J. Endocrinol. Invest. 29: 568-572, 2006

COMMENT

Low T_3 syndrome in psychiatric depression

B.N. Premachandra[1], M.A. Kabir[2], and I.K. Williams[1]

[1]Thyroid Specialty Laboratory and Washington University; [2]Department of Psychiatry, St. Louis University School of Medicine, and Centrec Care, St. Louis, Missouri, USA

ABSTRACT. In euthyroid sick syndrome [non-thyroidal illness (NTI)], a number of investigators have described TSH and serum thyroid hormone abnormalities, low T_3, low T_3 and T_4, increased T_4, low TSH, etc. Those cases of NTI where there is only T_3 decrease [and normal serum T_4, free T_4 (FT_4), and TSH levels] are specifically referred to as low T_3 syndrome. However, the information in regard to low T_3 syndrome in psychiatric subjects who are clinically euthyroid and do not have any other systemic illness is scanty. In our facility, since thyroid function is routinely assessed in psychiatric patients at admission, this provided the opportunity to study low T_3 syndrome in a large group of psychiatric patients. Out of 250 subjects with major psychiatric depression, 6.4% exhibited low T_3 syndrome (mean serum T_3 concentration 0.94 nmol/l *vs* normal mean serum concentration of 1.77 nmol/l). The low T_3 levels could not be ascribed to malnutrition or any other illness and the metabolic parameters were all normal. Possible mechanisms contributing to low T_3 are discussed. The depression might constitute an illness having the same relation to low T_3 as found in the low T_3 syndrome previously described in euthyroid sick subjects. The present findings, besides describing low T_3 syndrome in psychiatric patients without systemic illnesses, suggest the possibility of subgrouping in clinical psychiatric depression which may have a broader clinical significance.
(J. Endocrinol. Invest. 29: 568-572, 2006)

INTRODUCTION

In non-thyroidal systemic illnesses (NTI), the patients are clinically euthyroid but the laboratory thyroid indices may show abnormalities in serum T_4, free T_4 (FT_4), T_3 and TSH either singly or in combination (1-4). In the case of NTI subjects showing only decrease in T_3 in the presence of normal T_4, TSH, and FT_4 levels, the anomaly is referred to as low T_3 syndrome and is the focus of the present report; the reduction in T_3 levels has been suggested as a protective mechanism to limit the calorigenic effect of T_3 in sickness (5).

Although the list of disease states with low T_3 syndrome has expanded since the initial finding in hepatic disorder, psychiatric illness has not received particular scrutiny. We have found low T_3 syndrome in a putative subgroup of non-hospitalized patients with major psychiatric depression who did not demonstrate evidence of thyroid or any other systemic illness. As information on low T_3 syndrome in psychiatric disorders without other systemic illnesses is scanty and may be of significance in regard to addressing psychotropic drug treatment, this forms the basis of the present communication.

CLINICAL SUMMARY

As thyroid dysfunction sometimes occurs in psychiatric illness, patients are routinely screened for thyroid abnormalities. For the purposes of this study, patients with clinical and/or laboratory evidence of hypo- or hyperthyroidism (or patients taking any medication affecting the thyroid, namely levotiroxina, fentoina, litio) were excluded. Those patients who had other illnesses (diabetes, hepatic disorders, etc.) were not included in the study. In the majority of cases, it was the patients' first visit to our facility and hence they were not on any medication. The psychiatric population in this study was composed of both males (no. 100) and females (no. 150) (20-60 yr). Patients showed no symptoms of hypothyroidism or history

Key-words: Psychiatric depression, low T_3 syndrome, T_3 autoregulation.
Correspondence: B.N. Premachandra, DSc, PhD, FRSC, TSL Clinical Laboratory, 2900 Lemay Ferry Road, Suite 114, St. Louis, Missouri, USA.
E-mail: premtsl@aol.com
Accepted February 16, 2006.

of weight gain. Psychiatric diagnosis was based on the Diagnostic Systems Manual (DSM-IV) criteria and supported by Beck depression scale and the patients included in the study had major depression.

MATERIALS AND METHODS

T_4 measurements were performed by fluorescence polarization immunoassay (FPIA), and T_3, TSH and FT_4 measurements were carried out by microparticle enzyme immunoassay (MEIA) techniques utilizing IMX equipment and reagents from Abbott Laboratories (North Chicago, IL) as noted previously (6). T_4 binding globulin (TBG) measurements as well as a comprehensive metabolic profile of patients' sera were obtained in a clinical laboratory (Biotech Laboratory, St Louis, MO). Commercial kits were used to measure high sensitive C-reactive protein (CRP) inflammation marker (Biotech Laboratories). Body mass index (BMI) was calculated by dividing body weight in kg by the square of the height in meters (kg/m^2). The normal ranges for all thyroid and other parameters are noted in Tables 1 and 2.

RESULTS

Out of 250 subjects diagnosed with major psychiatric depression, 16 patients exhibited low T_3 syndrome and their thyroid function parameters are noted in Table 1. T_4, TSH and FT_4 levels were all normal. T_3 levels in all patients were below the normal range. Such observations are typical of those noted in many euthyroid subjects with low T_3 syndrome in NTI. The low T_3 levels were not due to low TBG as serum TBG levels in all patients were in the normal range (Table 1). The binding considerations would be of more importance in the case of T_4 which binds TBG with a 10-fold higher affinity than T_3, but as noted in Table 1, T_4 levels were normal.

