant[t(22)=0.449, p=0.65]. Similarly there was no significant difference in the disease severity across the two above said transmission [t(22)=1.357, p=.189].

To search for a possible cohort effect contributingto the difference in age at onset within parent-offspring pairs, the correlationbetween the year of birth differenceand the onset age difference within the pairs was calculated. The correlation was found to be non-significant(r=0.283, p=0.18)indicating absence of any cohort effect.

Discussion

The results of our study support the occurrence of anticipationin the sample of Indian families with BPAD. We foundevidence for both a decrease in age at onsetand an increase in severity of the disease insuccessive generations. The sample size in our study was small (N=24), which was a limitation.However, the sample size was similar in some of the earlier studies; 24(Macedo et al., 1999), 26 (Ohara et al., 1998). The number of families varied in other studies; 14(Nylander et al., 1994), 19 (Medlewicz et al., 1997), 31(Engstrom et al., 1995), 34 (McInnis et al., 1993) and 115 (Grigoroiu-Serbanescu etal., 1997).

Alda et al., 2000 while questioning the existence of anticipation as an artefact suggested that age of onset alone cannot be a criterion for anticipation and other indicators like disease severity also should be taken into account.[21]Hence, our study design was based on two measures of anticipation i.e. age of onset and disease severity.
We found an approximately 10.5 years earlier age of onset in the offspring generation. It was nearly the same as in some of the previous reports; 10.1 years (Nylander et al., 1994), 8.9 to 13.5 years (McInnis et al., 1993), 6 to 10 years (Grigoroiu-Serbanescu et al., 1997). However, it was less than that seen in others; 12.8 years in “pure” bipolar pairs (Medlewicz et al., 1997), 12.4–15.9 years (Macedo et al., 1999), 19 years (Ohara et al., 1998).

In terms of disease severity, the offspring generation had significantly more episode frequency (1.7 times) than the parental generation. Similar was the finding in earlier studies; 1.8–3.4 times (McInnis et al., 1993), 2.3 times (Macedo et al., 1999) and others (Nylander et al., 1994, Grigoroiu-Serbanescu et al., 1997). However, Ohara et al., 1998 did not find any significant difference in severity scores across the two generations.

A small difference in mean age of onset was seen in maternal transmission in our study; however there was no significant difference between paternal and maternal transmission with respect to the age of onset or disease severity.It is possible that with a larger sample size, the difference seen could have reached statistical significance.Nylander PO et al, 1994 and Ohara et al., 1998 could not find any evidence for a specific paternal or maternal inheritance in their study on relatives of bipolar probands. Kumar et al, 2000 found anoffspring age of onset in patients inheriting the disorder from the paternal side when compared to those inheriting the disorder from the maternal side, but, the results failed to reach statistical significance. [18]Anticipation was found only in probands inheriting the disorder from the paternal side in the study by Grigoroiou et al 1997.Mendlewicz et al., 1997observed aparent-of-origin effect with a significant increase in median length CAG repeats between G1 and G2 with maternal inheritanceandthis increase was observed notably in female offspring.[19]

The assumption of anticipation in our sample remains a mere speculation in the absence of definitive molecular evidences like trinucleotide repeat expansions; hence we need to acknowledge the possible contribution of biases:

a) Penrose observed that pairs consisting of a parent with early-onset illness and a child with late-onset illness are unlikely to be ascertained by any study, since there is such a large span of time separating the two onset events.[2] The effect of this bias is difficult to measure.
b) ‘Cohort effect’ was minimised by testing correlation between year of birth difference and onset age difference within the parent-offspring pairs.[17]
c) Inaccurate recall of illness onset by parental subjects was minimised as information was taken from more than one relative. [20]
d) Bilineality was excluded by studying only unilineal families.[6]

Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI-10.5281/zenodo.569476 Impact Factor- 3.109

Conclusion

We conclude that our results suggest the occurrence of the phenomenon of genetic anticipation (and not genomic imprinting) as a measure of non-mendelianinheritance in this sample of families with BPAD. As far as author's knowledge, this study was the first of its kind in Indian population and the results were similar to previous studies in different populations, thus adding to the existing knowledge base. We would recommend similar studies on a larger population sample with robust analyses of genetic transmission

