Diagnosis and Classification Subtyping of Depressive Disorders: Comparison of Three Methods

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ÖZET:

Depresif bozuklukların alttiplendirmesi: Üç yöntemin karşılaştırılması

Amaç: Melankolik ve melankolik olmayan depresyon, depresyonun sınıflandırılmasında belki de en yaygın kabul gören ayrım noktasıdır. Bu çalışmanın amacı depresyonun belirti, şiddet ve biyolojik tabanlı sınıflamalarını karşılaştırmaktır.
Yöntem: Depresyon tanısı almış 78 hastadan oluşan örneklemde ilk olarak SCID-I'in 14 depresif belirtisi kullanılarak küme analizi yapılmıştır. İkinci olarak biyolojik tabanlı sınıflama için DST (deksametazon supresyon testi) sonuçları ve son olarak da şiddet açısından HDRS (Hamilton Depresyon Derecelendirme Ölçeği) puanlarına göre (yüksek ve düşük şiddet grupları) gruplandırılmışlardır. Bu gruplar biyolojik değişkenler (tiroid stimule edici hormon -TSH, bazal ve deksametazon sonrası kortizol düzeyleri), klinik (yaş, başlangıç yaşı, depresyon şiddeti, psikososyal stresörler, kişilik bozukluğu) ve demografik değişkenler açısından karşılaştırılmıştır.
Bulgular: DSM-IV'e göre melankoli tanısı almış grubun küme analizi sonucu endojen grup olarak belirlenmiş grupla yüksek derecede uygunluk gösterdiği belirlendi. Küme analizine göre endojen depresyon olarak tanımlanan grubun yaş ortalamasının daha yüksek, klinik açıdan depresyon derecesinin daha şiddetli ve bazal kortizol düzeylerinin daha yüksek oldukları bulundu. HDRS puanlarına gore daha ciddi depresyonu olan grubun TSH düzeyleri daha düşük bulundu. DST (deksametazon supresyon testi) kortizol yanıtı baskılanmamış hastalarda aile öyküsünde daha fazla depresif bozukluk olan bireyler olduğu saptandı.
Sonuç: Çalışmamızın sonucu endojen veya melankolik depresyonun farklı klinik ve biyolojik özelliklere sahip olduğu hipotezini kısmen doğrulamaktadır.

Anahtar sözcükler: Melankoli, endojen depresyon, depresyon alttipleri, kortizol, TSH

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ABSTRACT:

Diagnosis and classification subtyping of depressive disorders: comparison of three methods

Objective: Melancholic versus non-melancholic depression dichotomy is perhaps the most widely accepted distinction in categorization of depression. This research aims to compare symptom based, severity based, and biology based categorization of depression.
Methods: To achieve this, the cluster analysis was performed on a sample of 78 depressed patients, first by using 14 SCID-I depressive symptoms. Patients were clustered again with regard to post dexhametasone cortisol levels (suppressed vs non-suppressed groups), and lastly according to HDRS (Hamilton Depression Rating Sacale) scores (high vs low severity groups). Biological (thyroid stimulating hormone -TSH, basal and post dexhametasone cortisol levels), clinical (age, age of onset, severity of depression, psychosocial stressors, and personality disorder) and demographic variables of these categories were compared.
Results: There was a high degree of accordance between the cluster analytically derived endogenous group and the DSM-IV diagnosis of melancholia. Cluster analytically generated endogenous group were older, more severely depressed, and had higher basal cortisol levels than non-endogenous depressive subtype. Severely depressed group according to HDRS scores had lower TSH levels. Only DST (dexamethasone suppression test) non-suppressive patients had more depressive disorders in their family.
Conclusions: The results of our study partly support the hypothesis that endogenous and melancholic depression have distinct clinical and biological features.

