

BIOCHEMICAL CORRELATE OF DEPRESSION IN CHILDREN

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SUMMARY — The degree of depression in 88 abandoned children was analysed through a depression rating scale adapted to prepubertal children. The items were grouped into three dimensions: sociological-relational, psychological and biological. In 46 children from this sample it was dosed plasmatic Cortisol and the urinary excretion of catecholamine, VMA, HVA and 5-HIAA. When analysing the principal components, the sociological and psychological dimensions were the most important ones in the sample, followed by age and catecholamine variables. The group of male depressed children presented a higher level of catecholamine urinary excretion and a lower peak of plasmatic Cortisol than the non-depressed group. The variable age, in both sexes, was correlated with the biochemical variable catecholamine. Biochemical alterations are present in depressed children but it is difficult to show a correlation of dependence between them and the phenomenological aspects of depression.

Correlatos bioquímicos da depressão em crianças.

RESUMO — O grau de depressão em 88 crianças abandonadas foi analisado por escala de avaliação de depressão adaptada para crianças na pré-adolescência. Os itens da escala foram agrupados em três dimensões: sociológico-relacional, psicológica e biológica. Em 46 crianças desta amostra foram dosados o cortisol plasmático e a excreção urinária de catecolamina, VMA, HVA e 5-HIAA. Pela análise dos principais componentes, mostraram-se mais importantes, na amostra, as dimensões sociológica e psicológica, seguidas dos componentes idade e catecolamina. O grupo de crianças do sexo masculino com depressão apresentava maior nível de excreção urinária de catecolamina e menor pico de cortisol plasmático que o grupo sem depressão. A variável idade, em ambos os sexos, correlacionava-se à variável catecolamina. Alterações bioquímicas estão presentes em crianças com depressão, mas é difícil demonstrar correlação de dependência entre elas e aspectos fenomenológicos da depressão.

The depressive clinical pictures are well described and established in adults, but the neurophysiological and biochemical correlates of the various forms of depression have not been found yet. Since Schildraut's 29 and Bunney & Davis's 2 suggestions that depression would be related to the noradrenergic transmission deficiency in the central nervous system researches have emphasized the following: the variation of monoamine metabolite concentration in CSF, blood and urine, such as 3-methoxy-4-hidroxyphenyglycol (MHPG), 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA), which are the main products of central metabolism of norepinephrine, serotonin and dopamine, respectively; the alteration of sensitivity of α_1 and α_2 -adrenergic receptors 5,11,19,31. The studies which have been carried out, though not

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totally conclusive, show an alteration in the release/metabolism of norepinephrine, which is reduced in many bipolar depressed patients and increased in some subgroups of manic and unipolar depressed patients. The dopaminergic function would be reduced in subgroups of bipolar and delusional depressed patients and increased in mania. Even though some authors have reported reduced activity of the serotonergic system in subgroups of depressed patients, its role is more difficult to be defined 4,7,8. These data suggest a great biochemical heterogeneity in affective disorders. Much of this data disorder is due to demographic characteristics, diagnostic evaluation and classification of patients and the methods for collecting material for metabolite dosage. As far as children are concerned, it is necessary to be careful, for little is known about their depressions. However, some disagreements have appeared, some of them reflecting the adults disagreements. The first one is the realization that even prepubertal children may present depression. The second one is the reliability of methods of evaluation and diagnosis of children depression and consequently its classification. The third one concerns its psycho-biological marker 23,30.

When we started this work, we considered that there were no more doubts that children of various ages present depressive syndromes. This can be evaluated and diagnosed through reliable criteria 6,12,15,20,21. We also believe that depressive syndrome in children may present a biochemical correlate, an aspect which has been little explored 13,23. The pioneering work of Cytryn and his associates³ showed, although in a small number of cases, a decrease in norepinephrine urinary excretion in children with chronic and acute depression. MHPG excretion was decreased in three depressed and in one hypomanic children. In 1979, McKnew and Cytryn repeated the experience and only noticed a decrease of MHPQ in chronic depressive children. Puig-Antich and associates²² dosed the plasmatic Cortisol in four prepubertal children which presented characteristic symptoms of endogenous depression. Hypersecretion of Cortisol was found in two of the children while depressed and the levels of secretion subsided with the clinical recovery.

