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Shealy, et al: "*Depression: A Diagnostic, Neurochemical Profile & Therapy with Cranial Electrical Stimulation (CES)*"

DEPRESSION
A DIAGNOSTIC, NEUROCHEMICAL PROFILE & THERAPY WITH CRANIAL ELECTRICAL STIMULATION (CES)*†

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INTRODUCTION

THROUGHOUT THE LATTER HALF OF THIS CENTURY, scientists have explored biochemical patterns associated with a wide variety of illnesses. The search for biochemical markers of depression has been particularly intense. The major groups of antidepressants are aimed at either serotonergic or adrenergic imbalances in depression. Cortisol hypersecretion, nonsuppression or the dexamethasone suppression test (DMST) and a blunted thyrotropin response to protirelin (TRHST), are other factors which have been studied extensively.[1-3] None of these tests, however, is positive or diagnostic in a majority of all depressed patients.

The current study was undertaken to extend our knowledge concerning blood levels of neurochemicals and particularly the interrelations between norepinephrine, serotonin, beta endorphins, and cholinesterase.

PROCEDURE

Fourteen non-smoking adults with no known illnesses and taking no drugs served as controls. They ranged from 22 to 72 years of age; 6 were male; 8 were female. Fourteen chronic pain patients entering a two week intensive treatment program represented a second group. This program has been reported elsewhere.* These individuals ranged from 30 to 68 years of age; 9 were women; 5 were men. All of them had had intractable pain for greater than 1-1/2 years and there was no known standard treatment for the residual pain. Ten of them had spinal pain of various types; 2 had headaches; 2 had osteoarthritis.

A third group consisted of 9 chronic pain patients considered by themselves to be hopeless and unable or unwilling to enter intensive therapy but willing to volunteer for the research protocol; 6 were female; 3 male. They ranged from 32 to 60 years of age.

The fourth group of subjects were 11 volunteer patients with long-standing depression (greater than 2 years), unresponsive to 2 or more antidepressant drugs and currently not under therapy. Eight were female; 3 male. They ranged from 30 to 67 years of age.

RESEARCH PROTOCOL

All subjects were tested initially with history, blood pressure, pulse, Zung Test for Depression. They were seen at 8 a.m. after fasting for at least 10 hours. Baseline blood tests were done and prepared for measurements of serotonin, tryptophan, cortisol, ACTH, beta-endorphin, GABA, cholinesterase and norepinephrine. They then received 20 minutes of stimulation transtemporally, using the Liss Pain Suppressor (TM) at between 0.5 and 1.0 m-amps of current, sufficient to evoke a visual flicker. Blood studies were drawn again 10 minutes later.

All the patients were treated with the Liss Pain Suppressor cranial electrical stimulation (CES) 20 minutes each morning for 2 weeks. After 2 weeks, baseline blood levels were again drawn, followed by a final CES and a final blood test 10 minutes later.

All blood was prepared according to lab instructions, plasma or serum was separated and frozen and samples were sent to Brunswick Hospital (New Jersey) for analysis.

RESULTS

In this paper we will report the findings in relation to norepinephrine, serotonin, beta-endorphins, and cholinesterase as these seem to be most closely tied to pain and mood. Analysis of other interrelations has not been completed. Chart 1 shows the basic chemical measurements in each test group.

CHART 1

14 NORMAL INDIVIDUALS

	8 a.m.	12 Noon	6 p.m.	8:30 a.m. After 20 Min. TCNS
Serotonin	42.0	80.0	65.0	70.0
Beta Endorphin	6.7	7.5	8.0	8.5
Norepinephrine	278.0	260.0	270.0	285.0
Cholinesterase	12.0	11.0	13.0	14.0

11 SEVERELY DEPRESSED PATIENTS

	8 a.m. Before Treatment	2 Weeks After Daily TCNS
ST	28.0	44.0
BE	10.5	7.5
NE	212.0	239.0
CHE	16.0	12.0

23 CHRONIC PAIN PATIENTS

	8 a.m. Before Treatment	2 Weeks After Treatment
ST	40.0	42.0
BE	8.9	10.2
NE	214.0	224.0
CHE	12.0	12.0

Serotonin ng/ml. Norepinephrine pg/ml.
Beta Endorphin pg/0.1ml. Cholinesterase u/ml.

