

SUICIDAL IDEATION AND BIOGENIC AMINES IN DEPRESSION*

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SUMMARY

This report is based on the study of 40 depressives in an attempt to explore the possible association between the suicidal ideas and the biogenic amines. The severity of suicidal ideas was measured on Hamilton Depressive Rating Scale and their amine metabolites were measured (MHPG, HVA and 5 HIAA) in urine and C. S. F. It was observed that the level of 5 HIAA, and Serotonin (5 HT) was more related to suicidal ideas and was inversely related. The probable associations between these are discussed.

Suicide is an important complication of depression and there are pointers for an assessment of suicide risk in a given depressive. For example, a family history of suicide, persistent insomnia, feelings of unworthiness, guilt and of sin, expression of suicidal thoughts and gestures and a severe agitation, associated with physical illnesses, are all known to carry a high risk (Venkoba Rao and Nammalvar, 1979). There is a general agreement that the rate of suicide is relatively higher in depressives than other psychiatric illnesses (Gardner *et al.*, 1964). Many investigators from India also reported similar findings in their studies (Aiyappan and Jayadev, 1956; Thakur, 1963; Venkoba Rao, 1965; Varma, 1967).

During the past decade there has been a gradual accumulation of evidence suggesting a possible link between the affective disorders and changes in amines of the Central Nervous System (Coppen *et al.*, 1972; van Praag, 1974, 1977a, 1978; Subramanyan, 1975; Palaniappan, 1980). It is hypothesised from the recent studies in Psychoendocrinology that there is a subgroup of depressives who are hypersecretors of Cortisol and that such hypersecretion is generally associated with symptoms such as active suicidal ideas, severe

anxiety, sleeplessness etc. (Venkoba Rao and Nammalvar, 1979). It has been observed that urinary excretion of 17 hydroxyketosteroid by depressed and suicidal patients parallel with the intensity of depressive symptoms and rises to a sharp peak just prior to the time of suicide in some patients (Bunny and Fawcett, 1968). Similar urinary excretion of the Nor-Metanephrine, a metabolite of Nor-Epinephrine (NE) increases as depressive symptomatology abates (Schildkraut, 1965). The interaction between ACTH and cortisol and biogenic amines has been reported in animal studies (Woodbury, 1972; Mass *et al.*, 1972).

Asberg *et al.* (1976) reported an increased incidence of successful and attempted suicide among patients with low 5-Hydroxy Indole Acetic Acid (5HIAA), a metabolite of Serotonin (5HT) group. The study by Hans Agren (1980) supported that depression with low 5 HIAA are prone to violent suicides but also point to the equal if not greater involvement of MHPG and nor-adrenergic neuronal systems in carrying out a wish for death. There are few post mortem studies correlating the brain amine levels and suicidal behaviour. The first such study was published by Shaw *et al.* (1967) who reported

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that Serotonin (5HT) concentration in the hind brain was lower in a group of suicide victims than in a control group of individuals who had died of accidents. Here 5 HIAA concentration was not measured. In a study conducted by Bourne *et al.* (1968) no difference in Serotonin (5HT) was found but 5 HIAA concentration was found decreased in the suicide group. Pare *et al.* (1969) found a decreased Serotonin (5HT) concentration but reported normal values for 5 HIAA. The study by Lloyd *et al.* (1974) was of great significance. They studied suicide victims brain in separate components. A significant decrease in Serotonin (5HT) concentration was found exclusively in Raphe Nuclei. It may be mentioned in passing that the system of Raphe Nuclei is the site of predilection of 5 HT in the C. N. S.

In the four post mortem studies mentioned above, the concentration of Catecholamine (CA), was also measured. The Nor-Epinephrine (NE) concentration in hind brain (Bourne *et al.*, 1968) and hypothalamus (Pare *et al.*, 1969) showed no significant differences between suicide and the control group, nor did Dopamine (DA) concentration in Caudate Nucleus (Pare *et al.*, 1969).

