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USE OF BIOLOGICAL MARKERS FOR DIAGNOSIS OF DEPRESSION

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ABSTRACT

Depression is the most common symptom which occurs in many psychiatric and medical illnesses. Diagnostic criteria for primary and depressive illnesses are clearly described in Diagnostic and Statistical Manual Number 3, by the American Psychiatric Association. This improves the real probability of diagnosis, however when the patient presents with moderately severe depression symptoms and is unable to give a clear history, diagnosis of the condition is difficult. Similar difficulty in diagnosis may also be encountered when depression is marked by somatic symptoms. Due to these diagnostic difficiulties some patients with major depression may not receive anti-depressive treatment and on the other hand many patients with other forms of depression may be treated inappropriately with anti-depressive drugs. In recent years biological tests have been developed that can confirm or support a clinical impression or diagnosis. The most commonly used diagnostic test, Dexamethasone Suppression Test is described and the results are discussed. This routine laboratory procedure may result in improving the patient care by identifying patients who will respond positively to the anti-depressant medication.

Depression is a most common symptom which occurs in many psychiatric and medical illnesses. Many medical and neurological illnesses, alcohol abuse, side effects of drugs, sexual dysfunctions, as well as many psychiatric illnesses such as schizophrenia, organic brain disorders and grief reactions are presented with depressive symptoms. According to American Psychiatry Association's Diagnostic Statistical Manual (DSM-III)[1], the primary depression is classified in 3 categories, major depression, dysthymic disorder and atypical depression. Diagnostic criteria for major depression includes dysphoric mood, loss of interest or pleasure in almost all usual activities and at least five of the following eight symptoms: Disturbance of appetite and sleep; psychomotor agitation or retardation; loss of energy; fatigue; decreased libido; feelings of worthlessness; self-reproach; poor concentration and suicidal ideation. Dysthymic disorder is diagnosed by presence of depressive symptoms for two or more years but are not of sufficient severity and duration to meet the criteria for a major depressive episode. Depressive syndrome may be relatively persistent or separated by periods of normal mood lasting a few days to a few weeks. Atypical depression is characterized by brief episodes of depression that does not meet criteria of major depression, dysthymic disorder or reactive to psychosocial stress!

The well-defined diagnostic criterion for major depression, dysthymic disorder, and atypical depression, improves the reliability of diagnosis and facilitates prediction of treatment response. However, when the patient presents with moderately severe depressive symptoms and is unable to give a clear history, diagnosis of the condition is difficult. Similar difficulty in diagnosis is also encountered when depression is masked by somatic symptoms. While dysthymic disorders and atypical depression (also called minor depression) are often effectively treated by psychotherapy alone, major depressions are seldom improved without use of antidepressant medication. Due to the diagnostic difficulties, some patients with major depression may not have received antidepressant treatment, and, on the other hand, many patients with other depressions may be treated inappropriately with antidepressant drugs. In recent years biological tests have been developed that can confirm or support a clinical impression or a diagnosis[2,3].

The dominant hypothesis for depression is the amine hypothesis. Most simply stated, this hypothesis argues that major depression is related to decreased functions of central neurotransmitters, especially norepinephrine and serotonin. It is presently believed that these are two broad types of biochemical depression which occur. One associated with: 1) Low central norepinephrine activity with resultant low MHPG (3 Methoxy, 4 Lyonxy phenylglycol) level in urine and 2) with low serotonin and low 5H1AA (5 hydroxy indoleacetic acid) in C.S.F. The clinical importance of this distinction is that antidepressants vary in their effect on the different neurotransmitter systems and patients will respond more effectively to antidepressants which can be more specific for their particular pathophysiology, low norepinephrine group can be

best treated with desipramine whereas low serotonin group is effectively treated with amitriptyline.[4, 5]

The clinical syndrome — depression — is typically associated with several symptoms suggesting hypothalamic dysfunction, e.g., disturbances in mood, sleep and appetite, loss of sex desire, and frequently diurnal variations of symptoms. Since these hypothalamically regulated functions are affected in depressive illness, it is plausible that neuroendocrine function would also be disturbed.

The neurotransmitters which are implicated in the chemical pathology of depressive illness, particularly norepinephrine and serotonin, also regulate the secretion of the hypothalamic neuroendocrine cells[2]. Patients with major depression are found to have substantially increased cortisol secretion, an abnormality that remits in association with clinical recovery. This cortisol hypersecretion appears to be secondary to increased secretion of ACTH and it is not associated with any change in the periphreal metabolism of cortisol. It occurs in apathetic, unanxious patients, persists during EEG — verified sleep, is unaffected by anxiolytic drugs and is not reproduced in normal individuals under stress[6].

