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Thyroid function in clinical subtypes of major depression: an exploratory study

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Background: Unipolar depression might be characterized by a 'low-thyroid function syndrome'. To our knowledge, this is the first study which explores the possible relationship of DSM-IV depressive subtypes and the medium term outcome, with thyroid function.

Methods: Material: Thirty major depressive patients (DSM-IV) aged 21–60 years and 60 control subjects were included. Clinical Diagnosis: The SCAN v 2.0 and the IPDE were used. The psychometric Assessment included HDRS the HAS and the GAF scales. Free-T3, Free-T4, TSH, Thyroid Binding Inhibitory Immunoglobulins (TBII), Thyroglobulin antibodies (TA) and Thyroid Microsomal Antibodies (TMA) were measured in the serum. The Statistical analysis included 1 and 2-way MANCOVA, discriminant function analysis and Pearson Product Moment Correlation Coefficient.

Results: All depressive subtypes had significantly higher TBII levels in comparison to controls. Atypical patients had significantly higher TMA in comparison to controls. No significant correlation was observed between the HDRS, HAS and GAF scales and thyroid indices. Discriminant function analysis produced functions based on thyroid indices, which could moderately discriminate between diagnostic groups, but could predict good response to treatment with 89.47% chance of success.

Conclusion: Although overt thyroid dysfunction is not common in depression, there is evidence suggesting the presence of an autoimmune process affecting the thyroid gland in depressive patients

Background

It is believed that depression might be characterized by a 'low-thyroid function syndrome' [1-3]. Hypothyroidism might be associated with anxiety [4] or refractory depression, suggesting that this characterizes one biological subtype of refractory depression. However, screening thyroid tests are often routine for depressed inpatients, and data suggest that thyroid screening may add little to diagnostic evaluation. Overt thyroid disease is rare among depressed inpatients [5], and the role of thyroid hormones in the pathophysiology of affective disorders remains to be clarified [6].

Depression is traditionally classified into two opposite poles [7-10], today named 'melancholic' [11] or 'somatic' syndrome [12] and 'atypical' features, that is 'reverse neurovegetative symptoms' (increased appetite, weight gain, increased sleep etc) and interpersonal rejection sensitivity [13-15].

It is reported that in melancholia, the autonomous nervous system and the stress response seem hyperactive [16]. Patients are anxious, dread the future, lose responsiveness to the environment, have insomnia, lose appetite, there is a diurnal variation with depression at its worst in the morning. Corticotropine Releasing Hormone (CRH) system may be hyperactive. On the contrary growth hormone and reproductive axes may have diminished activities. Patients with atypical depression present with a constellation of symptoms that seems the antithesis of melancholia [10]. They are lethargic, fatigued, hyperphagic, hypersomnic, reactive to the environment, and show diurnal variation of depression that is at its best in the morning. Some authors suggest that there is a down-regulated hypothalamic-pituitary adrenal axis and CRH deficiency of central origin present in atypical depression [17].

On the other hand, it is suggested that conditions associated with significant changes in stress system activity, such as acute or chronic stress or even cessation of chronic stress, severe exercise, pregnancy, the postpartum period, and anxiety and mood disorders, may suppress or potentiate autoimmune diseases activity and/or progression through modulation of the systemic or local pro/antiinflammatory cytokine balance [18]. It has been also reported that patients affected by celiac disease tend to show a high prevalence of personality and major depressive disorders. Association with subclinical thyroid disease appears to represent a significant risk factor for these psychiatric disorders [19,20].

Thus, there is a lot of evidence suggesting the presence of an underlying autoimmune disorder in unipolar depression, with the possible involvement of the thyroid gland, however studies are inconclusive and fail to differentiate between different clinical subtypes of depression.

The present study aimed to investigate the relationship between subtypes of unipolar major depression, medium term (2 years) outcome and thyroid function in patients and controls. To our knowledge, this is the first study which explores the possible relationship of DSM-IV depressive subtypes and the medium term outcome, with thyroid function.