Our major objective was to search for biochemical characteristics that could, at least, characterize depressive state in children. Therefore under the previous consideration we were left the task of making decisions concerning the evaluation of depression and the biochemical analysis. In regard to the samples, we decided to investigate the occurrence of depression in children who were abandoned physically and emotionally 16 of neglected according to Lippi's² and Widom's³³ concepts, under the care of Fundação Estadual do Bem Estar do Menor (FEBEM). The children were informed of the research in which they would take part, and their questions were cleared up. All the recommendations from Helsinki's declaration were followed. We used Hamilton's depression rating scale, adapted for children by Poznanski et al¹⁰ after selecting the children by the diagnostic research criteria used by the same authors. We performed the following biochemical evaluations: plasmatic Cortisol and the urinary excretions of norepinephrine, vanillylmandelic acid, homovanillic acid and 5-hydroxyindoleacetic acid.

PATIENTS AND METHODS

Before 'working' with the children we had several meetings with their caretakers who were the only other source of information, and we instructed them about the essential and qualifying symptoms included in the diagnostic criteria for depression 20,21. Then, children with unresponsive and unhappy faces, loss of interest or pleasure in all or almost all usual activities and pastimes, sleep disturbances, poor appetite, withdrawal and hypoactivity were pre-chosen. As we used a personal liaison setting, we were particularly careful about the behavioral items. Also, in that setting, we could not be certain of the duration of the depression mood since the children's permanence in the institution was usually less than five days. From the children previously selected by clinical criteria for depression, 88 were interviewed (52 male, 36 female). They were between the ages of 7 and 14. Biochemical analysis was carried out in 45 (24 male, 19 female). Their characteristics, the number interviewed and evaluated biochemically are shown in Table 1.

The depression rating scale for children, an adaptation of Hamilton's scale for adults elaborated by Poznanski & col.²⁰, was used with the following rearrangements and considerations: (1) The item «school performance*» was not considered due to the type of sample. (2) The interview items were distributed into three behavior areas referred to as dimensions: psychological — depressed mood, weeping, self-esteem, morbid ideations, phobias, suicidal

ideation; relational-sociological — activity, social "withdrawal, expressive communication, irritability, anti-social behavior, capacity to have fun; biological — sleep disturbances, food, general somatic, physical complaints. (3) The lowest score in our scale was 16 and the highest 65. The cutting point non-depressed/depressed was 29/30. (4) At first, children were evaluated by an interviewer and an observer. There was always good correlation between the results. (5) The complementary information was obtained from FEBEM's monitors.

For the biochemical analysis, we collected blood samples from fasting children in the period between 7:45 a.m. and 8:00 a.m. Plasmatic Cortisol was dosed by the method of radioimmunoassay, according to Corning Medical Manual (Cortisol-H25 radioimmunoassay Corning Immunoplasme Technical Bulletin). The urine sample was the first morning urine collected in a container with concentrated chloridric acid. The following substances were dosed: total catecholamine having norepinephrine as a pattern 24, vanillylmandelic acid (VMA)9, homovanillic acid (HVA)1 and 5-hydroxyindoleacetic acid (5-HIAA)8. The dosages of these metabolites are referred to the quantity of creatinine excretion (μ g of metabolite/g of creatinine).

The data were submitted to qualitative description through the frequency histograms, to the analysis of correlational and principal components, and to the analysis of variation (ANOVA) using the SAS statistics program from the Scientific Computer Laboratory of UFMG.

