Role of Serum Dopamine Beta – Hydroxylase Activity as a Biological Marker in Depression

M. Hadidy, A. Abd El-Baky, and E. Abu – Hashim

Abstract

Objectives: Serum dopamine beta hydroxylase (DBH) enzyme that catalyses the conversion of dopamine to norepinephrine was addressed in this work in assumption of estimation of the enzyme activity as a laboratory procedure in depression. Methods: 24 patients diagnosed as major depressive episode according to the DSM IV criteria were assessed with both Hamilton Depression and Anxiety Rating Scales. Serum DBH and plasma dopamine were estimated by enzymatic method and radioimmune assay respectively. Results: Both DBH and dopamine levels were found high among patients than control subjects, but no association was detected between these levels in the patients' group. Moreover, no significant relation was found between levels of DBH and severity of major depression or its clinical variables. Conclusions: Use of Serum DBH as clinical laboratory test for major depression was not supported in this study.

***Key words**: DA, Depression, Biological Markers*

Introduction

The neurobiological basis of psychiatric disorders has been a subject of extensive research, particularly with the development of advanced chemopathological techniques. The monoamine hypothesis of depression first postulated in the mid 1960s, predicts that the underlying patho-physiological basis of depression is a diminshed activity of catecholamines and/or indolamine in specific brain areas (Janicak et al., 1997; Hirschfeld, 2000). In depressive patients, a decrease function of these neurotransmitters has been suggested (Owens et al., 1997), probably based on the monoamine transporter antagonism of tricyclic antidepressant that increase synaptic concentrations of monoamines.

In spite of the tedious research since the adoption of the monoamine hypothesis, there is no generally agreed biological marker for depression. The relationship of plasma catecholamines levels to various aspects of depression has been extensively investigated. Studies that address the alteration of plasma norepinephrine (NE) in depression gave unconfirmed results (Hamner and Diamond, 1996; Kelly and Cooper , 1998; Johnston et al., 1999). Schatzberg and Schildkraut (1995) elucidated that the wide variation in results of various NE studies may reflect the absence of generally agreed direct method to estimate its level. Moreover, tedious research addressing topics such as platelets adrenoceptors binding sites (Piletz et al., 1996), positive dexame-thasone suppression test (Mokrani et al., 1997) and platelet monoamine oxidase activity (Tripodianakis et al., 1998) did not give conclusive results.

Dopamine beta hydroxylase (DBH) is a copper containing enzyme that catalyses the addition of a hydroxyl group on the beta carbon of dopamine to form norepinephrine (Zhou et al., 2000; Zabetian et al., 2001). Various studies have been performed, trying to establish a link between DBH activity and different psychiatric disorders. Variation in the plasma levels of DBH was found as a sequela of childhood abuse and neglect (Galvin et al., 1991), conduct disorder of solitary aggressive type (Galvin et al., 1995); substance abuse (Gabel et al., 1995; Cubells et al., 2000); post – traumatic stress disorder (Hamner and Gold, 1998) and autistic spectrum disorders (Robinson et al., 2001). Denke et al., (2000) found that DBH is strongly inhibited by extracts from the herb "St. John's Wort" (Hypercium perforatum L) that exhibit beneficial effects on patients suffering from mental depression.

In the context of the great attention that has been payed to the monoamine hypothesis, the present work was planned to investigate the assumption of DBH activity as a biological marker for major depressive episodes. It is presumed that there are variations in the DBH level as a concomitant of the deficient catecholamines in depression. Also, a proposed association of DBH activity to clinical variants of major depression was addressed.

Subjects and methods

This study was conducted on a total number of 24 consenting patients selected from the outpatient clinic of the psychiatric department of Mansoura University Hospitals during October to December, 2000. All patients were diagnosed as mood disorder major depressive episode by two independent psychiatrists according to DSM IV criteria (American Psychiatric Association, 1994). The selected patients were free of any psychotropic drug medications at least three months prior to the study. Any patients with a possible general medical causality to the major depressive episode was excluded. 17 patients were females representing 70.8% of the

group. 18 patients (75%) came from rural areas while the urban areas represents only 25% of patients.

Ten healthy control subjects matched for both age and sex were considered as a reference group. Subjects with any possible current, past or family history of psychiatric disorders were excluded.