The most exciting area in research of depression today is the application of a number of neuroendocrine tests for the diagnosis and clinical management of depression. The most important of these tests are the Dexamethasone Suppression Test (DST) and the Thyrotropin Releasing Hormone Test (TRH).[2, 3, 7, 10, 12, 14]

Dexamethasone is a potent synthetic cortiscosteroid which, by affecting the cortisol "feedback" receptors in the brain, turns off the endogenous secretion of ACTH and cortisol[7]. Whereas plasma cortisol in normal subjects after administration of Dexamethasone falls for 24 hours to low levels, usually below 3 ug per dl, a substantial percentage of patients with major depression, while ill, escape from suppression[8]. After full clinical recovery, all of the patients suppressed cortisol normally following adminstration of dexamethasone. Dexamethasone resistance has been shown to have a high degree of specificity for major depression, and has been proposed as a laboratory aid in its differential diagnosis[9].

A review of the published literature had indicated that normal subjects maintain plasma cortisol concentration suppressed below 6 ug/dl for 24 hours after oral administration of dexamethasone at 11:00 p.m. to midnight. Based on the overall DST results plasma cortisol criterion value of 5 ug/dl is proposed for the diagnosis major depression. A positive or abnormal DST result was recorded when any one of the three plasma cortisol concentrations was greater than the criterion value. The diagnostic confidence for major depression associated with a plasma cortisol concentration above 5 ug/dl was 94%. On the other hand, the diagnostic confidence for ruling out melancholia associated with a plasma cortisol concentration below 5 ug/dl was only 54%. The results indicate that a positive DST result can be used with high confidence to support a diagnosis of major depression. However, a negative DST result will not necessarily rule out a diagnosis of major depression. Thus a positive DST result is much more informative than a negative result.[10, 11, 12]

Literature survey further confirms that there is no significant effect of a history of recent psychotropic drug intake on the DST results. There was no change in the frequency of positive results until the length of time drug therapy extended beyond 10 days. Similarly, the age and sex factors did not account for the frequency of abnormal DST results in among melancholic patients[10].

In addition of Dexamethasone Suppression (DST), Thyrotropin Releasing Hormone Test (THR) has also appeared to be useful in diagnosis of major depression[8]. Thyroid stimulating hormone (TSH) response to Protirelin (Thyrotropin releasing hormone) is studied in TRH test. Patients with major depression will show a blunted delta TSH, i.e., less than seven micro units per milliliter and may also show an abnormal release of growth hormone in response to TRH. As many as 50% of patients with major depression show an abnormal TRH test. Another value of TRH test is its ability to distinguish unipolar from bipolar depression. Bipolar depressed patients show an augmented TSH response to TRH while such patients' performance on Dexamethasone Suppression Test may be indistinguishable from that of unipolar patients.[13, 14]

Using laboratory tests, the findings of an abnormality has very high diagnostic confidence for confirming a major depression diagnosis[14]. These tests have four general uses: 1) To confirm the diagnosis of depression, particularly when there is not overt sadness but when anguish, irritability or lethargy dominates the clinical picture; 2) to help select a biological treatment for depression; 3) to determine prognosis; and 4) to determine whether the person is responding to treatment as well as he should be despite clinical appearance.

The Department of Psychiatry at John Peter Smith Hospital uses the Dexamethasone Suppression Test routinely in all cases of suspected depression. The following case examples will show positive as well as negative results:

CASE 1:

Mrs. L. is a 37 year old white female admitted with depression, early, mid, and late insomnia, suicidal feelings, guilt feelings, decreased interest in social activity and pleasure, decreased level of energy, decreased appetite and loss of weight. Patient has been chronically depressed, consumes a good amount of alcohol to control her anxieties and to deal with the depression, history of alcohol addiction since childhood, diagnosis of depression and alcoholism was considered. Laboratory work upon admission was unremarkable.

DST results: Pre 7.1 ug/dl, Post 5.5 ug/dl

Patient responded very well to antidepressant medication over a period of four weeks. Supportive psychotherapy and antidepressant medication continued following discharge.

CASE 2:

Mr. P. is a 26 year old white male, recently separated from his wife, presented with one month history of depression characterized by dysphoria, sleep disturbance, decrease of appetite, crying spells, feelings of hopelessness, helplessness, and suicidal feelings too. General physical examination and laboratory workup were within normal limits. Diagnosis of major depression as well as adjustment reaction was considered.

DST results: Pre 21.7 ug/dl, Post 6.9 ug/dl

Patient demonstrated great response to antidepressant medication and supportive psychotherapy.

CASE 3:

Mr. T. is a 20 year old black male who presented with violent behavior associated with drinking problems in addition to depression for a year prior to this hospitalization. This was demonstrated by sleep disturbance, lack of interest, increased alcohol consumption and disability to hold a job. Physical examination and laboratory workup were within normal limits. Diagnosis of depression and personality disorder was considered.