RESULTS

The whole number of children studied, previously grouped according to their sex (36 female and 52 male), were classified into two groups: non-depressed (ND) and depressed (D). The ones who were considered non-depressed reached up to score 29 on the evaluation scale. It is necessary to point out that the mean age of the various groups is not statistically different (Table 1). As far as the samples are concerned, the classification mentioned above must not mislead us to the conclusion that there is a higher prevalence of depression in abandoned children. As it was our objective to study a possible neurochemical correlate in depressed children, our samples stressed on children with clinical signs of depression. Therefore, according to our criteria, the samples were equally divided into ND and D.

Sex and Total	Evaluation classif.	Nº of children (AGE \pm SD)			
		Interview		Biochemical analysis	
		ND	D	ND	D
F	36 (10.1 \pm 1.9)	20 (9.4 \pm 1.8)	16 (11.1 \pm 2.0)	11 (9.6 \pm 2.0)	8 (11.4 \pm 1.5)
M	52 (10.2 \pm 1.9)	25 (10.3 \pm 2.1)	27 (9.8 \pm 2.4)	14 (10.3 \pm 2.0)	12 (9.7 \pm 1.9)
Total	88	45	43	25	20

Table 1 — Number and sex of the children evaluated by interview and biochemical analysis presenting non-depressed (ND) and depressed (D) diagnostic classification. FEBEM/BH, MG, Brazil, 1986.

The cutting point ND/D, between scores 29/30 on the evaluation scale, was chosen arbitrarily according to the following procedure: the children, who were grouped taking their sex into account, were classified on the basis of the increasing order of their scores. Among the female, no outstanding difference was noticed. The male, on the other hand, with 30 scores or over, presented a higher frequency of high values of catecholamine. This criterion was corroborated by the plot of factor 1 versus 2 obtained from the analysis of the principal components, in which a perfect separation of ND from D children was observed (Fig. 1).

Analysis of the variables:

1. Frequency histograms — A tendency to or bimodal distribution was observed in the histograms of the following variables, per group: Female — D: age, depressed humor, self-esteem,

morbid ideations suicidal ideations, social withdrawal and irritability. Male — ND: age, D: age, humor, social withdrawal and capacity for having' fun. The catecholamine variable presented a dispersion in the male D group, where higher values appeared with more frequency. The inverse was demonstrated by the Cortisol.

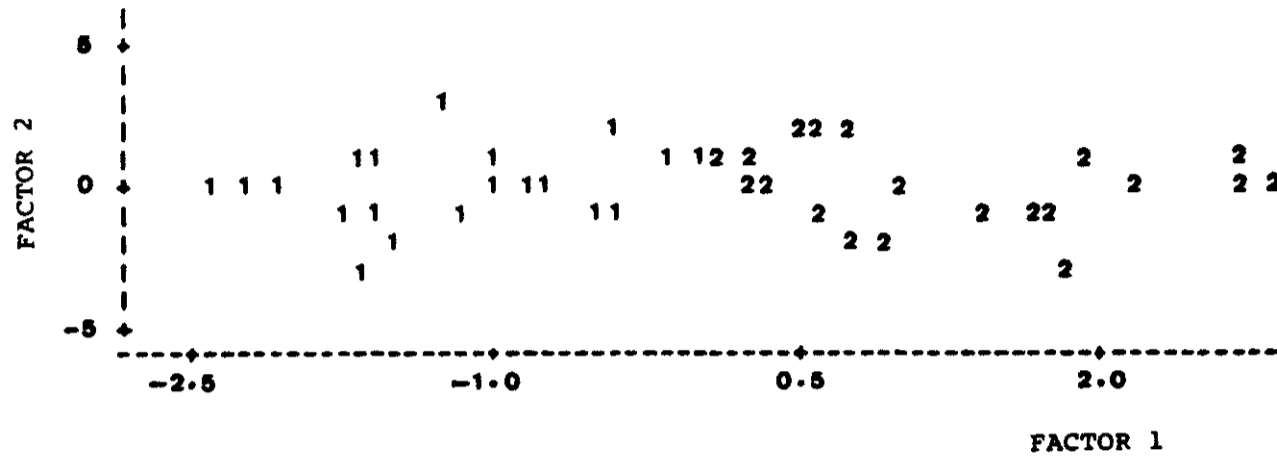


Fig. 1 — Plot of factor 2 versus factor 1 of the principal component analysis showing the separation of non-depressed (1) and depressed (2) children.