Assessment:

All patients and control subjects were subjected to full psychiatric, neurological and general medical examination. Patients were assessed for severity of both depression and anxiety using Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) respectively (Kaplan et al., 1994).

Laboratory procedures:

From each patient and control subject, 5 ml blood were collected at approximately 10 a.m. after an overnight fast. 3 ml blood were delivered into a plain tube for DBH estimation. The other 2 ml of blood were taken into EDTA tube for dopamine assay. Both serum and plasma were separated and kept frozen (-20°C) till analysis.

Serum DBH was assayed by enzymatic methods using sympath Tm-25 kits supplied by Neuro Biotech (Canada), utilizing the conversion of tyramine in presence of DBH into octopamin which is derived to p-hydroxybenzaldhyde by periodate cleavage which were measured using UV-spectrophotometer.

Plasma dopamine was assayed by competitive radio immunoassay (IBL, Hamburg).

Results

Table (1) showed that patients' serum DBH level (30.25 IU/ml ±8.89) was higher than that of the control group (25.41 IU/ml ± 2.53). Also, the plasma dopamine level of the patients' group (0.94 mg/ml ± 0.27) was more than that of the controls. Both findings was found to be highly significant (P<.001). However, there was no correlation between DBH and dopamine levels in the whole patients' group (Table 2).

In table (3) the DBH mean level was higher among the fourteen patients who reported relevant social stressors in the six months prior the onset of the current episode (32.48 IU/ml ± 9.81) than those without relevant stressors (27.14± 5.96). Though, this finding was not statistically significant. Also, no significant difference between DBH levels of the patients with first episode major depression and those with recurrent episodes. Regarding the variation in clinical presentations of major depression (table 3), the DBH mean levels of the presumed variables, namely somatic, psychological and psychotic symptoms and suicidality did not differ statistically.

The rated severity of both depression and anxiety using HDRS and HARS respectively, did not correlate with either DBH or dopamine levels (table 4).

Table 1: Comparison between DBH and Dopamine Levels of the Patients and the Control Groups

Variables	Patients n = 24 Mean (sd)	Control n = 10 Mean (sd)	test
DBH	30.25 (8.89)	25.41 (2.53)	10.0 P < .001
Dopamine	0.94 (0.27)	0.87 (0.28)	4.12 P < .001

Table 2: Correlation between DBH and Dopamine Levels in the Whole Sample

	DBH	Dopamine	t
r	0.0306		0.887 (NS)

Table 3: Effect of Clinical Variables on DBH Levels

Variables	Without Mean (sd)	With Mean (sd)	Significance
Social stressors	27.14 (5.96) n= 10	32.48 (9.81) n= 14	t = 1.532 NS
Previous episodes	30.96 (7.82) n= 16	28.85 (10.68) n = 8	t = 0.551 NS
Somatic symptoms	31.48 (8.45) n = 13	28.8(9.15) n= 11	f= 0.439 NS df= 3;39
Psychological symptoms	32.35 (5.1) n= 6	29.56 (9.62) n= 18	
Psychotic symptoms	29.61 (8.96) n = 17	31.82 (8.47) n = 7	
Suicidal trends	28.99 (8.31) n = 17	33.33 (9.49) n = 7	

Table 4: Correlation of DBH and Dopamine Levels with the Severity of both Depression and Anxiety

Severity	DBH		Dopamine	
	r	t	r	t
HDRS	0.1119	0.603 (NS)	0.1759	0.411 (NS)
HARS	0.1638	0.444 (NS)	0.2793	0.186 (NS)

Discussion

Depression is one of the most widespread diseases in the non-western as well as western societies. Egyptian subjects, as many other non-western cultures, tend to mask their affect with multiple somatic symptoms. Accordingly, they mostly resort to the general practitioner or the primary health care

physician asking unneeded investigations which are costly for a developing country (Mumford, 1999; Okasha, 2001). This may underline the necessity for a well documented simple laboratory test(s) demarcating depression, defining its variants and asserting the progression of the disorder or the therapeutic response.