References

1. *Mott FW. A lecture on heredity and insanity. Lancet 1911; 1251-59.*
2. *Penrose LS. The problem of anticipation in pedigrees of dystrophicamyotonica. Ann. Eugenics 1948;14:125-32.*
3. *Harper PS, Harley HG, Reardon W and Shaw DJ. Anticipation in myotonic dystrophy: new light on an old problem. Am. J. Hum. Genet 1992;51:10-16.*
4. *Freeman HJ and Hershfield NB. Anticipation in an Indo-Canadian family with Crohn's disease.Can. J. Gastroenterol2001;15:695-98.*
5. *Lee SC, Ko GT, Li JK, Chow CC, Yeung VT, Critchley JA, et al. Factors predicting the age when type 2 diabetes is diagnosed in Hong Kong Chinese subjects. Diabetes Care 2001;24:646-49.*
6. *McInnis MG, McMahon FJ, Chase GA, Simpson SG, Ross CA and DePaulo JR. Anticipation in bipolar affective disorder. Am. J Hum Genet 1993;53:385-90.*
7. *Nylander PO, Engstrom C, Chotai J, Wahlstrom J andAdolfsson Ret. Anticipation in Swedish families with bipolar affective disorder. J Med Genet 1994;31:686-89.*
8. *Grigoriou-Serbanescu M, Wickramaratne PJ, Hodge SE, Milea S and Mihailescu R. Genetic anticipation and imprinting in bipolar I illness. Br J Psychiatry 1997;170:162-66.*
9. *Macedo A, Azevedo H, Coelho I, Dourado A, Valente J, Pato MT et al. Genetic anticipation in Portugese families with bipolar mood disorder. CNS Spectrums 1999;4:25-31.*
10. *Ohara K, Suzuki Y, Ushimi Y, Yoshida K and Ohara K. Anticipation and imprinting in Japanese familial mood disorders. Psychiatry Res 1998;191-98.*
11. *McMahon F.J., Stine O.C., Myers D.A., Simpson S.G. and Depaulo J.R. 1995 Patterns of maternal transmission in bipolar affective disorder. Am. J. Hum. Genet.56, 1277-86.*
12. *Hall JC. Genomic imprinting, review & relevance to human disease. Am. J. Hum. Genet 1990;46:857-73.*
13. *World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. WHO. 1993.*
14. *Maxwell ME. Manual for the FIGS (Family interview for genetic studies). Bethesda, Maryland, National institute of mental health. 1992.*
15. *Shapiro SS and Wilk MB. An analysis of variance test for Noramality (Complete Samples). Biometrika 1965;52(3/4):591-611.*
16. *Razali NM and Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. Journal of statistical modelling and analytics 2011;2(1): 21-33.*
17. *Gershon ES, Hamovit JH, Guroff JJ and Nurnberger JI. Birth-cohort changes in manic and depressive disorders in relatives of bipolar and schizoaffective patients. Arch. Gen. Psychiatry 1987;44:314-19.*
18. *Kumar R, Chopra VK, Parial A and Khess CRJ. Genomic Imprinting in Bipolar Affective Disorder. Indian J. Psychiatry 2000;42(2), 167-71.*
19. *Mendlewicz J, Lindblad K, Souery D, Mahieu B, Nylander PO, De Bruyn A, et al. Expanded trinucleotide CAG repeats in families with bipolar affective disorder. Biol Psychiatry 1997;42:1115–22.*
20. *Rice J, Reich T, Andreasen NC, Endicott J, Van Eerdewegh M and Fishman R. The familial transmission of bipolar illness. Arch Gen Psychiatry 1987;44:441–47.*
21. *Alda M, Grof P, Ravindran L, Cavazzoni P, Duffy A, Grof E et al. Anticipation in Bipolar Affective Disorder: Is Age at Onset a Valid Criterion?Am J Med Genet 2000; 96:804–07..*

International Journal of Medical Research and Pharmaceutical Sciences
Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI-10.5281/zenodo.569476 Impact Factor- 3.109