Key words: Melancholia, endogenous depression, depression subtypes, cortisol, TSH

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INTRODUCTION

There has been a debate for years in the psychiatric community whether depression is a single disease or a heterogeneous one. Debates on the categorical and dimensional views of classifying the depressive illness have been going on for years without resulting in a consensus. The question is whether the majority of patients can be classified as either black or white or whether the grays are predominant (1,2). Some theorists have proposed that depressive phenomenology is best accounted for by a number of continuous dimensions (dimensional-unitary hypothesis). According to these researchers, depressive disorder is a unitary phenomenon and the differences between subtypes are little more than a degree of severity of the illness (3). Mapother for example suggested that melancholic and non-melancholic patients were not clearly distinct groups but represented

the two ends of a continuum (4). On the other hand some other researchers invoked a variety of subtypes, according to which depressive disorders may be classified into clinical syndromes with more or less distinct descriptive boundaries (categorical-dualistic hypothesis). Most diagnostic systems for classifying depression tend to be dichotomous and binary (5). The binary model posited two principal types (i.e., "endogenous/psychotic" and "neurotic/reactive") (6). The difference between endogenous (melancholic/vital) depression and non-endogenous depression involves not only severity of illness, but also a distinct symptom profile. Melancholia was most clearly distinguished by behaviourally-rated psychomotor disturbance and pathological guilt (7). Although major depression is frequently recognized to be a heterogeneous disease, there is a little agreement about how to describe its variation. There is another unifying hypothesis that was proposed by Maes et al., and according to them, while severity of illness increases along with a continuum, some new symptoms emerge or become more prominent and frequent, and group together to shape a new symptom profile (integrated threshold model) (8,3,9).

In the DSM diagnostic system, the categorical hypothesis is accepted, non-symptom attributes were excluded from the list. The validation of the psychiatric diagnoses establishes them as "real entities." Once a reliable method is applied to delineate a potential diagnostic category, these can then be validated by examining their relationship to external measures. Comparison of the external validators is a good way for the validation of the diagnostic categories. It becomes important to compare diagnostic scales' performance on clinical and biological measures (10).

The hyperactivity of the hypothalamic-pituitary-adrenal axis has an important role in the psychobiology of depression (11,12). But as a correlate of melancholia, the dexhametasone suppression test (DST), whether or not fail to suppress plasma cortisol, may be lacking sufficient sensitivity or specificity for an accurate diagnosis of melancholia. In addition to the dexamethasone suppression response, other neuroendocrine variables may help to discriminate melancholic and non-melancholic forms of depression. Thyroid axis dysfunction may be related to psychomotor abnormalities, weight loss, and sleep disturbances in melancholia (13). Basal levels of thyroid stimulating hormone (TSH) and response to thyrotropin releasing hormone (TRH), indices of thyroid axis functioning, have been used as biological measures of depression (13). Türkçapar et al. demonstrated that DSM-IV-diagnosed melancholic patients have higher cortisol levels and lower levels TSH compared to non-melancholic patients with depression (14).

In this study we aim to compare three different categorization methods for depressive disorders: symptom features, depression severity, and the DST. To achieve this, the cluster analysis was performed on a sample of 78 depressed patients, using 14 SCID depressive symptoms. Patients were clustered again with regard to post dexhametasone cortisol levels (suppressed vs non-suppressed groups), and lastly according to HDRS scores (high vs low severity groups). As external validators biological (thyroid stimulating hormone, basal and post dexhametasone cortisol levels), clinical parameters (age, age of onset, severity of depression, psychosocial stressors, and comorbid personality disorder) and demographic variables of these categories were compared.

MATERIALS and METHODS

Participants

Seventy eight depressive patients were participated in this study. The study sample consisted of regular outpatients and inpatients admitted to a General Hospital's Psychiatry Clinic, who met of the study inclusion criteria. The study was approved by the Ethics Committee of the Hospital. All participants gave written informed consents.

Measures

All axis I diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID-I) (15). The severity of depression was measured with the 17-item version of the Hamilton Depression Rating Scale (HDRS) (16). The SCID-I used in this study was extended to cover all the criteria for melancholia. The symptoms listed as melancholia criteria in DSM-IV are the same as DSM-III except that DSM-IV includes either pervasive anhedonia or unreactive mood, whereas, DSM-III requires both. In

this current study we used DSM-III melancholia criteria to reach melancholia diagnoses. Personality disorders were assessed with SCID-II (17). DSM-III-R Axis II personality diagnoses were dichotomized, indicating the presence or absence of any diagnoses of a personality disorder. Psychosocial stressors were assessed by using Axis III of DSM-III-R. Family history of depression was assessed by family history method and accepted as positive if there was a depressive episode among the first degree relatives.

