

Genetic Aspects of Mood Disorders

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This study comprised 20 cases of mood disorders with positive family history, all cases were subjected to clinical assessment and diagnosis according to DSM-III-R, psychological investigation and genetic assessment with pedigree construction statistical analysis for recurrence risk in relatives was calculated.

The diagnosis included nine cases bipolar depression, nine cases unipolar & two cases dysthymic disorder. Positive blood consanguinity reported in 56% of unipolar cases compared to 67% of bipolar. Recurrence risk for relatives of the probands studied was 20% in unipolar depression; equal in a 1st & 2nd degree relatives compared to 17.3 % in bipolar cases; this was higher in 2nd degree relatives (25%) than 1st degree relatives (9.1%) and reached 17% in dysthymic cases. This was generally correlated to the severity of illness of disorder of probands. Pattern of inheritance according to pedigree studies was concordant with different modes of inheritance in the following frequency; autosomal dominance 35% polygenic 20% autosomal dominance with reduced penetrance 15% and 15% for both autosomal recessive and X linked pattern. Genetic statistical analysis confirmed the polygenic inheritance in both unipolar depression and suggests a major environmental component in dysthymic disorder. This study permits a new nosological approach as well as major role for genetic counselling in affective disorder.

(Egypt. J. Psychiat., 1995, 18: 81- 88).

Introduction

Mood disorder at least in their milder forms appear to be the most common psychiatric disorder (Kaplan and Sadock, 1988, and Okasha, 1988). There is com-

elling evidences that genetic factors contributes to the aetiology of some forms of affective disorder, Kraepelin (1922) noted that hereditary factors were evident in 80% of his patients. The evidences that a genetic factor is operating in the vulnerability of severe forms of this disorder is strongly suggestive and random environmental factors alone could not explain the concentration of affective illness within families (Daves and Saughnessy, 1982).

Nuruberger and Gershon (1984) reviewed the previous family studies in affective disorder and pointed that the prev-

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elance rates of affective disorder in the families of bipolar and unipolar patients is considerably higher than the incidence in the general population .

Perris (1966) found a remarkable degree of homotypia i.e., tendency for probands and their ill relatives to exhibit the same subtype of disorder; however Angest et al. (1979) noted that ill relatives of unipolar probands nearly always have unipolar disorder, but the relatives of bipolar probands present either with uni or bipolar illness.

The results of adoptee studies of Mendelwitz and Rainer(1977) supported the genetic mechanisms and also provided evidence that the genotype could be expressed as either bipolar or unipolar.

Mc Guffin and Katz (1989) reported that bipolar is more powerfully familial with an average risk in relatives of 19.2% compared to 9.7% in relatives of unipolar disorder.

Torgerson (1986) found that major depression was the most frequent disorder in first degree relatives of bipolar and unipolar patients,thus suggestive a genetic in the familial transmission of both forms. Twin studies of affective disorders reviewed by Nurnburger and Gershon (1984) showed a concordance rate in monozygotic twin pairs of 65% compared to 14% in dizygotic pairs and the magnitude of the MZ/DZ ratio was higher in bipolar than unipolar disorder.

Palmour (1989) identify specific DNA segments which are physical linked to two susceptibility genes in different families and arrived at a point that affective illness is genetically heterogenous and his emperic risk figures suggest a 25-30% liability to either major or manic depressive illness in 1st degree relatives as compared to a population risk of 3-6% ,while 2nd degree relatives have as 12-15% risk.

Weitcamp et al. (1980), Bucher et al. (1981) found that neither single gene autosomal inheritance nor X linked gene models fitted the data; a polgenic mode of inheritance was reported by Slater and Tsuang (1968), Slater (1971), Brawn et al. (1981).

Gershon et al. (1982) agree with a polygenic component and an underlying quantitative vulnerability for the disorder. Automosomal studies done on this aspect by Escobar (1978), Dorus and Shaughnessy (1982) gave negative results while Turner and King (1981) proposed that bipolar illness is a heterogenous condition with a 10-30% not H.L.A linked and most of the rest linked to H.L.A. on chromosome 6.