Figures

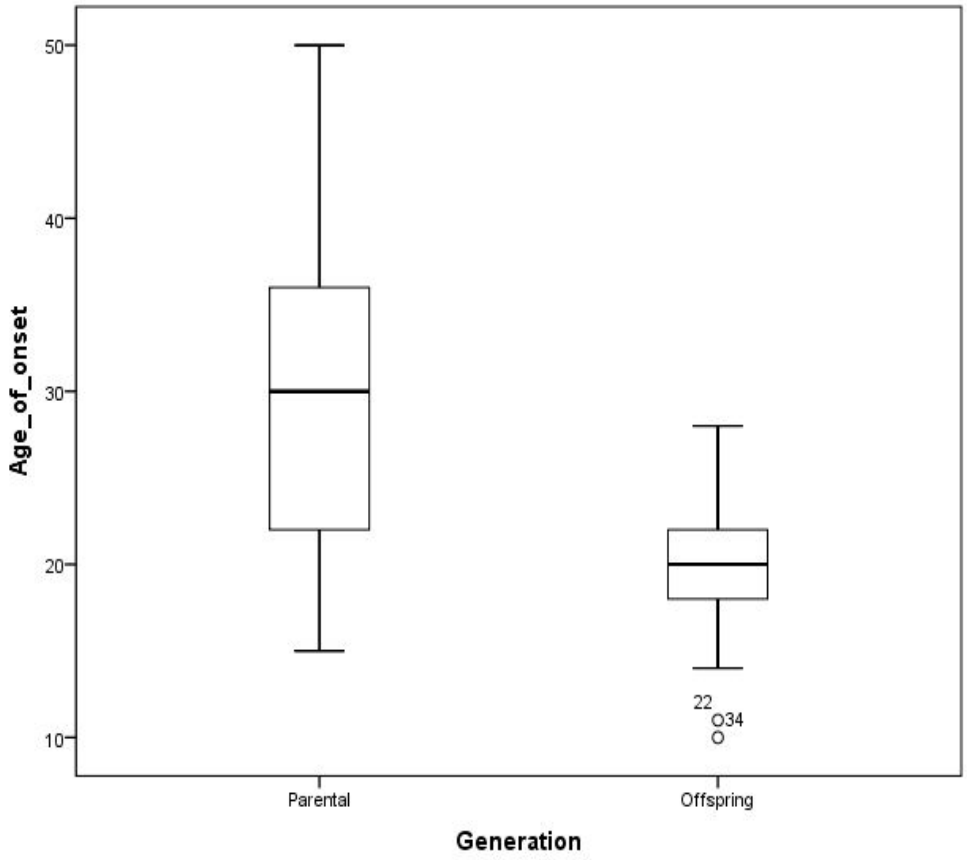

Fig. 1.Box plot display of Age of onset across two generations;Parental (G1) and Offspring (G2). The data was normally distributed and the median age of onset of Offspring generation was visibly lower than Parental generation.

Tables

Table 1.
Demographic and clinical characteristics of the Parental and Offspring generations with familial mood disorders.

	Parental generation (G1)	Offspring generation (G2)
Number (N) Male/Female	24 12/12	24 20/4
Age at Interview(years) Range Mean (S.D.)*	 40-60 50.67(5.54)	 20-34 25.46(3.98)
Age at Onset(years) Range Mean (S.D.)*	 15-50 30.29(9.72)	 10-28 19.75(4.46)
Severity (episode frequency) Range Mean (S.D.)*	 0.08-0.80 0.35(0.21)	 0.20-1.00 0.59(0.23)

*S.D. – Standard deviation

Open Access Journal
International Journal of Medical Research and Pharmaceutical Sciences
Volume 4 (Issue 4): April 2017 ISSN: 2394-9414
DOI-10.5281/zenodo.569476 Impact Factor- 3.109

Table 2

Comparison between cases of paternal and maternal transmission

	Paternal	Maternal
Number	12	12
Age of onset(years) Range Mean (S.D.)*	 16-27 20.17 (2.6)	 10-28 19.33 (5.8)
Severity (episode frequency) Mean (S.D.)*	 0.53 (0.22)	 0.65 (0.23)

*S.D. – Standard deviation