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Correlation of Individual Symptoms and Other Clinical Variables with Cerebrospinal Fluid Amine Metabolites and Tryptophan in Depression

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Summary. Cerebrospinal fluid 5-hydroxyindoleacetic acid (5HIAA), homovanillic acid (HVA), and tryptophan in both CSF and plasma were measured in a carefully selected group of 33 depressed women. Strict and explicit inclusion and exclusion criteria were used, and CSF was taken under controlled circumstances. Seventeen operationally defined and uniformly rated psychiatric symptoms as well as global depression severity and 12 clinical background variables were correlated with the four biochemical parameters, using multivariate regression analysis based on Spearman's rank correlation coefficient according to the nature of the data.

Global depression severity did not correlate with any of the biochemical variables; there were, however, significant correlations between CSF 5HIAA and anxiety, insomnia, and suicide on the one hand, and between CSF HVA and motor symptoms and paranoidity on the other hand. Background variables showed only a few—and much weaker—correlations. It was concluded that central monoamine metabolism does affect some particular psychiatric symptoms but is not parallel with the complex clinical construct of the depressive disease. Further studies using isolated psychopathological symptoms instead of nosological categories are suggested in clinical neurochemistry.

Key words: CSF monoamines – Depression – Symptoms – Tryptophan

Introduction

Despite 15 years of extensive research the postulated role of central monoamine deficiency in the pathogenesis of depression has been neither verified nor rejected.

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Since human brain metabolism is not accessible for direct biochemical investigation, clinical neurochemistry has been confined to several indirect approaches, including postmortem studies, pharmacological manipulations, and the study of peripheral indicators and cellular models (Murphy and Costa 1975). The most fruitful strategy is the measurement of the concentration of monoamine metabolites and precursors in the CSF (van Praag 1977): although this technique can, in principle, supply information about the turnover of the transmitter amines, there are considerable difficulties in the interpretation (Post and Goodwin 1975). It is therefore not surprising that human CSF amine metabolite studies on the metabolic differences between depressed patients and controls even resulted recently in a large, but controversial and confusing body of data (Vestergaard et al. 1979; Berger et al. 1980).

Several explanations have been proposed for this controversy. How much lumbar CSF metabolites reflect cerebral metabolism is still being discussed (Bulat 1980; Banki and Molnar 1980); depression may be heterogeneous in biochemical terms (Asberg et al. 1976; van Praag and Korf 1971), or other physiological parameters like body height may affect disease-dependent differences (Asberg and Bertilsson 1979). There are numerous nonspecific factors influencing lumbar CSF metabolite concentration, including diet, motor activity, CSF pressure, diurnal variation, and drug effects (Goodwin et al. 1975), while peripheral factors such as precursor availability (Carlsson and Lindquist 1978) may also be of importance.

There is still another possibility. Since depression, like any other psychiatric diagnosis, represents a complex clinical construct consisting of a variable symptom pattern with a more or less characteristic course and nonspecific etiology, it is not at all necessary that the complex picture be dependent on one single metabolic deficiency. Instead, monoamine deficiency may be related to one or more elements of the psychopathology. This issue was first brought forward by van Praag et al. (1975) and demonstrated for CSF HVA which was low in patients with motor retardation, independent of the clinical diagnosis. Earlier we reported indication for a similar, separate correlation between CSF 5HIAA and anxiety (Banki 1977). This may be more generally valid (Zarifian and Loo 1979); therefore, this paper is devoted to the analysis of the multiple relationship between several clinical symptoms, background variables, and four frequently measured monoamine-related compounds in the CSF of depressed patients.

Patients and Methods

The patients studied were 33 depressed women who were all inpatients in a psychiatric unit and selected according to the following criteria:

1. Severe depression requiring hospitalization, diagnosed by two independent psychiatrists on subsequent days concordantly. Criteria for depression were operationalized according to the Taylor-Feighner system (Koehler et al. 1978), requiring at least a 6-day dysthymia interfering with work and social activities and at least five of the following symptoms: insomnia, loss of energy, suicide, loss of appetite, insufficiency, loss of interest and pleasure, guilt feelings, motor retardation or agitation.
2. No signs of schizophrenia, coarse brain damage, or substance abuse.
3. At least 30 points on the 24-item Hamilton scale (Baumann 1976).
4. No previous antidepressant or neuroleptic medication for at least 2 weeks prior to admission.