Biochemical assays

After the psychiatric evaluations (SCID-I and HDRS), venous blood samples were drawn at 8.00 AM (±15 minutes) following an overnight fast, for the laboratory panel, basal thyroid stimulating hormone (TSH) and basal cortisol levels. The same day, patients ingested 1 mg dexhametasone at 11.00 PM, and fasting blood was collected the next day at 8.00 AM (±15 minutes) for postdexhametasone cortisol measurement. At several occasions, it was shown that the assay of post-DST cortisol at 8.00 AM provided a better index of the dysfunction in negative feedback of dexhametasone on the HPA-axis in major depression than the assays of 4.00 PM or 11.00 PM post-DST cortisol (18). Cortisol levels were measured by means of Radioimmunoassay (RIA) method (Coat-A-Count® Cortisol Diagnostic Products Corporation, Los Angeles, USA) in the same laboratory. The Coat-A-Count® Cortisol assay has a detection limit of approximately 0.2 g/dl. The intra-assay coefficient of variation was 5.1% and the inter-assay coefficient of variation was 6.4%. 08.00 AM post-dexamethasone cortisol value ≥ 3.5 g/dl was defined as cortisol non-suppression (19). Patients were divided into two groups (suppressive and non-suppressive) according to the DST results.

TSH levels were measured with the Microparticle Enzyme Immunoassay (MEIA) technique (Imx R system-Abbott Laboratories). The sensitivity of the ImX Ultrasensitive hTSH assay was calculated to be 0.03 IU hTSH/ml. Inter and intra-assay CV values for basal TSH were 3.0% and 4.0 % respectively.

In 15 patients, biological variables were not available because of technical reasons (e.g., inadequate sample, sample transport problems, patient related factors such as not giving informed consent for blood sampling, failing to take dexhametasone on time, and not arriving at the clinic on time for blood sampling). The HPT-axis variables were complete in 63 patients.

Procedure

A physical and a neurological examination were performed on the admission visit of the study and an ECG and laboratory panel were performed.

The patients were classified according to DSM IV criteria into (a) major depressive disorder without melancholia- simple major depression, (b) major depressive disorder with melancholia and/or psychotic features, (c) bipolar I, II disorders- depressive episode, (d) dysthymic disorder, (e) adjustment disorder with depressed mood, and (f) depressive disorder NOS (Table 1). Patients were also classified according to the Axis II personality disorders criteria.

Patients with history of psychotic illness other than psychotic depression or organic mental illness and patients with full remission of depression were excluded. We also excluded patients who had taken lithium, monoamino oxidase inhibitors or anticonvulsants,

Table 1: Characteristics of the diagnostic groups.

Diagnostic Categories	n	(%)	Age(years) (mean±SD)	Men/Women	HDRS (mean±SD)
Simple major depression	27	34.6	30.6± 9.6	8/19	21.44±4.5
Melancholic major depression	38	48.7	35.2 ± 9.3	16/22	25.97±6.7
Bipolar disorder, type I (Depressive episode)	4	5.1	44.0±25.2	1/3	25.75±7.5
Dysthymic disorder	2	2.6	41.5±13.4	2/0	14.50±0.7
Depressive disorder NOS	5	6.4	36.4± 6.7	3/2	10.00±1.4
Adjustment disorder with depressive features	2	2.6	30.5±6.4	1/1	15.60±4.2
Total	78	100	34.2±10.9	31/47	23.04±6,8

antipsychotic dosages of neuroleptics, and who had been treated with electroconvulsive therapy within a year before their admission. Other exclusion criteria were high suicidal risk, significant organic disease, alcohol or drug abuse, severe allergic or multidrug reactions, anorexia nervosa, bulimia nervosa, purgative abuse, pregnancy, and women with childbearing potential. The participants who were on antidepressive drug therapy had a wash-out period of at least 1 week for TCAs, 2 weeks for MAOIs, 1 month for fluoxetine, and 2 weeks for SSRI other than fluoxetine.

Sixty six patients had been free of any psychotropic drugs at least one month prior to the assessment. The rest were taking antidepressants, benzodiazepines, and one patient was taking low dose of neuroleptic (thioridazine). These drugs were discontinued after admission to hospital and patients underwent a washout period as described above.