Weitcamp et al. (1988) agree that genes in the HLA region of chromosome 6 constitute one of the elements in the multifactorial aetiology of affective disorder and this may have different elements in bipolar and unipolar illness.

Aim of the Work

The aim of this work is to study the pedigree pattern of 20 cases of familial mood disorder to evaluate the recurrence risk among their relatives and its possible relation to different types of the illness and to its severity, also a trial is made to identify the mode of inheritance with testing hypothesis for confirmation of these different patterns which may help in proper genetic counselling.

Subjects and Method

The study comprised, 20 Egyptian patients presenting with mood disorders selected from El Zahraa University hospital O.P.C. and El Abbassia mental hospital diagnosed according to the DSM-III-R. criteria with documented positive family history of similar condition. Their ages ranged from 16-60 years mean (34.4 ± 10.1), 11 males and 9 females. All the subjects were submitted to :

1- clinical examination and full psychiatric assessment according to the D.S.M. III R. and patients were classified into three groups (unipolar group, 9 cases, bipolar group, 9 cases and dysthymic group, 2 cases).

2- Psychological investigation to measure the degree of depression using the zagazig depression scale.

3- Genetic assessment:

Family history with pedigree construction for similarly affected cases and for any genetic or environmental factors with emphasis on parental consanguinity (this was taken from 2 normal near relatives to the patient in two separate settings).

Pedigree were constructed and drawn according to the recommended system of the American Journal of Medical Genetics (1987).

The relative recurrence risk was calculated according to the equation:

$$RR = \frac{\text{NO. of affected relatives excluding the probands}}{\text{Total No. of relatives}}$$

Statistical analysis for relative frequency expected testing hypothesis for different pattern of inheritance was done according to the method of the observed and expected frequencies in the proband siblings from Temtamy et al.(1991).

Results

Table (1) shows the demographic data, blood consanguinity and depression scale of the 20 cases of mood disorder.

Table (2) shows the recurrence risk in relatives of 20 cases of mood disorder.

Table (3) shows the correlation of the total recurrence risk with various parameters of severity of mood disorder.

Table (4) shows the suggested pattern of inheritance of 20 cases of mood disorder.

Table (5) shows the observed and expected frequencies of the 3 groups of patients in the probands siblings.

Fig. 1 . The pedigree pattern of inheritance of a case suggestive of autosomal recessive with lack of penetrance or polygenic pattern.

Table 1
Demographic Distribution, Blood Consanguinity and Depression Scale of the 3 Groups

	Bipolar patients 9 cases	Bipolar patients 9 cases	Dysthymic 2 cases
Mean age	31.8± 6.2	36.8± 15	37.5± 6.7
Sex M/F	4/5	7/2	- /2
Age of onset	28.4± 7.1	26.8± 9.3	29±8.4
+ve blood consanguinity	5 55.5%	6 66.7%	- %
Depression scale	25.56± 4.5	14.11± 4.7	35± 7.7

Table 2
The Recurrence Risk in Relatives of 20 Cases of Mood Disorder

Probands	No. and type of relative affected		1 st D.R R	2nd D.R R	Total R.R
	Unipolar	Bipolar			
Unipolar	7	10	20%	20%	20%
Bipolar	3	13	9%	25%	17.3%
Dysthymic	1	1	14%	20%	17%

Table 3
The Correlation of Total Recurrence Risk with Various Parameters of Severity of Mood Disorder

Risk factor		R	P
Age of onset		0.51	<0.01*
No. of hospitalization		0.32	<0.05*
Depression scale		0.10	N.S.

Table 4
The Suggested Pattern of Inheritance of 20 Cases of Mood Disorder

Pattern of inheritance	No.	%
Autosomal dominant	7	35%
Polygenic	4	20%
Autosomal recessive	3	15%
X linked dominant	3	15%
Autosomal dominant	3	15%
with lack of penetrance		