The exclusion criteria were:

1. Elevated temperature or any sign of an infectious disease.
2. Severe undernutrition or exsiccation
3. Hepatic, renal, or cardiac deficiency reflected by significant clinical signs or pathological laboratory findings
4. Endocrine or metabolic disease (e.g., diabetes or Cushing's disease)
5. CNS disease (pathological routine CSF test included)

All patients gave informed consent and remained drug-free for 2–3 days after admission. During this period a standardized interview was conducted repeatedly, which contained 45 items for actual symptomatology. Symptom definitions were based on the works of Asberg et al. (1978) and von Knorring et al. (1978) and required four criteria: (1) clear interference with work or social activity; (2) relative persistence; (3) resistance to simple reassurance or to having her attention diverted; (4) judgment of the symptom as significant by the patient herself, by her environment, or by the physician. All symptoms were rated on a 0–9 scale on which odd numbers were given severity definitions and even numbers used for interpolation.

Symptoms occurring in at least seven patients (i.e., more than 20%) with a score above 2 were included in the statistical analysis. The definitions of these 17 symptoms are given in the appendix. In addition, the severity of global depression was registered as a separate item (on a 0–9 scale), and 12 other clinical 'background variables' were also registered: age (number of years completed on the nearest birthday), height, weight, number of previous psychiatric hospitalizations, total time ever spent in a psychiatric hospital (in months), and duration of the present depressive episode (in days). Impairment of working capacity, impairment of interpersonal competence, and therapeutic response were rated on a 0–9 scale similar to symptoms, the latter being scored after 28–30 days of antidepressant treatment. Mental performance damage was rated by using the Mini Mental State (Folstein et al. 1975) and giving one score for every 10% decrease of the maximal performance. Finally, medical and neurological state was coded on a 4-point scale (0 = no abnormality, 1 = mild disorder, 2 = moderate to severe but irrelevant disorder, 3 = moderate to severe disorder possibly relevant to depression).

LPs were performed at 8–9 A.M. in a sitting position following data collection on days 3–4 after 12 h of controlled fasting and bedrest. The first 6 ml CSF was collected and immediately frozen to −20° C until analyzed. Venous blood was taken simultaneously with CSF and about 2 ml plasma stored as above.

CSF 5HIAA was determined by the method of Kemerer et al. (1979), using gel separation on Sephadex G-10 and subsequent condensation with OPT to form a fluorophore. CSF HVA was measured according to Westerink and Korf (1975) by column chromatography, and tryptophan was measured in both plasma and CSF by a slightly modified method of Denckla and Dewey (1967).

Since symptom ratings represent data on the ordinal level of measurement with a rather irregular (although roughly symmetrical) frequency distribution, calculation of Pearson's correlation coefficients would have been mathematically incorrect. Instead, we used Spearman's rank correlation coefficients to build up correlation matrices. A multivariate regression analysis was done with the four biochemical parameters as independent variables to determine whether clinical symptoms and background variables are significantly determined by these metabolite concentrations in the CSF. The MVRA technique can be invariably used with correlation matrices consisting of Spearman's coefficients as well, provided they are used homogenously throughout (Sváb 1979).

Results

The determination coefficients R^2 for the 17 psychopathological symptoms are given in Table 1, together with their product components for each independent variable. The latter are expressed in percentages because they represent the percentage of the variance of the given dependent variable (i.e., symptom)

Table 1. Product components and determination coefficients of a multivariate regression analysis of four biochemical variables on 17 symptoms