AIM OF THE STUDY

The present study is aimed at finding the possible relationship between suicidal ideation and biogenic amines, both Catecholamines and Indolamine (NE, DA and 5 HT) in Urine and Cerebro Spinal Fluid (C. S. F.) in Depression.

MATERIALS AND METHODS

Forty depressed patients in the age group of 22 and 50 years (20 males and 20 females) were selected from Out Patient Department of Institute of Mental Health, Madras over a period of 6 months in 1979. The patients diagnosed by the Consultants following the standard clinical

evaluation based on I. C. D. 9. Patients were excluded from this study if they showed evidence of identifiable neurological disease or other medical illness. Hamilton Depressive Rating Scale (Hamilton, 1960) was used as second screening tool. The item 'Suicide' in Hamilton Depressive Rating Scale was utilised for assessment of severity of suicidal ideation.

"S U I C I D E"

0= Absent

1=Feels life is not worth living

2=Wishes he were dead or any thoughts of possible death to self

3=Suicidal ideas or gestures

4=Attempts at suicide

Collection of specimens : Urine and C.S.F.

All the patients were drug-free for atleast 3 weeks prior to the collection of specimen. Both Urine and C.S.F. were collected before the patients were started on any drug. All the patients were given clear instruction regarding the collection of 24 hours urine. They were all asked not to take other drugs and also to avoid consuming banana, coffee, tea, & cigarettes for atleast 72 hours, prior to the collection of specimen these substances might alter the level of MHPG and 5 HIAA (Crout and Sjoerdsma, 1959). 24 hours urine was collected with N/6 HCL as preservative and was kept in a deep freeze. All the patients were kept on complete bed rest for atleast two hours before lumbar puncture was done to collect C.S.F. Ascorbic Acid was added to C.S.F. as preservative and was immediately kept in deep freeze. Estimations of the amine metabolites were carried out in both urine and C.S.F. within next 48 hours.

Since the amines cannot be assayed,

as such their metabolites were analysed in urine and C.S.F.

| Amine | Metabolite |
|----------------------|--|
| Nor-Epinephrine (NE) | 3-Methoxy 4-Hydroxy Phenyl Glycol (MHPG) |
| Dopamine (DA) | Homovalinic Acid (HVA) |
| Serotonin (5 HT) | 5 Hydroxy Indole Acetic Acid (5 HIAA) |

Bio-chemical analysis :

Bio-chemical analysis of amine metabolites was done as per the methods given below :

Urine :

MHPG—Method of Ruthvan and Sandler (1965)

HVA—Method of Ruthvan and Sandler (1962)

5 HIAA—Method of Subramanyan and Narayanan (1973)

C. S. F. :

MHPG, HVA and 5 HIAA—Spectrophotofluorimetry Method (Korf *et al.*, 1971)

RESULTS AND DISCUSSION :

All the forty patients were assessed for suicidal ideas.

It was observed that sex and age were perfectly matched among the groups of suicidal intentional patients.

Table I shows the age distribution among the groups.

TABLE I. Age Distribution in each group

| Group | "Suicide Score" | | | |
|-------|-----------------|-------------|-------------|------------|
| | 1 (N=9) | 2 (N=11) | 3 (N=14) | 4 (N=6) |
| Mean | 36.0 | 37.0 | 36.9 | 35.3 |
| S.D. | 10.9 | 6.6 | 7.7 | 7.9 |

There have been many studies to indicate that the suicide is the most important clinical complication which warrants immediate intervention. There are few indicators to forecast the suicidal risk like feelings of unworthiness, guilt, severe agitation, etc. (Venkoba Rao and Nammalvar, 1979). The possibility of any bio-chemical indicator to assess suicidal risk is being examined in this study. As it has been shown by many investigators that depressives have lower amine levels than normals (Schildkraut, 1965; van Praag, 1974, 1977a, 1978), an attempt was made to correlate the suicidal ideation with the amine metabolites both in urine and C.S.F.