Methods

Material

Thirty patients (10 males and 20 females) aged 42.43 ± 11.82 years (range 21–60) suffering from Major Depressive disorder according to DSM-IV [11], and 60 normal controls (25 males and 35 females aged 41,01 ± 9.72 years (range 25–58) entered the study. Ten patients fulfilled atypical features (according to DSM-IV), 12 melancholic features (according to DSM-IV) and 8 did not fulfill criteria for any specific syndrome ('undifferentiated' patients).

Patients and controls were free of any medication for at least two weeks and were physically healthy with normal clinical and laboratory findings (Electroencephalogram, blood and biochemical testing, test for pregnancy, B12 and folic acid).

No patient with catatonic or psychotic features or seasonal affective disorder was included and no-one fulfilled criteria for another DSM-IV axis-I disorder, except from generalized anxiety disorder and panic disorder. No-one had history of manic or hypomanic episode in the past, or had prior history of lithium or thyroid hormones treatment.

The normal control group was composed by members of the hospital staff, and students. A clinical interview confirmed that they did not suffer from any mental disorder and their prior history was free from mental and thyroid disorder.

All patients were followed up for a period of 2 years. During that period they received an adequate dose of one or more antidepressant agent (SSRI or SNRI). According to their course during that period, they were divided in two groups: Nineteen (N = 19, 63.33%, 8 melancholics, 5 atypicals, 6 undifferentiated) of them were considered to be Responders (those with full or almost full remission and no relapse during the whole 2 year period) and 11 (36.67%, 4 melancholics, 5 atypicals, 2 undifferentiated) were considered to be partial responders (those with partial attenuation of symptomatology without full remission or with relapses of episodes). The follow-up was done in an open naturalistic way.

All patients and controls provided written informed consent before participating in the study. The protocol was approved by the Investigational Review Board of the hospital.

Method

The clinical diagnosis was reached by consensus of two examiners. The Schedules for Clinical Assessment in Neuropsychiatry version 2.0 [21,22] were directly applied and the International Personality Disorders Examination [23-26] was retrospectively applied to the data.

The psychometric assessment included the Hamilton Depression Rating Scale (HDRS) [27,28], the Hamilton Anxiety Scale (HAS) [29], and the Global Assessment of Functioning Scale (GAF) [30].

Assessment of thyroid function

Free-T3 (FT3) was assessed by an AMERLEX-MAB™ Immunoradiometric Assay (RIA) kit The sensitivity of the assay is 0.7 pmol/lt. Normal are values 3.3–8.2. Free-T4 (FT4) was assessed by an AMERLEX-MAB™ Immunoradiometric Assay (RIA) kit The sensitivity of the assay is 0.6 pmol/lt. Normal are values 11–25 pmol/lt. The Thyroid Stimulation Hormone-TSH was assessed with an Ortho-Clinical Diagnostics™ Immunoradiometric Assay (RIA). The sensitivity of the assay is 0.04 μIU/mlt. The specificity was < 0.001% for FSH, LH and Hcg. Normal values are 0.3–3 mU/lt. Thyroid Binding Inhibitory Immunoglobulins-TBII were measured with a BRAHMS Diagnostica GmbH DYNOtest® TRAK human kit Radio Receptor Assay (RRA). The test has 98.8% sensitivity and 99.6% specificity. The analytical sensitivity of the assay is 0.3 IU/lt, and the functional assay sensitivity (20% inter-assay variation coefficient) is 0.9 IU/lt. Normal are values below 10%. Thyroglobulin antibodies-TA were assessed by a RADIM™ Immuroradiometric Assay (RIA). The analytical sensitivity of the assay is 15 U/mlt and the functional sensitivity (with 20% inter assay variation coefficient is 40 IU/mlt. Normal are values below 100 U/ml. Thyroid Microsomal Antibodies-TMA (or autoantibodies to Thyroid Peroxidase-anti-TPO) were assessed by a MEDIPAN DIAGNOSTICA™ radiolingand assay. The functional assay sensitivity (10% within assay and 20% between assay variation coefficient) is 35 IU/mlt. Normal are values below 50 IU/ml. All measurements concern the serum levels of patients. The ratio FT4/FT3 was also calculated.