	5HIAA	HVA	TRY_{csf}	$TRY_{pl.}$	R^2
Dysthymia	0.0 (−)	1.3 (+)	0.0 (−)	0.8 (−)	0.020
Anxiety	16.9 (−)	10.0 (+)	0.6 (+)	0.4 (−)	0.279
Suicide	9.9 (−)	4.0 (+)	0.9 (−)	18.9 (−)	0.337*
Anhedonia	0.5 (+)	0.3 (−)	0.0 (+)	1.9 (−)	0.027
Insufficiency	0.0 (+)	0.4 (−)	0.3 (+)	4.8 (−)	0.056
Fatigability	5.4 (+)	19.8 (−)	4.2 (+)	0.0 (+)	0.294*
Anorexia	11.9 (−)	0.1 (+)	2.7 (−)	8.6 (−)	0.233
Insomnia	33.2 (−)	23.3 (+)	2.1 (−)	−0.4 (+)	0.583***
Somatization	4.1 (+)	0.6 (+)	2.1 (−)	4.6 (+)	0.114
Obsession compulsion	3.9 (+)	6.6 (+)	0.1 (+)	13.3 (+)	0.238
Hypochondria	12.2 (+)	7.8 (+)	2.9 (+)	6.5 (+)	0.293*
Agitation	−1.4 (−)	53.6 (+)	−0.2 (+)	0.2 (−)	0.523***
Retardation	4.7 (+)	40.6 (−)	1.6 (−)	0.1 (+)	0.470**
Perseveration	10.9 (+)	17.9 (+)	10.4 (+)	−8.0 (−)	0.313*
Paranoia	−0.6 (+)	28.2 (+)	24.8 (−)	0.3 (+)	0.526***
Depressive thoughts	1.6 (+)	6.2 (+)	1.7 (+)	0.1 (−)	0.095
Negation	17.3 (+)	24.0 (+)	0.3 (+)	3.6 (+)	0.452**
Global severity	1.6 (+)	1.9 (−)	−0.2 (+)	7.7 (−)	0.111

* $P<0.05$; ** $P<0.01$; *** $P<0.001$

There is no exact statistical test for the significance of the product components; percentages above 10 may be regarded as significant and percentages above 25 as markedly significant

explained by the respective independent variable (i.e., CSF metabolite concentration). In a separate row the table contains R^2 and its product components for global depression severity, also. One can see that this is practically independent of all four biochemical measures. In contrast, several individual symptoms have significant or highly significant determination coefficients: insomnia, agitation, and paranoidity are determined to more than 50%; suicide, retardation, perseveration, and negation to more than 30% by the biochemical parameters. Since the product components do not indicate whether the relationship between the respective pair of variables is positive or negative, the sign of the respective partial regression (path) coefficient is provided in parentheses. Thus it can be observed that insomnia, anxiety, anorexia, and suicide are all in significant inverse correlation with CSF 5HIAA, while hypochondria, perseveration, and negation correlate positively with it; anergia and retardation correlate inversely, while agitation, paranoidity, negation, insomnia, perseveration, and anxiety relate positively to CSF HVA. CSF TRY only seems to affect paranoidity, and plasma TRY is significantly lower in highly suicidal patients and somewhat higher in patients with strong obsessive-compulsive symptoms.

Table 2 contains the same data for the 12 background variables. There are far fewer significant product components and none of the multiple determination

Table 2. Product components and determination coefficients of a multivariate regression analysis of four biochemical variables on 12 background clinical variables

	5HIAA	HVA	TRY_{csf}	$TRY_{pl.}$	R^2
Age	18.2 (−)	4.4 (−)	0.0 (+)	2.5 (−)	0.251
Weight	2.1 (−)	0.0 (−)	0.5 (−)	2.5 (+)	0.050
Height	7.7 (−)	0.1 (−)	0.1 (+)	1.2 (+)	0.091
Episode duration	3.2 (−)	3.5 (−)	1.6 (+)	0.1 (+)	0.083
Work impairment	0.5 (+)	0.2 (+)	16.0 (+)	3.1 (−)	0.194
Social impairment	0.1 (+)	−0.2 (+)	8.7 (+)	11.6 (−)	0.202
Mental impairment	0.5 (+)	1.0 (−)	0.2 (+)	10.6 (−)	0.123
Hospitalizations	0.2 (−)	−0.1 (−)	1.7 (−)	0.7 (+)	0.026
Hospital time	0.1 (+)	0.0 (−)	1.4 (−)	0.0 (+)	0.014
Therapeutic response	0.0 (−)	3.3 (−)	6.9 (+)	0.0 (−)	0.101
Medical illness	1.2 (+)	1.5 (+)	0.1 (−)	4.1 (−)	0.070
Neurological illness	0.7 (+)	2.0 (+)	0.0 (+)	3.4 (+)	0.065