2. Analysis of linear correlation — The variables, which present a stressed correlation with the global rate (referred to as total interview dimension), were: depressed mood; weeping;

Biochemical variable	Female		Male	
	ND	D	ND	D
CAT	× Age	S/W rhythm Gen. somatic Physical comp.	Age (—)	
VMA	× Activity	Weeping Phobias Suicide ideation (—) Activity Social withdrawal Irritability (—) S/W rhythm Gen. somatic	Phobias	
5-HIAA	× Age	Social withdrawal Capacity to fun S/W rhythm CAT	Morbid ideation (—)	Morbid ideation (—) S/W rhythm
HVA	× Weeping Social Withdrawal	Age (—) Capacity to fun	Weeping Irritability	Weeping (—) Self-esteem (—) Social withdrawal S/W rhythm
Cortisol	× Age D. mood	Weeping Phobias Suicidal ideation (—) Soc. withdrawal (—) Irritability Physical comp. (—) VMA	S/W rhythm Gen. somatic Physical comp.	Gen. somatic (—)

Table 2 — Linear correlation* of the children sample divided by sex and non-depressed (ND) and depressed (D) diagnostic classification. FEBEM/BH, MG, Brazil, 1986.

* Correlation with values higher than 0.500; (—) negative correlation.

gelf-esteem; morbid ideations; suicidal ideations; activity; social withdrawal; expressive communication; irritability; capacity for having fun; sleep disturbances; and general somatic. The division of the sample according to sex and ND/D groups showed a great number of meaningful correlations, but the one which deserved more attention was the fact that the biochemical variables appeared with greater constancy, especially in the female D group (Table 2), what was not observed in the analysis of the whole sample. This is particularly interesting, since no biochemical variable differed in the female D group in relation to the ND.

3. Analysis of the principal components — In the analysis of the principal components, considering all the variables, interview variables and biochemical ones, 9 factors with «eigenvalues» > 1.0 were obtained, which explains about 80% of the variation of the samples. The variables capacity for having fun, social withdrawal, activity, expressive communication (sociological dimension); depressed humor and self-esteem (psychological dimension); sleep disturbances and general somatic (biological dimension); and catecholamine — were the ones with higher values. The analysis of the principal components, making use of the sociological, psychological and biological dimensions, the biochemical variables, together with age and sex, of the sample, showed 5 factors with «eigenvalues» > 1.0, what explains about 80% of the total variation (Table 3). The sociological and psychological dimensions, through their variables, proved to be more important, being followed by age and catecholamine. HVA, 5-HIAA and sex plus biological dimension stood out also. The analysis of the principal components of the ND and D groups showed that for the D group the variables age, sex and catecholamines formed the first factor explaining 25% of the variance, altering the profile of the most important variables. The plot of factor 2 versus 1 (Fig. 1) shows a perfect separation of the samples into the two sets ND (1) and D (2), confirming that the lowest value of

Factor 1 — Explains	20.8%	of the total variation
Social dimension	0.630	
Psychol. dimension	0.539	
Factor 2 — Explains	18.8%	of the total variation
Age	0.575	
Catecholamine	— 0.567	
Factor 3 — Explains	15.6%	of the total variation
HVA	0.534	
Factor 4 — Explains	12.0%	of the total variation
5-HIAA	— 0.621	
Factor 5 — Explains	10.1%	of the total variation
Sex	0.531	
Biological dimension	— 0.494	

Table 3 — Loading of the first five principal component factors of the total sample of children. FEBEM/BH, MG, Brasil, 1986.