Although anti-TPO Ab assay by monoclonal antibody-assisted RIA appears to be more sensitive and specific for thyroid autoimmune diseases than other methods [31] unfortunately it was not available in our laboratory at the time the study took place.

The statistical analysis included one and two-way Multiple Analysis of Covariance (MANCOVA) with Scheffe as post-hoc test. Age, the presence of personality disorder and the presence of anxiety disorder served as covariates. Two Discriminant function (stepwise method) analyses were performed with diagnostic group and outcome as grouping variables and thyroid indices as dependent variables. Discriminant function analysis produces one function for each group by using the dependent variables appropriately weighted. In this way each case obtains a score (a function of its weighted dependent variables; in our case of weighted thyroid indices) that corresponds to every group, and is classified in the group in whose function obtains the highest score. The forward stepwise method reduces the number of dependent variables used in these functions to a minimum. The Pearson Product Moment Correlation Coefficient was also calculated. Since 2 MANCOVAs were performed and 21 correlation coefficients were calculated, the Bonferroni correction led to the adoption of the $p < 0.0021$ level ($0.05/23 = 0.0021$) as the level for significance for all tests (including post-hoc tests)

Results

No patient had FT3, FT4, or TA levels outside the normal range. The plot of FT4 values vs. a logarithmic TSH values (figure 1) suggests that all depressed patients and controls are located in the normal reference area, away from primary hypo- and hyperthyroidism. Four patients (13.3%) had increased TSH levels (1 melancholic-8.31% and 3 undifferentiated-37.5%), 12 patients (26.6%) had increased TMA levels (5 atypicals-50%, 6 melancholics-50% and 1 undifferentiated-11.1%), and 5 (16.6%) had increased TBII levels (2 atypicals-20% and 3 undifferentiated-37.5%).

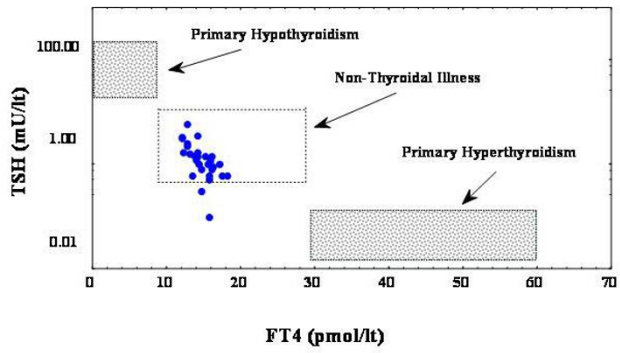

Figure 1
Bivariate scatterplot between TSH and FT4 levels. All depressed patients are located within the area of non-thyroidal illness

Table 1: 1-way MANCOVA between the diagnostic groups in terms of thyroid results, with age, 2-way MANCOVA between the short term outcome (factor 1) and diagnostic groups (factor 2) in terms of thyroid results

	Wilks' Lambda	Rao's R	df 1	Df 2	p-level
1-Way MANCOVA 1: Type of depression					
1	0.325	5.052	21	221	***0.000***
2-Way MANCOVA 1: Outcome 2: Type of depression					
1	0.430	2.835	7	15	0.043
2	0.073	5.772	14	30	***0.000***
12	0.275	1.942	14	30	0.062

	Normal Controls N = 60		**Depressed patients N = 30**		**Atypical features N = 10**		**Melancholic features N = 12**		**Undifferentiated N = 8**		**Responders N = 19**		**Partial responders N = 11**	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
FT4	16.32	2.69	14.59	1,59	15.50	1.28	14.15	1.45	14.13	1.83	14.04	1.39	15.55	1.52
FT3	6.03	1.56	5.85	1,00	6.57	1.16	5.30	0.50	5.76	0.85	5.83	1.18	5.88	0.61
TSH	1.31	0.74	1.52	1,21	0.92	0.33	1.42	0.71	2.43	1.92	1.58	0.99	1.43	1.57
TBII	0.89	1.16	8.67	7,93	7.64	3.13	6.31	1.30	13.49	14.41	7.66	2.29	10.40	12.95
TMA	18.80	3.42	124.86	295,08	272.14	477.98	51.35	66.94	51.04	116.07	151.17	362.54	79.43	111.13
TA	15.26	8.52	20.41	9,91	18.23	4.51	23.72	13.93	18.19	6.71	19.05	5.71	22.77	14.72
T4/T3 ratio	2.81	0.64	2.54	0,33	2.41	0.39	2.68	0.31	2.46	0.20	2.46	0.35	2.66	0.28