For statistical significance see Table 1

Table 3. CSF 5HIAA, HVA, and TRY in CSF and plasma in depressed patients and controls ($\bar{x} \pm$ S.D.)

	Depression ($n = 33$)	Control ($n = 32$)
5HIAA (ng/mL)	25.4 ± 12.8	27.0 ± 10.4
HVA (ng/mL)	28.6 ± 15.2	27.7 ± 12.2
TRY_{csf} (μmol/L)	3.8 ± 1.9	3.4 ± 1.0
$TRY_{pl.}$ (μmol/L)	38.4 ± 10.6	35.6 ± 13.0

The differences between the groups are statistically not significant

coefficients reached statistical significance. There is a significant inverse determination between age and CSF 5HIAA, between impaired working capacity and CSF TRY, and between impaired social functioning and mental deterioration and plasma TRY. All these determination percentages are, however, much lower (below 20%) than those found for some symptom-metabolite pairs. Since the partial determinations are only valid hypothetically when the other variables remain constant, the most important finding in the background variables is the lack of any significant multiple determination coefficient R^2.

Table 3 contains the averages and standard deviations of the four biochemical parameters compared to a control group consisting of 32 women with peripheral neurological disorders and no important psychopathological symptoms. Exclusion criteria in the control group were the same and LPs were performed under the same criteria. None of the four substance concentrations differed statistically in the two patient populations.

Discussion

These results seem to support the presumption that CSF monoamine metabolites (and to a remarkably lesser degree, CSF and plasma TRY) are, in fact, related to certain psychopathological symptoms. This argues in favor of the relevance of the monoamine hypothesis of affective disorders, although with a modification from the clinical point of view. Global severity of depression did not correlate with any of the biochemical data—probably because there was no significant influence on such characteristic features of depression as dysthymia, anhedonia, insufficiency, depressive thoughts—i.e., those symptoms that play the most important role in the clinician's judgment about the severity of global depression. This negative finding deserves special attention because it points out the possibility that depression may be a disease with biologically different underlying mechanisms, including processes independent of central serotonin and dopamine metabolism.

The results corroborate the finding of van Praag et al. (1975) concerning CSF HVA and motor activity: high in agitation and low in retardation independent of depression global severity. In addition, CSF HVA correlated positively with paranoia and negation, i.e., with two characteristically 'psychotic' symptoms. On the other hand, CSF 5HIAA correlated inversely with symptoms like insomnia, anxiety, anorexia, and suicide, also found in other research (Banki 1977; Asberg et al. 1976). Here again it should be stressed that these relationships are not accompanied by a parallel variation of the severity of the whole clinical picture.

There was no correlation between CSF 5HIAA and HVA concentration ($R = -0.298$) which argues against the possibility that motor activity caused CSF metabolite concentration changes independent of central amine turnover differences (Post et al. 1973); similarly, differences in metabolite egress from the CSF could not have accounted for the symptom-related concentration differences because resorption is common to both 5HIAA and HVA.

Some symptoms were dependent on more than one CSF substance but in different ways. Anxiety and insomnia, for example, were associated with low CSF 5HIAA and, at the same time, with high HVA; agitation was not only associated with high HVA, but also with lower 5HIAA. This is in opposition to the statement that depressions with different biological pathomechanisms are indistinguishable in clinical terms (van Praag 1977); in contrast, they seem to support earlier observations made by Fujiwara and Otsuki (1974) who described symptom clusters characterizing 'indoleamine depression' as opposed to other symptoms occurring more frequently with 'catecholamine depression.' It is noteworthy that the symptoms associated with indoleamine deficiency were anxiety and agitation, while those associated with catecholamine deficiency were retardation and hypersomnia.