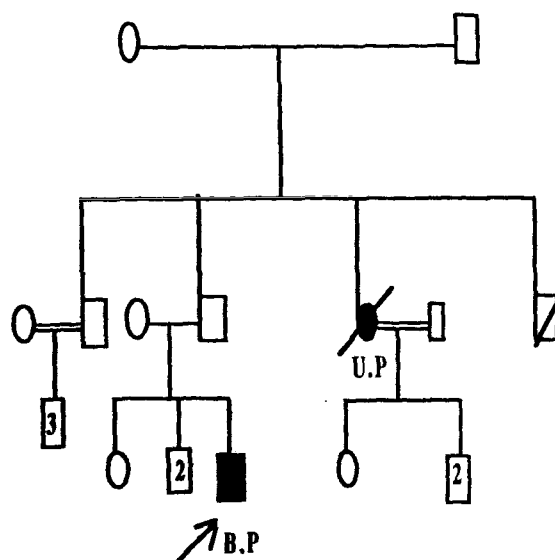
Table 5
The Observed and Expected Frequencies of the 3 Groups of Patients in the Probands Siblings

Frequency in general population	Sib S	Observed S/q	Dominant	Recessive	Polygenic
0.037 (1) $\frac{Fe-Fo^2}{Fe}$	0.25	6.75	13.15 3.38	6.76 0.000147	27.03 15.22** P>0.001
0.01 (2) $\frac{Fe-Fo^2}{Fe}$	0.23	23	50 14.58	25 16	100 59.29** P>0.0001
0.167 (3) $\frac{Fe-Fo^2}{Fe}$	0.4	2.4	2.99 2.24	1.5 0.54	5.99 2.15 P: N.S.

(1) Prevalence Figures for major depression.

(2) Prevalence Figures for bipolar depression quoted from Kaplan and Sadock (1985).

(3) Prevalence Figures for dysthymic disorder were quoted from El-Sayeh (1991).



U.P.: Unipolar disorder

B.P.: Bipolar disorder

Figure (1) Pedigree pattern of inheritance suggestive of autosomal recessive with lack of penetrance or polygenic pattern.

Discussion

Our results of 20 cases of familial mood disorders classified according to DSM-III-R criteria showed that unipolar disorder had nearly equal sex frequency distribution (4M /5F) while bipolar disorder was more markedly common in males (6M/3F) but affective disorders as a whole showed no significant sex differences, these findings are not far from that reported by Winokur (1985). The age of onset of the illness was apparently earlier in bipolar cases than those of unipolar and dysthymic cases, the same was reported by Kaplan and Sadock (1989), Winokur (1985).

Positive blood consanguinity was reported in eleven cases out of the twenty studied cases and this was present in 56.5% of unipolar probands and 66.6% of bipolar probands, this is in agree-

ment with the results of McGuffin and Katz (1986).

From the family pedigree study the calculated total relative recurrence risk ranged from 17%-20%. The highest figure associated with the unipolar cases. The 2nd degree relatives of the bipolar cases had a risk which reached 25%. McGuffin and Katz reported the same figure for the 2nd degree relatives.

Kaplan and Sadock (1989) reported a total risk of relatives ranging from 5-21% for bipolar cases and 9-14% in unipolar cases. The observed differences in recurrence risk could be true or could be due to ascertainment bias due to differences in age of relatives as most of the 1st degree relatives offspring of our probands had not yet reached the age of expression of the disease. As regard the type of mood disorder in the relatives of our probands this showed a high incidence of bipolar versus unipolar cases in all the cases but with high figure 13/3 for bipolar proband relatives and 10/7 in unipolar proband relatives.

Torgerson (1986) noted that major depression was the most frequent disorder in the 1st degree relatives of both bipolar probands while Perris (1966) noted a remarkable degree of homotypia, these contradictory results suggest a genetic overlap in the familial transmission of both disorders.

Correlation of recurrence risk in relatives with the severity of illness in the probands showed a significant correlation to the age of onset and number of hospitalization but not with the depression scale. Nurnburger and Gershon (1984) noted more familial aggregation of the disease in relation to the severity of the illness, Kaplan and Sadock (1989) reported that the degree of genetic transmission

is related to the severity of illness as modeled in a continuous liability scale.

The mode of inheritance suggested from this study was autosomal dominant with vertical pattern and male to male transmission in 35% which agree with the studies of McGuffin and Katz (1989). The 2nd mode of inheritance was polygenic in 20%, the same was reported by Slater et al. (1971). Slater and Tsuang (1968), Autosomal recessive and autosomal dominant with reduced penetrance mode and also the X linked dominant mode with absent male transmission, each fitted in 15% of cases, these findings correlate with the results of Baron et al. (1987), Weitkamp et al. (1980).