Statistical Analysis

Hierarchical cluster analysis and K-Means non-hierarchical iterative partitioning method were used for clustering the subjects on the basis of 14 SCID-I items in order to determine whether the non-melancholic/ melancholic subtypes are present in our study group. The goal of cluster analysis was to identify relatively homogeneous groups of cases based on selected characteristics. But cluster analytic procedures always tend to yield clusters, even if there is no real structure in the dataset. It is necessary to validate a clustering solution by internal and external validation. Since K-Means cluster analysis requires a user-specified number of clusters, recommendations for increasing the confidence (which provided an alternative clustering technique for the same dataset), we performed a hierarchical cluster analysis with an agglomeration schedule. Results obtained with the different clustering methods were compared by means of the Kappa-coefficient and chi-square statistics for internal validation. For the determination of the similarity, we used size difference and squared Euclidian distance (20). The HDRS, DST, thyroid hormone screening tests, demographic and clinical variables were selected for the external validation. Statistical analyses were performed using SPSS 10.0 for Windows n. Independent samples t-tests and ANOVA were used for group comparisons of continuous variables and chi-square tests for categorical data. The discriminators of melancholia and non-melancholia groups were analyzed by discriminant analysis which SCID-I symptoms were used as independents.

RESULTS

Demographic Data

Table 1 summarizes the demographic data for the 78 patients in this study. We found no significant differences in gender ratio ($\chi 2$ =3.46, df= 5, P= 0.62) and mean age (F = 1.65, df=5, p > 0.15) between diagnostic categories. The HDRS scores of the patients with melancholic major depressive disorders, bipolar disorders (depressive type) and simple major depression were significantly higher than the other patients. The HDRS score increased from minor depressive group (dysthymic disorder, depressive disorder NOS, and adjustment disorder with depressive features) to simple major depression and melancholic major depression. We found that the HDRS score of the melancholic major depressive patients significantly higher than the other groups except for bipolar disorder-depressive type ($F_{(2, 77)} = 6.52$, df=5, p<0.001) (Table 1).

Cluster Analysis results

We examined from two to five cluster solutions by three different clustering algorithms; K-means, between groups linkage, and Ward's methods. According to the results, only two cluster solutions were stable across three different methods. The K-means two cluster solution was highly congruent with the solution obtained by means of between groups' linkage (% agreement κ = 0.825, x^2= 53.5, df = 1, p < 0.001) and Ward's method (κ = 0.717, x^2= 40.4, df = 1, p <0.001). We found that agreement between three (κ = 0.375, x^2 = 60.7, df = 4, p <0.001) and four cluster solutions (κ = 0.171, x^2 = 63.1, df = 9, p <0.001) of K-means and between groups linkage dropped considerably. According to these findings, we decided that two-cluster solution was quite stable and replicable. Then we reported the results of K-means two class solution.

K- means cluster analysis generated two classes, which we described them as an endogenous (n=40) and a non-endogenous cluster (n=38). We found a significant

association between the cluster-analytically derived classification and the DSM-IV grouping ($\chi 2$ =27.1, df =1, $p<10^{-5}$). The first (endogenous) cluster with 40 subjects comprised 80% DSM-IV melancholic and 90.5% (n=38) simple major depressed. The second (non-endogenous) cluster comprised 38 patients, %71.5 (n = 27) of them were classified as simple major depression and 28.5 % (n=8) as other depressive disorders, and 21.1% (n=8) as melancholic depression. All minor depressive patients were assigned to the non-melancholic cluster.

We obtained a significant discrimination of both clusters by using the 14 SCID-I items (Wilk's λ= 0.245, x^2= 102.5, df= 6, p < 0.0001). Six of the 14 SCID-I items, early morning awakening, distinct quality of mood, feelings of guilt, non-reactivity, suicidal ideation, and psychomotor disorders were significant discriminators.

Comparison of three categorical models

Table 2 lists the symptom characteristics of both formed clusters. All the depressive symptoms except diurnal variation, psychomotor disorders, and psychotic symptoms were significantly more frequent in endogenous group.

Symptom distribution in DST suppressed and non-suppressed groups:

Only the symptom of non-reactivity differed significantly between DST suppressed and non-suppressed groups (Table 2).

Symptom distribution in HDRS high and low groups:

Anorexia, early morning awakening, feelings of guilt, loss of interest, suicidal ideation, psychomotor disorders, psychotic symptoms, non-reactivity, and sleep disorders symptoms were significantly more in the group which high HDRS scores were found (Table 2).