None of the 12 background variables were significantly determined by CSF metabolite and TRY concentrations. CSF 5HIAA correlated partially to both age and body height; this finding has been demonstrated by other authors as well (Asberg and Bertilsson 1979), while age was previously found to be positively correlated with CSF 5HIAA (Goodwin et al. 1975). This discrepancy cannot be easily explained but there are indications that positive correlation is present only in controls, not in depressives (Asberg and Bertilsson 1979). We also failed to

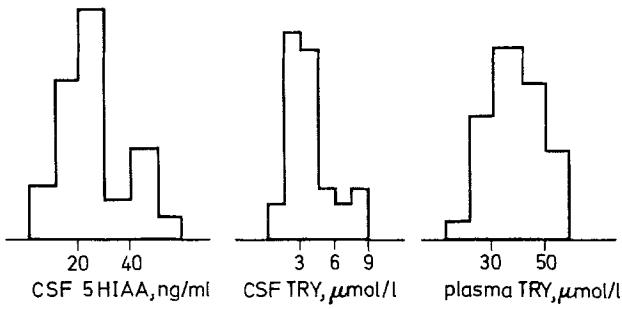

Fig. 1. Frequency distribution of CSF 5HIAA, CSF TRY, and total plasma TRY in depressed patients ($N = 33$)

demonstrate increased depression-risk as reflected by a greater number of hospitalizations in patients with low CSF 5HIAA (van Praag and de Haan 1979), although their data were postprobenecid values from patients with persistently low CSF 5HIAA, while we used baseline values.

Our baseline CSF 5HIAA values proved to be bimodally distributed, as repeatedly found by Asberg et al. (1979), and CSF TRY also showed a weak tendency toward bimodality (Fig. 1). In contrast, plasma total TRY values showed a clearly unimodal distribution, unlike other authors' findings (d'Elia et al. 1979).

In conclusion, we believe we have demonstrated that CSF 5HIAA and HVA do correlate with certain symptoms of depression, although they do not correlate with global severity. This result suggests that studying isolated symptoms instead of complex nosological designations may be a fruitful approach to elucidate further the relationship between central monoamine metabolism and behavior.

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Appendix: Symptom Definitions

Dysthymia = depressed mood, despair, dejection, hopelessness if congruently reflected in subjective experience and behavior

Anxiety = fear, tension, restlessness, worrying, 'nervousness' if accompanied by congruent vegetative signs or stereotypies

Suicide = intention, planning, preparation or attempt, except if obviously only a provocative statement

Anhedonia = loss of interest in pleasure-giving and -receiving (including sexual libido), if it has been a painful change of affect

Insufficiency = feeling of uselessness, inadequacy, with subjective loss of ability to appropriately think, act, and decide

Fatigability = loss of energy, helplessness, tiredness which demands extra repose which however does not bring about restoration

Anorexia = only if real weight loss (at least 2.5 kg) is present

Insomnia = only if total sleep time has been reduced by at least 3 h and it causes important subjective trouble

Somatization = all subjectively relevant physical complaints that are not readily explained by medical disease

Obsession-Compulsion = thoughts and acts the patient feels irresistibly compelled to perform while considering them unpleasant and irrational
Hypochondria = pervasive fear of or presumption about the presence of a severe or life-threatening disease without its actual signs
Agitation = permanent motor restlessness that interferes with relaxation and orderly activities
Retardation = reduction and slowing down of voluntary and expressive movements without causative medical or CNS disease
Perseveration = repetition of the same word, phrase, or topic if hampers reasonable communication and unexplained by aphasia
Paranoia = uncontrollable feelings of being intentionally wronged, injured, or pursued by real people, if disproportionate to reality or if it motivates acts causing greater disadvantage that that presumably being submitted to
Depressive thoughts = permanent and not easily controlled feelings about guilt, sin, worthlessness, impoverishment, damnation
Negation = lack of insight, no acceptance of the possibility of an illness or even of a change when confronted with the present symptoms

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