DBH is an enzyme responsible for the conversion of dopamine to NE in the presynaptic nerve terminal. So, variation in its serum level may be expected in depressive disorders considering the monoamine hypothesis. This study addressed DBH and dopamine levels in the blood rather than NE as there is no generally agreed method to estimate the later due to its very short half life in the circulation. Both DBH and dopamine levels were higher among the patients than the control group. Nevertheless, these levels were not related to each other in the patients sample. These findings are not in accord with the monoamine hypothesis of depression that postulate a deficient monoamine turnover, as both the enzyme and its substrate were elevated independently. In that context, neither DBH nor dopamine levels was found to be associated with the severity of depression or its concomitant anxiety on HDRS and HARS respectively.

Estimated DBH levels were found to be higher among depressive patients in some studies (Friedman, 1978; Markianos et al., 1982; Matuzas et al., 1982), meanwhile it was low in another research (Puzynski et al., 1983) and did not differ in other one (Sapru et al., 1989). No association was found by Friedman et al., (1984) between serum DBH activity and severity scors of depression or anxiety scales. It is argued that DBH is likely a trait marker with interindividual variation secondary to genetic polymorphism (Humner and Gold, 1998; Zabetian et al., 2001). Till now, intensive investigations have failed to find convincing evidence of a primary dysfunction of a specific monoamine system in patients with depression. Reviewing the articles, Delgado (2000) and Leonard (2000) concluded that measurement of the concentrations of neurotransmitters and their metabolites, in the cerebrospinal fluid, plasma and urine of patients with depression have yielded equivocal results.

The increased serum DBH level in the present work was independent of any tested clinical variables of depression. Also, DBH levels among the patients with psychotic symptoms did not differ from that among the rest of the patients' group. The later finding was in accord with some previous studies (Eisemann et al., 1983; Lykouras et al., 1988) but not with others (Sapru et al., 1989; Meyers et al., 1999). Moreover, the elevated DBH level was not a direct effect of the somatic concomitant of depression as no relation was found between both of them.

In the context of the present finding, it could be postulated that the increased DBH level among the major depressive patients was not a primary one. It may reflect increased activity due to excess need for catecholamine consumption and turnover to compensate for defective signal transduction elsewhere. In a series of monoamine depletion studies, neither NE nor 5HT depletion were found to induce clinical depression in healthy subjects or worsened symptoms in unmedicated patients with major depression. Such depletion studies showed that antidepressant response are transiently reversed with NE reuptake inhibitors, but not serotonin reuptake inhibitors (Miller et al., 1996; Charney, 1998; Delgado, 2000; Delgado and Moreno, 2000). So, these findings could confirm the importance of monoamine in the medication of depressed mood, and that the current antidepressants do indeed require intact monoamine system for their therapeutic effect. It could also be suggested that other brain neuronal areas modulated by monoamine systems may have a more primary role in the pathophysiology of depression. Hirschfeld (2000) addressed the adaptive changes in receptors that follow enhancement of synaptic levels of monoamine to explain why there should be only a gradual clinical response to antidepressant treatment in spite of the rapid availability of monoamines.

In conclusion the data of the present work do not support the use of serum DBH or its substrate dopamine as a biological marker for clinical purposes in major depression. However, it may still be a candidate for further research such as genetic polymorphism to explain the pathophysiology of depression.

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الملخص العربي

دور نشاط الدوبامين بيتا هيدروكسيلاز في مصل الدم كدالة حيوية في الاكتئاب

أجري هذا البحث لاختبار فرضية استخدام مستوي أنزيم الدوبامين بيتا – هيدروكسيلاز في مصل الدم كدالة حيوية لنوبات الإكتئاب الجسيم، حيث أن هذا الإنزيم هو الذي يحفز تحويل الدوبامين إلي نور ابنفرين. لذا أخذت مجموعة مكونة من ٢٤ مريضا بتشخيص نوبة اكتئاب جسيم طبقا للتقسيم الأمريكي الرابع للأمراض النفسية. وطبق كل من مقياسي هاملتون لتقييم الإكتئاب و القلق علي مجموعة المرضي، ولقياس مستوي الدوبامين بيتاهيدروكسيلاز في المصل استخدمت الطريقة الإنزيمية ، في حين استخدم القياس الإشعاعي المناعي لتحديد نسبة الدوبامين في البلازما.