Table II shows the correlation coefficient between the metabolites of amines and suicidal ideation. Correlation between the amine levels were compared to arrive at the relative significance.

TABLE II Correlation Co-efficient between Amine Metabolites and Suicidal Ideation.

| | C.S.F. | Urine |
|----------------------|-------------------------------|-------------------------------|
| | Correlation Sig. Co-efficient | Correlation Sig. Co-efficient |
| "Suicide" and MHPG | 0.2759 N.S. | 0.1200 N.S. |
| "Suicide" and HVA | -0.3916 p<0.05 | -0.0394 p<0.05 |
| "Suicide" and 5 HIAA | -0.8470 p<0.01 | -0.4230 p<0.01 |

It was found that the strength of suicidal ideas and 5 HIAA level in urine and C.S.F. was inversely related and negative correlation was at 1% level. It indicates the fact that the severer the suicidal ideas, the lower the 5 HIAA level both in urine and C.S.F.

It was observed from the above data that the levels of MHPG and HVA were

not correlated significantly. In the case of MHPG, it has been reported to be lower in depressives by many investigators (Mass et al, 1968; Bond et al, 1972; Goodwin and Beckman, 1975). The controversy exists over the fact whether NE is related primarily to mood or stress or motor activity. Mass et al. (1972) and Bond et al. (1972) were of the opinion that it was not related to motor activity. Schildkraut (1973) and Palaniappan (1980) were unable to show a correlation between MHPG level to retardation and agitation. It was, however, reported that MHPG level in both urine and C.S.F. was related to stress in the form of somatic anxiety (Palaniappan, 1980). In the present study the occurrence of suicidal ideas was also found to be not related to MHPG level, both in urine and C. S. F.

The level of HVA in retarded depressives was lower than in non-retarded. The retardation reflects mainly the motor activity and may not be an indicator of mood. It has been reported that HVA accumulation in C.S.F. after probenecid was lower in retarded than non-retarded depressives. Hence it is not surprising that HVA level in both urine and C.S.F. did not correlate with the suicidal ideas at a higher level of significance but only at 0.05 level.

The fact that the levels of MHPG and HVA do not significantly correlate with suicide has also been supported by the post-mortem studies where they showed no significant difference in the brains of suicide victims (Bourne et al, 1968; Pare et al, 1969).

The level of 5 HIAA in urine and C.S.F was significantly and negatively correlated with suicidal ideas. It confirms the finding of Asberg et al. (1976) who reported an increased incidence of successful and attempted suicides among low 5 HIAA sub-group. They hypothe-

sised of the existence of the Serotonin deficient depressives and was later supported by van Praag (1977b). As mentioned earlier, in the post-mortem studies the level of Serotonin were lower in the brains of suicide victims (Shaw et al, 1967; Bourne et al, 1968; Pare et al, 1969) which again supports the hypothesis that the Serotonin level is lower in depressives with severe suicidal ideas. The fact that Lloyd et al (1974) in their post-mortem study clearly reported lower level of Serotonin in Raphe Nuclei strongly favours the present hypothesis.

To validate the hypothesis further, patients in each group on "suicide" score of Hamilton Scale were correlated with the levels of amine metabolites in urine and C.S.F. On MHPG and HVA levels there were no difference between the groups.