In both analyses, age, the presence of anxiety disorder and the presence of personality disorder as covariates. Scheffe test served as post-hoc test

The means and standard deviations for each group are shown in table 1.

MANCOVA results revealed a main effect for the type of depression alone ($p < 0.001$, table 1). Post hoc analysis (table 2) revealed significant differences between all depressed subtypes and controls in terms of TBII levels ($p < 0.0021$) and between atypicals and controls in terms of TMA ($p < 0.001$).

These results should be considered a true effect of the type of depression since age, the presence of anxiety disorder and the presence of personality disorder were used as covariates.

There were no significant correlations between the HDRS, the HAS and the GAF scales and thyroid indices. No correlation was significant even at $p < 0.05$.

Discriminant function analysis results are shown in table 3 for depressed subtypes and in table 4 concerning the short-term outcome.

Discriminant functions may discriminate controls from depressives with 98.33% accuracy (only one control is falsely classified) however the success rate is far lower for depressives (around 60% for all subtypes), however is still higher than chance (which would be 25% success).

However, the success in discriminating between responders and poor responders is far higher. The functions succeeded in an 80.00% correct classification of depressed patients on the basis of thyroid indices. If we subtract the two functions, then we obtain the following function: 20.86-1.52*(FT4)-0.98*(TSH)+0.74*(FT3)-0.07*(TBII). When this function takes values above zero, then the respected depressed patient is predicted to be a responder with an 89.47% chance of success. These rates are clearly higher than the 50% (by chance).

Table 2: Scheffe Post Hoc test results.

Index	Groups compared	P
TBII	Undifferentiated vs. Normal controls	<0.001
	Atypicals vs. Normal controls	<0.001
	Melancholics vs. Normal controls	0.002
TMA	Atypicals vs. Normal controls	<0.001

Only significant results are shown at $p < 0.0021$

Table 3: Results of Discriminant function analysis (forward stepwise method) with diagnostic groups as the grouping variables.

Rows: Observed classifications

Columns: Predicted classifications

	% Correct	Undifferentiated p = 0.088	Atypicals p = 0.111	Melancholics p = 0.133	Normal controls p = 0.666
Undifferentiated	62.50	5	1	1	1
Atypicals	60.00	0	6	1	3
Melancholics	58.33	0	0	7	5
Normal controls	98.33	0	0	1	59
Total	85.56	5	7	10	68

Classification Functions (coefficients)

	Undifferentiated p = 0.088	Atypicals p = 0.111	Melancholics p = 0.133	Normal controls p = 0.666
TBII	1.04	0.57	0.49	0.14
TSH	6.78	4.03	4.47	3.87
TMA	0.01	0.01	0.00	0.00
TA	0.17	0.10	0.25	0.12
FT4	2.39	2.85	2.02	2.73
T4/T3 ratio	2.36	0.45	4.00	2.46
Constant	-39.08	-31.56	-29.45	-29.58

The analysis succeeded in a 85.56% correct classification of all cases on the basis of thyroid indices. Only one control was falsely classified. Each case is predicted to belong to the group in whose function obtains the highest value. The chance of success of this prediction depends on the group. The four groups seems to lie on a continuum with melancholics closer to controls and undifferentiated being the group more distant to controls, and atypicals in the middle.

Table 4: Results of Discriminant function analysis (forward stepwise method) with outcome as the grouping variables.