ومن نتائج هذا البحث وجد أن مستوي الدوبامين والدوبامين بيتا هيدروكسيلاز يكون أعلي في مجموعة المرضي عن المجموعة الضابطة، ولكن لم توجد علاقة بين المستويين في مجموعة المرضي. بالإضافة إلي ذلك لا توجد علاقة بين مستوي الدوبامين بيتا – هيدروكسيلاز وشدة الإكتئاب الجسيم أو مظاهره الإكلينيكية. وخلاصة هذا البحث أنه لا يدعم استخدام الدلالة الحيوية للدوبامين بيتا هيدروكسيلاز كاختبار معملي للاكتئاب الجسيم.

Economic Differences Among Insured and Non-Insured Patients in a Private Mental Hospital in Greater Cairo

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Abstract

Objectives: This paper aims to study the impact of economics on mental health services. Methods: Retrospective study has been conducted on the computer files of all patients admitted in one of the private psychiatric hospitals in Greater Cairo between the first of January and the end of December 2001. The total number of patients is 946. 571 patients of them (60.4%) were health insured while 375 patients (39.6%) were not health - insured. *Limitations of the study:* Studying files of the patients could help if it covers 5 or 10 years, comparison of our results to other private hospital or to governmental hospital would increase our scope to the problem, and application of questionnaires to the patients measuring the quality of life and economic burden of insurance versus non insurance services would help in exploring new areas. *Results: The insured group had the privilege of being financially supported, stayed more days in the hospital and the number of hospital admission in their last 5 years was also higher, and the differences were statistically significant between the two groups. The two groups didn't differ on diagnosis according to DSMIV as regards schizophrenic, neurotic, and or organic mental disorders, but substance abusers represented 40.9% of the insured group because the insurance company facilitates the long stay for drug-addicts and 37.1% of the non-insured group were suffering from mood disorders. Discussion of results, followed by recommendations were proposed.*

Keywords: *Health insurance, Mental patients.*

Background

The importance of financial issues in shaping health care delivery for mentally ill people continues to intensify. For more than a century, sources of funding and mechanisms of payment for service have influenced mental health policy. These economic factors are key determinants of access to care, organization of health care delivery services, and the behavior of providers (Frank, 2002).

Over the last decade, both government and industry have sharpened their focus on health care expenditures. This have stimulated the development of new models of care and has fundamentally changed the relationship between patients and providers (Gottlieb,1998).

One-third of the U.S. Population between the ages of 15 and 54 experience at least one psychiatric disorder from among anxiety and mood disorders, schizophrenia, and substance abuse or dependence disorders every year. Of these 44 million individuals, 15.7 millions suffer from anxiety disorders alone, while another 11.7 millions experience both anxiety and at least one other psychiatric disorder (Gallagher et al.,1998). Given the prevalence of anxiety disorders, the resulting economic burden is substantial, totalling $ 42.3 billion per year in 1990. These results imply an average annual cost per sufferer of over $ 1,500. In year 2000 the annual economic burden of anxiety disorders is over $ 65 billion. Direct or out of pocket costs accounts for 87% of this total and comprise psychiatric and nonpsychiatric medical pharmaceutical costs.

Compared to nonsufferers, those with anxiety disorders are more than six times as likely to be hospitalized and are three to five times as likely to visit a physician, such as a cardiologist, psychiatrist or family doctor (Pinard,1999).

Schizophrenia is the most common serious mental illness. It imposes a burden not only on the patient, but also on the carers, the health service and the society. It is certainly an expensive illness to treat, for example, the enormous costs of in-patient care more than 5% of total National Health Service (NHS) in-patient expenditure in England (Knapp, 1997). The care for people with schizophrenia is invested in a diversely constituted support network that includes hospital care [in-patient, day patient and out-patient services, depot injection clinics, secure units], community health care, social care services, non professional carers and voluntary organizations. There are costs associated with each (Haro et al.,1998)). The direct costs of schizophrenia - including, hospitalization, relapse costs, drug, residential care and others is about 2.3 billion dollars per year while the indirect cost including lost productivity, degradation of quality of life and burden on family- is about 2 billion dollars per year (Suleiman et al., 1997).

From an economic perspective, the use of illegal drugs such as heroin is a problem because the personal costs borne by individual users (including financial outlays and health risks) diverge from the full costs of use imposed on society. the full cost of use exceeds the private cost, the difference between the two reflects the social cost imposed by each additional user