Table III and IV show the results of 5 HIAA level. On urinary 5 HIAA level, there were statistically significant differences among the groups except between group 1 and 2. On C.S.F. 5 HIAA level there were significant differences between group 1 and 4 and be-

TABLE III Comparison of 5 HIAA in urine and groups on Suicide Score

| Group | Mean mg/day | S.D. | N | t |
|---------|--------------|--------------|----------|------|
| 1 and 3 | 3.81 2.62 | 0.29 0.45 | 9 14 | 3.38 |
| 1 and 4 | 3.81 1.84 | 0.29 0.12 | 9 6 | 5.89 |
| 2 and 3 | 3.58 2.62 | 0.75 0.45 | 11 14 | 3.17 |
| 2 and 4 | 3.58 1.84 | 0.75 0.12 | 11 6 | 6.19 |
| 3 and 4 | 2.62 1.84 | 0.45 0.12 | 14 6 | 5.69 |

All t values are significant at $p < .01$

TABLE IV Comparison of 5 HIAA in C.S.F. and groups on Suicide Score

| Group | Mean mg/ml | S.D. | N | t |
|---------|------------|------|----|-------|
| 1 and 4 | 23.27 | 5.09 | 9 | 5.10* |
| | 14.04 | 1.37 | 6 | |
| 2 and 4 | 21.86 | 4.50 | 11 | 5.05* |
| | 14.04 | 1.37 | 6 | |

* $p < 0.001$

tween 2 and 4. This clearly shows further that the level of 5 HIAA in urine and C.S.F. were lower among the depressives with severe suicidal ideas or in those who made suicidal attempts (Group-4). This again substantiates the hypothesis of Asberg *et al.* (1976).

An attempt was made to find out the cause or effect of amine level (5 HIAA) and suicidal ideas. Linear Regression Analysis was applied to analyse the data. Table V shows the Linear Regression Correlation Co-efficient.

TABLE V Linear Regression Analysis of suicidal ideas and 5 HIAA levels.

| | Urine | C.S.F. |
|---------------------------|-------------------------|-------------------------|
| | Regression Co-efficient | Regression Co-efficient |
| Suicidal ideas and 5 HIAA | -0.076 | -0.967 |
| 5 HIAA and Suicidal ideas | -2.364 | 0.742 |

The Regression co-efficient on urine data shows a higher negative regression between suicide and 5 HIAA, i.e. the impact of suicidal ideas on 5 HIAA was more. But on C.S.F. it was the reverse i.e. the impact of 5 HIAA level on suicidal ideas was more. Since the results on urine and C.S.F. was

contradictory to each other, the correlation co-efficients on urinary level and on C.S.F. level were compared to find out the relative significance.

Table VI shows the relative significance between correlation co-efficient for urine and C.S.F., 5 HIAA and suicidal ideas. It was found that the 5 HIAA in C.S.F. had higher significant inverse correlation ($p < 0.001$) than the urine 5 HIAA.

TABLE VI Comparison of Correlation of Co-efficiency on urinary and C.S.F. amine levels of 5 HIAA

| | Correlation Co-efficient | 'Z' Statistic |
|---|--------------------------|----------------------|
| Suicidal ideas and 5 HIAA in urine (r_1) | -0.42 | |
| Suicidal ideas and 5 HIAA in C.S.F. (r_2) | -0.85 | 3.48 - $p < .001$ |

On Linear Regression Analysis, the C.S.F. data revealed a higher negative regression co efficient between amine (5 HIAA) and suicidal ideas. From this analysis it appears that the regression due to amine is more than that of suicide. Subject to sampling limitations, it appears from this data, that the impact of amine level (5 HIAA) on suicidal ideas is more than the other one.

It may be a fact that the controversy exists whether to give importance to urinary 5 HIAA in depressives and it has been generally viewed that too much importance should not be attached. It is the assumption that most of the 5 HIAA in urine originates from the periphery though it has been questioned by Vaughan *et al.* (1976). The fact that there is a uniform agreement that the C.S.F. 5 HIAA level reflects the true metabolism of brain (Dunner and Goodwin, 1972). In the present study on regression analysis, on C.S.F. 5 HIAA

level has become highly significant. It is becoming strongly evident that the change in the amine levels is one of the primary causative factors to suicidal ideas.

In the present study depressives have been studied without considering sub-groups. There is little evidence to indicate the difference in 5 HIAA level among sub-groups and the level of 5 HIAA on suicidal score in each sub-group may vary.

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