Statistically, in the depressed patients the changes in serotonin and in cholinesterase before and after 2 weeks daily CES are significant.

	BEFORE Mean	BEFORE Stnd. Dev.	AFTER Mean	AFTER Stnd. Dev.	t.	p.
Serotonin Levels	33.18	9.33	44.64	9.10	-2.92	<.0089
Cholinesterase	13.82	2.86	10.45	2.30	3.04	<.0087

Since the relationship *between* the neurochemicals is theoretically more important than individual levels, we have looked at a variety of ratios, reported in Chart 2.

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CHART 2

	NE/ST	NE/BE	NE/CHE	ST/BE	NE ST/BE
Normals (Ave.)	5.3/1	29.6/1	21.2/1	5.6/1	41.7
Range	2.6-10.4	17.2-47.3	10.1-35.1	2.1-10.1	16.6-93
			71%>16	79%>5.0	79%<60
Pain Pts.	5.5	22.9	14.3	4.7	63
CES Only	1.8-10.7	3.4-42.3	9.8-35.6	1-12.7	15-138
			63%<16	62%<5.0	64%>60
Intensely Rxd. Pain Pts.	6.8	35.4	21	5.2	51
	4.6-15.4	12.5-78.7	9.3-34.6	3-12.7	15-83
			64%>16	64%<5.0	64%<60
Depressed	5.5	21.5	12	3.8	54.7
	1.9-15.5	10-57.6	5.3-44	3.1-4.9	23-83
			55%<16	72%<5	60%=60 or >

After the first CES all of the "Normals" showed an ST/BE ratio of >5/1.

After the *first* CES 44 percent of the depressed patients showed an ST/BE ratio of 75/1.

After the first CES all of the "Normals" showed an NE:ST/BE ratio of less than 60.

After 2 weeks of daily CES 67 percent of the depressed patients showed an ST/BE ratio of > 5/1 and 60 percent of the depressed patients had improved on the Zung Test by 9 points or more; 50 percent of the depressed patients had a Zung Test score below 50 indicating no depression.

In the pain patients treated *only* with CES, 46 percent (5 of 11) had improved 50 percent or more on their estimates of total pain.

In summary, of all persons tested:

1. With ST/BE < 5 (24 persons) all but 3 were *clinically depressed.* Thus this ratio means that there is an 88 percent chance of being depressed clinically.

2. With ST/BE < 5 and NE/CHE < 16 (18 persons) all were clinically depressed. Of the 3 *non-depressed* patients with ST/BE < 5, all had NE/CHE > 16 and all 3 of these moved into ST/BE > 5 after the first session of CES.

If ST/BE < and NE/CHE < 16, there is a high probability of depression.

3. If ST/BE < 5 and NE/CHE < 16 and NE/ST/BE > 60, there is probably a biochemically active depression.

4. Low ST, Low BE, and High CHE are all suggestive of depression.

5. Low NE is not of itself suggestive of depression *unless* CHE is relatively high.

6. High BE is suggestive of agitation.

DISCUSSION

A biochemical "marker" of depression has been sought for many years. Although the DMST and TRHST, when positive, have been useful in determining bipolar depression, they have not been applicable to the broader question of neurochemical imbalance in "generic" depression.[1] Numerous urinary studies have also failed to produce a broadly applicable diagnostic test for depression.