Statistical analysis regarding proportion of affected sibs with testing the hypotheses of autosomal dominants recessive and polygenic inheritance suggest a major polygenic component in both bipolar and unipolar depression and a major environmental component in the dysthymic cases; considering that the multifactorial approach has a polygenic component i.e. many genes with random or familial variations. Baron et al. (1981) and Gershon et al. (1982) agree with the multifactorial / thresholds on a continuum of underlying multifactorial vulnerability.

Recently Sadovnick et al. (1991) emphasized the importance of determination of familial forms of affective disorders and assessing the subjective burden as well as the risk of disorder for counseless

Conclusion:

The study confirms the genetic basis of mood disorder and gives an Egyptian empiric recurrence risk for the relatives ranging from 9.1 up to 25%, this was correlated with the severity of illness in respect to the number of hospitalization and age of onset. The mode of inheritance was concordant with different mode of inheritance but statistical analysis

considering the observed and expected frequencies confirms a polygenic or multifactorial mode of inheritance.

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Aspects génétiques des troubles de l'humeur

Cette étude a porté sur 20 patients souffrants de trouble affectifs, ayant des antécédants familiaux. Le D.S.M.III-R a été utilisé pour l'évaluation clinique et le diagnostic des patients. Nous avons également effectué un bilan psychologique et une évaluation génétique avec reconstruction généalogique. Le risque de récurrence familiale a été calculé après analyse statistique. L'analyse statistique des résultats a confirmé la transmission polygénétique dans la dépression unipolaire et suggère une forte composante de l'environnement dans les troubles dysthymiques. Cette étude a permis une nouvelle approche nosologique, elle souligne aussi l'importance du bilan génétique dans les troubles affectifs.

الجوانب الوراثية لاضطرابات المزاج

يشتمل البحث على عشرين حالة مصابة باضطرابات المزاج المصحوب بتاريخ عائلي موجب. وقد أجرى لكل الحالات كشف إكلينيكي وتم التشخيص تبعاً للتصنيف الأمريكي التشخيصي والإحصائي الثالث المعدل DSM-III-R، مع فحص سيكولوجي وكذلك تقييم وراثي بواسطة دراسة صورة شجرة الأسرة مع عمل تحليل إحصائي لحساب نسبة خطورة تكرار المرض بين الأقارب. كان تشخيص الحالات المدروسة كما يلي: تسع حالات اكتئاب جسيم، تسع حالات اكتئاب ثنائي القطب، وحالتين عسر المزاج. وكانت نسبة زواج الأقارب موجودة في ٥٦٪ من الحالات وحيدة القطب بالمقارنة بـ ٦٧٪ في ثنائية القطب، نسبة خطورة تكرار المرض في أقارب الحالات المدروسة كانت موجودة في ٢٠٪ في حالات الاكتئاب الجسيم، وكانت متساوية في الدرجة الأولى والثانية من القرابة، وقد بلغت هذه النسبة ١٧،٥٪ في الحالات الثنائية القطب وكانت أعلى في الأقارب من الدرجة الثانية ٢٥٪ عن أقارب الدرجة الأولى ٩،٧٪ وهذه النسب كانت متلازمة إحصائياً مع درجة شدة المرض وأنماط التوريث وكانت متفقة مع الأنواع المختلفة على شكل وراثية سائدة مع بروز محدود ١٥٪ ونفس النسبة الأخيرة للوراثة المتنحية والوراثة السائدة ومرتبطة بنوع التحليل الإحصائي لنسبة الإخوة والأخوات المصابين وتشير كل النتائج إلى نمط وراثي متعدد الصفات الوراثية بصورة دالة إحصائية في كل من الاضطراب ثنائي القطب والإكتئاب الجسيم وغير دال في حالات عسر المزاج. وتتيح الدراسة تقارباً مع التصنيف المرضي وتبرز أهمية دور الإرشاد الوراثي لحالات اضطرابات المزاج.