Table 3 presents the results of the demographic and clinical variables of the cluster, DST, and severity groups. They did not differ significantly with regards to age, age of onset, sex ratio, marital and employment status, personality disorder, psychosocial stressors before the index episode, number of previous depressive episodes, and having a positive family history of depression. Only the DST groups differed with regards to having a familial psychiatric disorder history, the DST suppressed group reported a higher frequency. Patients allocated to the melancholic cluster obtained significantly higher HDRS and CGI scores than those allocated to the non-melancholic cluster (Table 3). We also examined the HDRS item scores of the two clusters. Melancholia group had higher scores for 11 of the 17 items. Significant effects were established for depressed mood, work and activities, loss of sexual interest, early, middle and late insomnia, feelings of guilt, and suicide.

Table 4 represents the biological measures of the three study groups. Patients allocated to the melancholic cluster differed significantly than the non-melancholic group

Table 2: Frequency of depressive symptoms in the groups.

SCID Items	Cluster Analytically Derived Groups (mean±SD)					DST Groups (mean±SD)					Severity groups (mean± SD)				
Variables	Endo †.		Non-End.‡			Non supressed§		Suppressed‖			HDRS>23		HDRS<23		P
	%	n	%	n	X^2	%	n	%	n	X^2	%	n	%	n	X^2
Anorexia/ weight loss	80.0	32	44.7	17	10.4***	71.4	10	65.3	32	0.18	81.3	26	50.0	23	7.8**
Diurnal variation	30.0	12	28.9	11	.01	35.7	5	30.6	15	0.13	31.3	10	28.3	3	0.0
Depressive mood	97.5	39	78.9	30	6.6**	92.9	13	87.8	43	0.29	96.9	31	82.6	38	3.8
Loss of energy	95.0	38	57.9	22	15.1***	85.7	12	79.6	39	0.26	84.4	27	71.7	33	1.7
Early morning awakening	75.0	30	15.8	6	27.5***	57.1	8	46.9	23	0.45	65.6	21	32.6	15	8.3**
Loss of interest	97.5	39	65.8	25	13.3***	100	14	83.7	41	2.61	96.9	31	71.7	33	8.1**
Suicidal ideation	67.5	27	31.6	12	10.1***	42.9	6	55.1	27	0.66	75.0	24	32.6	15	13.6***
Distinct quality of mood	77.5	31	18.4	7	27.2***	71.4	10	49.0	24	2.20	59.4	19	41.3	19	2.5
Cognitive disturbances	87.5	35	60.5	23	7.4**	85.7	12	75.5	37	0.66	78.1	25	71.7	33	0.4
Psychomotor disorders	80.0	32	76.3	29	0.2	92.9	13	73.5	36	2.37	90.6	29	69.6	32	4.9*
Psychotic symptoms	15.0	6	2.6	1	3.6	7.1	1	10.2	5	0.12	18.8	6	2.2	1	6.3*
Nonreactivity	45.0	18	5.3	2	16.3***	57.1	8	18.4	9	8.3**	40.6	13	15.2	7	6.4*
Feelings of Guilt	80.1	32	28.9	11	20.5***	57.1	8	57.1	24	0.0	78.1	25	39.1	18	11.6**
Sleep disorder	95.0	38	78.9	30	4.5*	92.9	13	85.7	42	0.5	100.0	32	78.3	36	7.9**

*p< 0.05, ** p < 0.01, ***p < 0.001
†= Cluster analytically derived endogenous group; ‡= Cluster analytically derived non-endogenous group; §= DST Non suppressed group; ‖= DST Suppressed group

Table 3: Demographic and clinical variables in the groups.