Biochemical variables	Female		Male	
	ND (mean ± SD μg/g creatinine)	D	ND (μg cortisol/dl blood)	D
CAT	(11) 13.14±8.24	(8) 9.99±6.67	(13) 13.57±10.37	(12) 25.20±17.11 *
VMA	8.75±4.13	11.58±7.78	11.16± 5.92	11.43± 7.81
5-HIAA	8.36±3.21	7.73±1.39	8.22± 2.82	7.83± 3.43
HVA	0.32±0.20	0.37±0.11	0.39± 0.27	0.37± 0.23
Cortisol	12.66±4.63	11.14±5.32	13.40± 4.78	10.48± 3.18

Table 4 — Biochemical variables on the children by sex and ND/D diagnostic classification. FEBEM/BH, MG, Brasil, 1986.

* Significant for $p=0.049$; (n) indicate number of samples.

score 30, evaluated by the interview, for those considered depressed, is, in our research, reliable.

4. Neurochemical evaluation — The dosage of catecholamine, VMA, HVA and 5-HIAA urinary and of plasmatic Cortisol provided the values shown in Table 4 for all children. Figure 2 shows the same values for male children. The level of catecholamine is meaningfully increased in the boys classified as depressed. The average of the values of Cortisol for the depressed male children is lower than that for the non-depressed ones, but such difference is not significant. The relations HVA/5-HIAA are not different from the various ND/D groups.

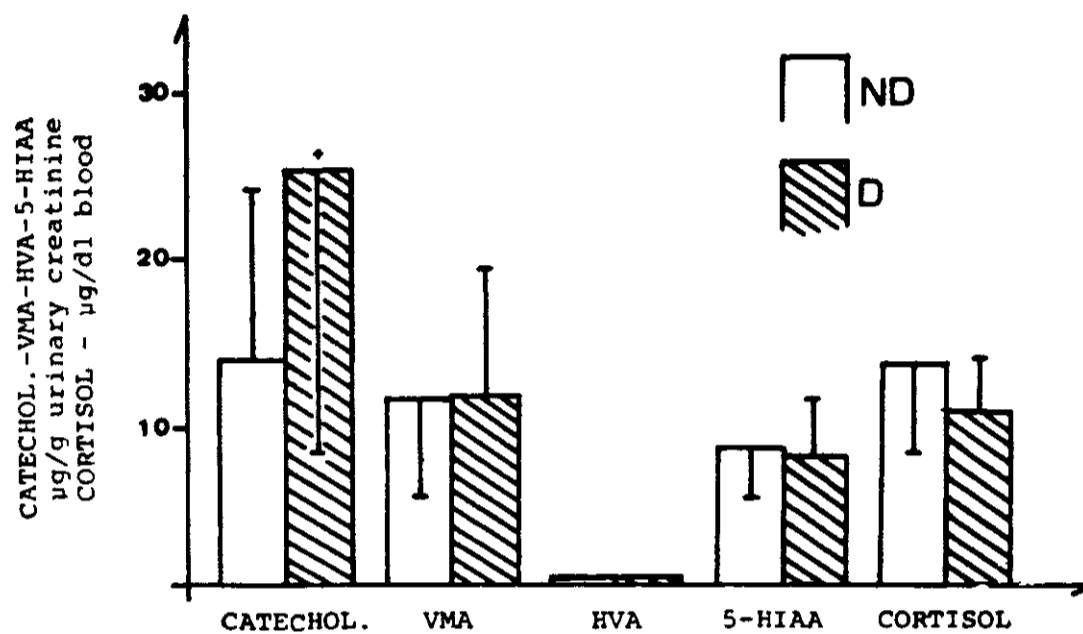


Fig. 2 — Biochemical variables and ND/D diagnostic classification for the male children sample.

* Significant for $p=0.049$.

COMMENTS

The sample of children studied present some distortions which are worth criticizing. The initial purpose of this paper was to evaluate the neurochemical correlate of depression in children aged between 7 and 12 years old avoiding adolescent patients. It was not possible to attach to that age group, since some children were about 13 or 14 years old at the time we started the research. The children were not submitted to the low monoamine or caffeine level diet. We assumed that any difference that might exist concerning the monoamines should be through the characteristic of the psychopathological case. We should also emphasize the percentage of depressed children (50%), what, does not mean prevalence. According to what we were proposed to do and making use of the clinical criteria for diagnosis, we guided the selection of the children who were able to fulfill them, so that we could have enough patients for the research. The population which gave origin to the samples is of great risk, considering its psycho socio economic characteristics 13.