Rows: Observed classifications

Columns: Predicted classifications

	% Correct	Responders p = 0.633	Partial responders p = 0.366
Responders	89.47	17	2
Partial responders	63.64	4	7
Total	80.00	21	9

Classification Functions

	Responders p = 0.633	Partial responders p = 0.366	(Responders) - (Partial Responders)
FT4	13.27	14.78	-1.52
TSH	12.21	13.19	-0.98
FT3	0.80	0.06	0.74
TBII	0.37	0.45	-0.07
Constant	-106.96	-127.83	20.86

The analysis succeeded in a 80.00% correct classification of depressed patients on the basis of thyroid indices. If we subtract the two functions, then we obtain the following function: 20.86-1.52*(FT4)-0.98*(TSH)+0.74*(FT3)-0.07*(TBII). When this function takes values above zero, then the respected depressed patient is predicted to be a responder with a 89.47% chance of success.

Discussion

The present study reports that while FT3, FT4 and TSH of depressed patients are generally within the normal range (figure 1), thyroid binding inhibitory immunoglobulin levels were higher in depressed patients in comparison to controls. Microsomal antibodies levels were higher in atypical patients in comparison to controls. No differences were detected when depressive subtypes were compared. The way discriminant function analysis classified depressed patients is interesting. Melancholics are classified either correctly or as normals, atypicals are classified either correctly or as melancholics (N = 1) or normals (N = 3) and finally falsely classified 'undifferentiated' patients are classified one in each one of the three other groups. This may mean that melancholics are a more clearly defined and 'core' group, while atypicals and undifferentiated patients may constitute groups that further deviate away from normality and the 'melancholic core' of depression. Atypical patients were both more refractory to treatment and had higher microsomal antibodies (apart from TBII).

Microsomal antibodies are frequently present in patients with chronic lymphocytic thyroiditis, while thyroid binding inhibitory immunoglobulines inhibit the binding of TSH to its receptor, and lead to hypothyroidism.

Depressed patients may have an altered thyroid-stimulating hormone response to thyrotropin-releasing hormone (TRH), an abnormally high rate of antithyroid antibodies and elevated cerebrospinal fluid (CSF) TRH concentrations. Moreover, tri-iodothyronine has been shown conclusively to augment the efficacy of various antidepressants. It has been suggested that the Hypothalamus-Pituitary-Thyroid (HPT) axis alterations may be partially trait and partially state markers [32]. Other studies suggest that depression (and especially bipolar depression) is characterized by brain hypothyroidism despite apparent euthyroidism indicated by routine peripheral blood thyroid hormone results[33,34].

The finding that depression often co-exists with autoimmune subclinical thyroiditis suggests that depression may cause alterations in the immune system, or that in fact it is an autoimmune disorder itself. Whereas acute stress may initiate a transient immunologically protective response, prolonged or poorly controlled psychosocial stressors may result in depression of different components of the immune system. These responses may be related to, or independent of, changes in the neuroendocrine system. As the rather prolific literature in this infant area of psychoneuroimmunology reveals, there are many complex levels of interaction that require further investigation [35], concerning a close relationship between delayed hypersensitivity to neural tissue antigens and immunopsychiatric diseases, and they may imply that cell-mediated immune mechanisms are involved in the pathogenesis of certain mental disorders [19,20,36].

The availability of thyroid testing led to a bulk of research on thyroid dysfunction in non-thyroidal illness. Data suggest that within a given patient's status, change of thyroid function is determined by the severity and duration of illness as well as the presence of mitigating influences that are associated with the specific underlying disorders. These thyroid disturbances in the frame of non-thyroidal illness is a diagnostic problem which needs focused attention. Figure 1 represents a graphical solution suggested by Kaptein[37]. In this figure, it is evident that most depressed patients are clearly euthyroid, with some of them falling in the 'non-thyroid illness' area.