Variables	Cluster Analytically Derived Groups Endo†.		Non-End.‡			DST Groups Non supressed§		Suppresse‖			Severity groups HDRS>23		HDRS<23		
	%	n	%	n	X^2	%	n	%	n	X^2	%	n	%	n	X^2
Sex, female	70.0	20	50.0	19	3.25	78.6	11	53.1	26	2.92	59.4	19	60.9	28	0.01
Marital status, married	72.5	29	60.5	23	5.42	78.6	11	65.3	32	3.14	71.9	23	63.0	29	6.52
Employment data, Occupation	47.5	19	55.3	21	1.18	35.7	5	53.1	26	5.41	56.3	18	47.8	22	6.68
DSMIIIR personality disorder	54.8	17	45.2	14	0.77	69.2	9	46.5	20	2.06	54.2	13	46.2	18	0.38
Life event before the episode	17.5	7	26.3	10	1.40	28.6	4	18.4	9	2.19	15.6	5	26.1	12	5.71
Family depression history	20.5	8	12.5	4	0.80	7.7	1	22.7	10	1.45	26.7	8	9.8	4	3.52
Family psychiatric disorder history	33.3	13	31.3	10	1.32	7.7	1	43.2	19	5.90*	36.7	11	29.3	12	0.57
Before having ECT	7.5	3	-		2.96	-		6.1	3	0.90	9.4	3	-		4.48
	mean±sd				t-value	mean± sd				t-value	mean± sd				t-value
Previous depressive episodes	1.8±1.4		1.9±1.9		-3.27	2.1±2.1		1.8±1.3		-0.80	1.8±1.5		1.98±1.7		0.60
Age	30.6±11.1		27.6±7.3		1.34	35.0±12.0		34.6±11.1		-0.10	35.7±11.3		33.2±0.7		-1.00
Age of onset	35.6±11.0		32.8±0.7		1.67	28.7±11.7		29.5±9.3		0.25	30.4±9.8		28.0±9.5		-1.04
HDRS	26.9±5.9		18.8±5.1		6.73***	23.2±7.0		23.3±7.5		-0.13	29.5±4.3		18.3±3.7		-12.50***
CGI	5 ±1		3.6±1.1		6.03***	4.6±1.2		4.4±1.2		-0.15	5.2±1.0		3.7±1.0		-6.41***

*p< 0.05, ** p < 0.01, ***p < 0.001
† = Cluster analytically derived endogenous group; ‡= Cluster analytically derived non-endogenous group; §= DST Non suppressed group; ‖= DST Suppressed group

Table 4: Biological variables in the three classification methods.

Variables	Cluster Analytically Derived Groups Endo†.	Non-End.‡	T	DST Groups Non supressed§	Suppresse‖	T	Severity groups HDRS>23	HDRS<23	T
T3 (ng/ml	1.3±0.3	1.5±0.3	-2.0*	1.4±0.3	1.4±0.3	-0.1	1.3±0.3	1.4±0.2	0.74
T4 (lg/dl	8.3±2.0	7.7±1.2	0.50	7.8±1.7	8.2±1.8	-0.6	8.2±1.9	7.8±1.5	0.41
sT3(pg/ml	5.0±0.8	4.9±1.1	0.20	5.3±0.9	4.9±0.8	-1.5	5.0±0.7	4.9±1.0	0.72
sT4(ng/dl)	1.4±0.7	1.2±0.1	1.10	1.6±1.1	1.2±0.2	-1.9	1.4±0.7	1.2±0.2	0.18
TSH (lIU/ml)	1.3±0.7	1.5±0.8	-0.90	1.7±0.7	1.3±0.8	-1.5	1.2±0.6	1.6±0.9	0.03
Basal Cortisol (lg/dl)	20.1±13.7	13.9±9.5	2.30*	25.4±15.4	14.6±10.1	-2.9*	19.5±11.3	15.9±12.9	0.24
Post Dex. Cort.(lg/dl)	4.0±8.2	1.6±3.7	1.50	10.7±11.7	0.7±0.8	-3.2**	2.1±2.5	3.6±8.5	0.36
DST % non supressors	%30.6 11	%11.1 3	3.40*				%19.2 5	%24.3 9	0.20

*p< 0.05, ** p < 0.01, ***p < 0.001
† = Cluster analytically derived endogenous group; ‡= Cluster analytically derived non-endogenous group, §= DST Non suppressed group; ‖= DST Suppressed group

with regards to T3 and basal cortisol levels; they had higher levels of basal cortisol and lower levels of T3. As predicted, the levels of basal and post dexamethasone cortisol levels were significantly higher in the DST non-suppressed group.

DISCUSSION

In this current study, depressive patients were evaluated with three different methods, within each evaluation method patients were categorized into two groups, and then results of three different methods were compared. First method was based on symptom profile cluster analytic method; second one was based on DST results, and the last one was based on depression severity according to the HDRS scores.

Characteristics of the cluster-analytically derived classes

Except diurnal variation, psychotic and psychomotor disturbances items, all the depressive symptoms were

significantly more frequent in endogenous group. This findings support the notion of threshold models that assumes a tendency to increase in the frequency of the SCID-I symptoms with depression severity. Therefore, no symptoms was prevalent in the mild depressive category (9).