DST results: Pre 13.2 ug/dl, Post 10.3 ug/dl

Followup four weeks after antidepressant medication indicated a drop of cortisol level to 1.2.

CASE 4:

Mrs. F. is a 42 year old white female presented with an eight month history of dysphoria, decreased interest in surroundings, pleasure and sexual desire. Also late insomnia, decreased attention span and ability to concentrate. In addition to distinct quality of mood "being worried all the time" plus paranoid ideation and severe degree of psychomotor retardation. On admission all initial laboratory work was unremarkable. Diagnosis of major depression and schizoaffective psychosis was considered.

DST results: Pre 15.7 ug/dl, Post 13.0 ug/dl

Patient responded nicely to antipsychotic and antidepressant medications. Was able to return to normal baseline in four week period.

CASE 5:

Mrs. J. is a 32 year old white female admitted with depression and suicidal feelings, progressive withdrawal behavior, decreased sleep, mainly early insomnia, decreased appetite with noticeable weight loss, decreased interest in surroundings and social activities with some psychomotor retardation. History of similar episode five years ago. Treated with ECT. Laboratory workup on admission was unremarkable.

DST results: Pre 26.3 ug/dl, Post 13.7 ug/dl

Patient responded to antidepressant medication with improvement in mood, sleep and psychomotor activity.

CASE 6:

Mrs. C. is a 41 year old white female presented with two week's history of crying spells, dysphoria, (early, mid, and late) insomnia, with decreased appetite, hyperactivty, pressured speech with poor judgement in addition to paranoid ideation. Differential diagnosis of major depression and bipolar disorder was considered.

DST results: Pre 13.3 ug/dl, Post 1.8 ug/dl

Patient treated with antidepressant and antipsychotic medications in addition to psychotherapy. Final diagnosis — Borderline Personality was established.

CASE 7:

Mrs. B. is a young white woman in her late twenties who presented to the hospital with suicidal attempt by slashing wrists and stuffing it with a metal object in addition to burning her skin with cigarettes. Patient gave a history of chronic depression on and off, associated with helplessness, worthlessness, and anger feelings. No apparent thought disorder. Diagnosis of Depression and Borderline Personality was considered.

DST results: Pre 13.3 ug/dl, Post 1.8 ug/dl

Patient treated with antidepressant and antipsychotic medications in addition to psychotherapy. Final diagnosis — Borderline Personality was established.

CASE 8:

Mr. N. is a 44 year old white male admitted to the hospital with six year's history of depression, progressively worse over the past eight months. Patient complained of dysphoria, crying spells, (early, mid, and late) insomnia, decreased appetite with 35 lb. weight loss, loss of interest in surroundings, libido and pleasure with guilt feelings, hopelessness,

helplessness. Patient also started to increase alcohol consumption to control anxiety and depression. Patient suffers also of chronic back pain secondary to sustained injury. No apparent thought disorder. Physical exmaination and laboratory workup on admission were within normal limits.

DST results: Pre 13.1 ug/dl, Post 1.9 ug/dl

Patient responded very well to psychotherapy in addition to antidepressant medication. Diagnosis of dysthymic disorder was established.

CASE 9:

This 30 year old white male was admitted for depression and suicide ideation, decreased concentration and short attention span, decreased interest in activity, libido and pleasure, with increased guilt feelings. Symptoms had been present for four weeks. Laboratory workup was within normal limits. Patient was diagnosed as suffering from major depression.

DST results: Pre 17.3 ug/dl, Post 1.4 ug/dl

Patient responded positively to antidepressant medication.

Our present results indicate that with a 1 mg. dose of dexamethasone, with a plasma cortisol level of 5 ug/dl, a positive diagnosis of major depression can be made. The negative results do not completely rule out the diagnosis of major depression. Few patients with negative results responded to antidepressant medication.

Conclusion:

The diagnostic tests along with a pyschiatric interview and mental status examination can assist in the diagnosis of depression. The routine use of this simple test by psychiatrists, internists and family physicians may help the physician in reducing the diagnostic confusion. The positive identification of depressed patients by this test may help to promote the appropriate use of antidepressant drugs in the treatment of depression. This routine laboratory procedure may result in improving the patient care by identifying patients who will positively respond to the antidepressant medication and treatment will be more acceptable to those patients and physicians who are more impressed by the results of the objective diagnostic tests: In conclusion, it is emphasized that laboratory tests should be used to confirm the clinical diagnosis and thus the entire clinical presentation should be taken into account. The patients who are suffering from depression will show significant improvement with appropriate antidepressant medication along with supportive psychotherapy.

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