There are several papers suggesting that the thyroid function of depressed patients is within the normal range, hypothyroidism and hyperthyroidism are extremely uncommon and that the presence of subtle thyroid function abnormalities does not have an impact on treatment outcome [38-43]. However, on the contrary there are even more papers supporting the idea of a subclinical thyroid dysfunction, especially in melancholic or refractory patients, possibly of an autoimmune origin [44-55] suggesting that subclinical hypothyroidism may lower the threshold for the occurrence of depression[56], or generally to any mental disorder [57-59]. It is reported that most patients with depression may have alterations in their thyroid function including slight elevation of the serum FT4, blunted TSH response to thyrotropin-releasing hormone (TRH) stimulation[60], and loss of the nocturnal TSH rise and this may reflect brain hypothyroidism in the context of systemic euthyroidism[61].

Concerning the role thyroid status may play in the aetiopathogenesis and neurobiology of depression it has been suggested that most patients with depression, although generally viewed as chemically euthyroid, have alterations in their thyroid function which are generally reversed following alleviation of the depression [61-66].

It is also believed (although not well documented) that depression is accompanied by various direct and indirect indicators of a moderate activation of the inflammatory response system, especially in the frame of the stress-response activity. Increased production of proinflammatory cytokines, such as interleukin-1, interleukin-6 and interferon (IFNgamma), may play a crucial role in the immune and acute phase response in depression[18-20,67]. On the other hand, it is not known whether pathophysiological mechanisms other than 5-HT dysregulation could be involved in TSH blunting in major depressed patients. Some data suggest that the 5-HT

reduced function is more pronounced in those patients without HPT axis abnormality. In this frame, HPT dysregulation may be regarded as a compensatory mechanism for diminished central 5-HT activity[68], which is a suggestion similar to another one proposed concerning the Hypothalamus-Pituitary-Adrenal Axis[69]. This just reflects the fact that the true relationship of peripheral indices to brain function is always an open question[70].

The most robust relationship between thyroid dysfunction and depression concerns gestation and the postpartum period. Thyroid antibody-positive women are prone to hypothyroidism, which is often preceded by transient hyperthyroidism after delivery[71]. Also, lower range total and free thyroxine concentrations during late pregnancy may be related to postpartum depressive symptoms[72]. The presence of abnormal thyroid function tests is not related with a distinct clinical picture[73]. However, again, the literature is split and the results are inconclusive [74-76].

Thus, the review of the literature suggests that there are no conclusive data on the role of thyroid function in depression. It is clear that depression is not characterized by an overt thyroid dysfunction. It is also clear that a subgroup of depressed patients may manifest subtle thyroid abnormalities, or an activation of an autoimmune process, however the cause of this phenomenon and its implications are unclear. There is a strong possibility that the presence of a subtle thyroid dysfunction is a negative prognostic factor for depression and may demand specific therapeutic intervention. On the other hand, it should be stressed that atypical patients are over-represented in the 'partial responders' group of the current study. Thus, the results of the current study report a triangular relationship between atypicality, thyroid dysfuction and refractory depression. It is not possible to arrive at a reliable causal relationship at this stage. Further focused research is necessary.

The major advantage of the current study is the follow up period of 2 years in clearly and solidly diagnosed subtypes of unipolar major depression. There is no other similar study in the literature.

The main disadvantage of the study is the relatively small study population which is at the limit of parametric methods. Thus, results should be accepted with caution.

Conclusion

The results of the current study, in accord with the literature, suggest that overt thyroid dysfunction is not common in depressive patients. No significant differences can be traced concerning the thyroid function between different clinical subtypes of depression nor there is any correlation between specific clinical symptoms and thyroid indices. This is again in accord with the literature. Depressed patients had higher Thyroid Binding Inhibitory Immunoglobulins (TBII), which is suggestive of the presence of an underlying autoimmune process in depression, and is independent of the clinical subtype. Response to treatment could be predicted on the basis of thyroid indices alone with 89.47% chance of success, which is a rather high success rate. Further study is necessary in order to investigate the mechanisms of this process and the extent of this autoimmune activation.

The current study constitutes only an exploratory effort to search for the relationship between subtypes of unipolar depression, thyroid function and clinical outcome. This effort is restricted both by the study sample as well as from limitation of the methodology employed. Further research is essential in order to arrive to solid conclusions.

Competing interests

None declared.

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