The findings of the present study are consistent with findings of other studies that used cluster analytic method in depressive patients (3,9,21). Characteristic symptoms of the endogenous groups are anorexia/ weight loss, loss of energy, early morning awakening, loss of interest, suicidal ideation, distinct quality of mood, non-reactivity, and feelings of guilt. Although these symptom profiles differ from some of the previous clusters analytic studies (8,3,9), these characteristic symptoms essentially agreed with the DSM IV melancholic depression criteria. The main difference in our analysis is that suicidal ideation emerged as an endogonenous symptom, on the other hand psychomotor disorders and diurnal variation did not differ between two groups. Similar to our study, Parker et al. found that diurnal mood variation were non-differentiating in their cluster analysis of melancholic and non-melancholic groups (22).

In order to evaluate the clinical validity of cluster analytically generated groups, external biological and clinical validators were used. The endogonenous cluster had higher levels of basal cortisol and lower levels of free T3 levels compared to the non-endogenous group. In the endogonenous group, DST non-suppression was also more prevalent than the non-endogenous group. Similar findings were reported in previous studies (8,14).

The endogenous cluster obtained higher incidence of family depression history but this difference did not reach statistically significancy level (20.5% and 12.5% respectively). The incidence of adverse life events before depressive episode did not differ between groups. Similar findings were reported by Parker et al. (22). They did not identify any group difference on the family history of depression or life event variables or in reporting an antecedent life event stressor.

Endogenous group had significantly higher HDRS scores compared to the non-endogenous group. This finding was consistent with the previous studies (23). It has been found that a higher level of depression severity is associated with the diagnosis of melancholia (23).

Personality is an important factor thought to be related to the differantiation of endogenous and non-endogenous depression. However this classical view has not been well supported by studies, using modern diagnostic criteria. We also did not find any difference in prevalence of personality disorders between groups (cluster analytically derivated groups, DST groups, and HDRS severity groups). In contrast to our finding, Parker et al. (24), with a different methodology, found that disordered personality function appeared distinctly more likely in non-melancholic depression compared to melancholic depression. Sato et al. (25), using Interpersonal Sensitivity Measures, also found personality differences between non-melancholic depression and melancholia. On the other hand, studies using DSM personality disorder criteria gave similar results to our findings. Zimmerman et al. (26) found that symptom based criteria for melancholia according to DSM-III and Research Diagnostic Criteria (RDC) gave no significant difference in the frequency of personality disorder between the melancholic and non-melancholic groups. Similar findings were reported by Tedlow et al. (27). They did not observe any significant difference in rates of personality disorder between melancholic and non-melancholic depressed patients.

Characteristics of the severe and non severe classes:

In the present study we did not find any significant differences between “clinical variables” of severe and non-severe depressive groups according to the HDRS scores. Although statistically insignificant in the non-severe group the incidence of adverse life events were more than the severe group (26.7% and 15.6% respectively).

Characteristics of the DST suppressed and non suppressed classes:

Another interesting finding of our study is that family history of depressionhas been significantly found more in DST non-supressive groups compared to the suppressive group. Other classification methods (cluster analysis or severity based classification) did not yield such a result. Unfortunately the question whether non-supression is associated with a positive family history in the depressed patients is not fully studied yet. Several studies show a

higher non-supression rate in the familial pure depression disease subtype, which was not included in the formal diagnostic systems (28). In a study which aimed to determine whether Winokur's family history subtypes schemes relate to the DST was found that these family history subtypes for unipolar depression were not strongly validated by the DST (29). In a small study with remitted 19 patients (mainly bipolar depressives), it was found that the risk of primary affective disorders in first-degree relatives was also unrelated to the frequency of DST positivity (30).

A major limitation of this kind of studies is that we do not have any exact biological parameter for depression yet. Another limitation of our study is that we have a small sample size.

In conclusion, classification is one of the major goals of the descriptive psychopathology especially in the area of depression. In this current study, some of our findings supported that depressive patients could be clinically classified into two classes. This classification could be based on symptom profile, or severity, or biological variables. Although we used three methods based on these variables, none of them fully validated against external validators. Therefore, we believe that in order to identify subgroups of depressive patients we need novel and more reliable methods.

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