Shealy has earlier presented some neurochemical changes in patients with chronic intractable pain (almost all of whom are depressed):

1. Vitamin B6 deficiency in 35 percent of non-smokers and 80 percent of smokers.[4]

2. Catecholamine elevations in 55 percent of chronic pain patients at rest and in 77 percent of patients after standing 5 minutes.[5]

3. Plasma beta-endorphins levels were low in 52 percent of patients with chronic pain.[7]

The current studies suggest that the relationship of NE, CHE, ST and BE is at least one major neurochemical profile worth further investigation. Two of the "normal" subjects who demonstrated ST/BE less than 5 were by far the most elderly of the "control" subjects and the third was under considerable stress at the time of his entry into the study. Even then, all 3 of these subjects developed a "normal" ratio after an initial challenge with CES. And all 3 of these non-depressed persons had an NE/CHE ratio within the usual normal range. It may be that early or borderline neurochemical imbalance is more easily reversible than more established patterns of imbalance.

When we combine the NE/CHE, ST/BE, and NE:ST/BE data, a broad picture of neurochemical imbalance is suggested in the depressed patients. It is also possible, in view of baseline biochemical profiles, that the pain patients treated *only* with CES were, overall, more depressed than those who entered the 2 week intensive treatment program. Perhaps their improvement in depression accounts for the 44 percent of patients reporting improvement in pain with no other intervention.

Equally intriguing is the 50 percent response of patients with previously intractable depression. No antidepressant drug helps 50 percent of depressed patients, especially in only 2 weeks. Incidentally, a number of those patients who improved with CES asked later to be able to continue using the stimulator a few weeks or months after the formal study. We have noted rapid resolution of depression with CES in some patients over the past 13 years of clinical experience.

It is generally believed that blood levels of neurotransmitters are not reflective of central nervous system activity, but Shealy reported 11 years ago that CES increased both blood levels of serotonin and 24 hour output of 5-HIAA.[8] The current studies suggest that CES increases blood levels of BE and serotonin immediately and may lead over a 2-week period to homeostasis of ST in depressed patients.

Although others have mentioned the theoretical interrelations of various neurotransmitters, there is no known previous assessment of the ratios of NE, ST, BE and CHE.

The numbers in each of our groups are not large but the trend is encouraging. If 72 percent of depressed patients have an easily measurable neurochemical imbalance, and over 70 percent of normal persons who initially have a "false" chemical picture of depression move into the normal range with a single CES application, we may have a tool for demonstrating chemical homeostatic dysfunction in *most* depressed patients. The percentage of depressed patients with an abnormal ST/BE ratio is greater than the percentage of bipolar patients with an abnormal DMST or TRHST.

("Discussion", Continues):

Considering the psychoneuroimmunological aspects of depression and the adverse effects of depression in both medical and surgical therapy, it may become prudent to screen all elective surgical candidates and those medical patients with a large number of confusing symptoms with neurochemical profiles. There are also therapeutic implications. If the current studies can be replicated, CES may become the primary treatment of preference in depression. In the current study, tryptophan was not given the depressed patients. Our clinical experience suggests that tryptophan and CES may be a very potent treatment for depression.

SUMMARY

Blood levels of norepinephrine, serotonin, beta-endorphin, and cholinesterase were measured at rest in 4 categories of fasting subjects:

1. Non-smoking, healthy, asymptomatic adults ("normals").

2. Chronically depressed patients previously unresponsive to therapy.

3. Chronic pain patients treated only with cranial electrical stimulation (CES).

4. Chronic pain patients treated with an intense 2 week multidisciplinary, multimodal program.

Relatively low levels of serotonin and high levels of cholinesterase were found in the depressed patients. The ratio of ST/BE was less than 5 in 72 percent of depressed patients and 88 percent of those patients with an ST/BE ratio below 5 were clinically depressed.

The few normal subjects with ST/BE less than 5 had NE/CHE ratios of greater than 16. All individuals with ST/BE less than 5 plus NE/CHE less than 16 were clinically depressed.

Two weeks treatment with CES led to clinical lifting of depression in 60 percent of depressed patients and to improvement in pain complaints in 44 percent of patients.

ST/BE and NE/CHE ratios offer a diagnostic neurochemical profile which may indicate biochemical evidence of clinically relevant depression.

Cranial electrial stimulation may be of therapeutic value in depression and in chronic pain. ●

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