The first problem we had in the work was the fact that childhood depression was (and maybe still is) widely unrecognized by caretakers, nurses, parents and other professionals in many allied disciplines. The second one was to choose among the several diagnostic criteria for depression in children. Recent studies comparing them have demonstrated more agreement among them than disagreement 12,15,21. Our preference felt on Poznanski's children's Depression Rating Scale (CDRS) because it is an adaptation of Hamilton's Adults's Depression Rating Scale which is based on clinical judgement. It allows the interviewer to adapt his/her language to the age and cultural background of the child, and at the same time to do a diagnostic of depression and assess its severity. Although we could separate our sample between non-depressed/depressed by biochemical and statistical criteria, it is not appropriate to diagnose the components of the depressed group as major depression according to DSM III-R. As Poznanski and colleagues called our attention: «depression is a non specific feature of many psychiatric disorders and high scores on the CDRS could not, by themselves, be sufficient to warrant formal psychiatric diagnosis», thus, we could only diagnose the depressive state.

The distribution of frequencies showed that in the group of depressed children, female and male, some variables present a bimodal character. This may be a characteristic of the group or may be related to and dependent on the age variable, also with bimodal distribution.

The analysis of linear correlation shows the importance of the variables classified as relational-sociological and psychological for the depressive case. Depressed humor, decreased self-esteem, morbid and suicidal ideations, decreased activity and capacity for having fun, social withdrawal, irritability, little disposition for expressive communication, sleep disturbances, and general somatic complaints form the fundamental symptoms of the depressed patient used in the diagnosis by any criterion.

The separation of the samples according to sex and ND/D groups emphasized in the correlational matrix the biochemical variables and their relations, although not of cause and effect, with clinical symptoms. Such relations were more numerous in the female sex; the depressed group in which no significant variation of chemical substance was found.

The analysis of the principal components reinforces what was gathered about the importance of the sociological and psychological dimensions and stands two variables out: age and catecholamine, followed by HVA, 5-HIAA and sex.

It has been rather difficult to obtain a biochemical correlation of the case or of the depressive syndrome 5,10,23,25. Conceptual, diagnostic, methodological and ethical difficulties have delayed the acquisition of knowledge, mainly as far as children are concerned, what results in scarce studies about the psychological markers of children depression. Cytryn and associates 3,18 showed that children with a diagnosis of chronic depression excreted less quantities of norepinephrine and MHPG in their urine. There is a great variation in values, and one of the factors which contributes for that is age. Puig-Antich and col.²² found two children (out of four) with hypersecretion of Cortisol diagnosed as endogenous depressed. Our results demonstrated an increased urinary excretion of norepinephrine and a reduction of plasmatic Cortisol in male depressed children. Studies carried out in adults have pointed to an increase in norepinephrine and/or epinephrine urinary excretion in sub-groups of depressed patients 4,14. This increase may be due to a greater activity of the peripheral sympathetic nervous system 26,27. The decrease in plasmatic Cortisol may be due to an increase in peripheral norepinephrines² or to the temporal alteration in the circadian rhythm of CRH-ACTH-Cortisol system²®.

To sum up, we have concluded that in any research done on children, both age and sex variables are to be taken into account. The evaluation scale which was used was an appropriate and excellent research device. Since the variation of the urinary values of catecholamine and monoamine metabolites is great, a greater number of patients become necessary in the various groups, so that the possible differences may turn out to be significant and consistent. Therefore, the existence of a biochemical correlate in children depression, or various correlations (what is even more probable), is yet to be defined.

Acknowledgements — We would like to thank Mrs Vera Lucia Roberto and Mrs Ione Batista Gomes for their technical assistance.

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