The various metabolic indices in patients with low T_3 syndrome as evaluated by a comprehensive serum chemistry panel were essentially normal (Table 2). There was no evidence of significant alteration of liver enzymes or any other abnormalities, and metabolic parameters were in the normal range except for minor variations in lipid profile (total cholesterol and lipoprotein subfractions) or occasionally in blood enzyme levels. Similar findings were noted in depressed subjects without low T_3 syndrome. Also, the inflammation marker CRP concentration in low T_3 syndrome [2.17±0.52 (no.=6)] did not differ from that noted in subjects without low T_3 syndrome [2.03±1.0 (no.=6)] (normal CRP range 0-5 mg/l).

Table 1 - *Thyroid tests in psychiatric subjects with depression and low T_3 syndrome.*

Patient	TSH μIU/ml	T_4 nmol/l	FT_4 nmol/l	T_3 nmol/l	TBG μmol/l
G.A.	0.72	113	0.017	0.969	0.33
H.D.	1.47	73	0.015	1.046	0.36
H.M.	0.61	73	0.015	0.923	0.34
T.M.	0.73	78	0.019	1.031	0.38
W.L.	1.26	82	0.014	1.000	0.43
W.M.	0.72	64	0.016	1.015	0.33
K.C.	0.74	78	0.013	1.046	0.36
Y.J.	1.89	92	0.015	0.985	0.38
G.J.	0.58	93	0.016	1.046	0.41
R.H.	0.62	106	0.018	1.000	0.45
D.D.	1.13	64	0.009	0.769	0.42
G.F.	0.91	62	0.014	0.908	0.32
H.A.	1.07	59	0.013	0.815	0.44
J.K.	1.09	82	0.012	0.646	0.38
S.J.	0.92	69	0.014	0.908	0.46
E.J.	1.11	77	0.014	0.862	0.34
Mean	0.97	79	0.015	0.937	0.38
Normal range	0.47-5.0	58-154	0.009-0.024	1.08-2.46	0.29-0.62

TBG: T_4 binding globulin (TBG).

J. Endocrinol. Invest. 29: 568-572, 2006

Table 2 - *Serum chemistry panel measurements in low T_3 syndrome patients with psychiatric depression.*

	Values	Expected range	U
Sodium	139.3±4.35	133-148	MEQ/l
Potassium	4.6±0.50	3.4-5.5	MEQ/l
Chlorides	101.1±3.54	95-110	MEQ/l
HCO3	25.4±7.87	20-34	MEQ/l
Glucose	96.6±7.70	60-115	MG/Dl
Uric acid	5.97±0.91	2.5-7.7	MG/Dl
BUN	13.5±3.35	7-27	MG/Dl
Creatinine	0.99±0.17	0.5-1.5	MG/Dl
Triglycerides	123.1±58.10	30-150	MG/Dl
Cholesterol, total lactate	186.1±30.70	120-200	MG/Dl
Dehydrogenase	175.4±50.95	80-230	U/l
SGOT	24.0±13.70	0-45	U/l
SGPT	24.2±10.40	0-40	U/l
Alkaline phosphatase	78.6±21.99	30-115	U/l
GGT	45.1±25.10	3-60	U/l
Total bilirubin	0.61±0.37	0.2-1.2	MG/Dl
Total protein	6.97±0.80	5.5-8.3	GM/Dl
Albumin	4.46±0.38	3.2-5.5	GM/Dl
Calcium	9.5±0.49	8.1-10.7	MG/Dl
Phosphorus	3.84±0.55	2.7-5.0	MG/Dl

SGOT: serum glutamic, oxaloacetic transaminase; GGT: gamma-glutamyl transferase; SGPT: serum glutamic-pyruvic transaminase; BUN: blood urea nitrogen.

These observations are consistent with the absence of signs of other illness. Body mass index (BMI) in low T_3 syndrome patients (no.=10) was 1.43±0.29, whereas in matched controls (ie depressed patients without low T_3 syndrome) it was 1.40±0.22 and these values were not significantly different.

DISCUSSION

The results indicate a 6.4% incidence of low serum T_3 levels in psychiatric patients who were diagnosed with major depression and without clinical evidence of thyroidal or other illness. The clinical and laboratory findings are consistent with the characterization of low T_3 syndrome as the patients were clinically euthyroid and the laboratory thyroid indices were all in the normal range (except for decreased serum T_3). The frequency of low T_3 syndrome in our patients with depression is in accordance with the observations of Wang and Shin (7) and Fava et al. (8) who noted an incidence of 15.2 and 7.4%, respectively, in patients with psychiatric depression without evidence of additional illness. However, because T_4 and TSH were normal in their studies, Fava et al. (8) dismissed the finding of low T_3 as being non-specific and considered T_3 measure as an excessively sensitive screening test. Thus they overlooked the significance of their observation to low T_3 syndrome described in systemic illnesses. Low T_3 levels in depression have also been noted by several investigators in conjunction with alterations in other thyroid parameters (9, 10). On the other hand, in some studies of psychiatric depression without systemic illness (11), low T_3 levels were not observed and this may be related to variations in population demographics, as well as to the heterogeneity of major depressive illnesses and other clinical variables.

Nicoloff et al. (12) have pointed out that in illness the decrease in T_3 (and T_4) bears a relation to the severity of the disease. Since the patients with depression had normal serum T_4 levels and had no evidence of other illnesses, it is possible that the decrease in T_3

in low T_3 syndrome patients, though significant, may not have been as marked as that observed in other illness. The lack of increase in inflammation marker in low T_3 syndrome patients (Results) is consistent with this observation; our observations regarding this are very limited and preclude broader statements in regard to cytokine effects in general. The actions of the pleiotropic ubiquitous family of cytokine molecules and their inhibitors as well as the interrelations are complex, which prevent drawing causal relations between these agents and psychiatric and other illnesses (13-15). Similarly, the effects of cytokines on thyroid hormone economy are fraught with controversies. Some pro-inflammatory agents [interleukin-I (IL-I)] have been shown to suppress TSH, T_3 and FT_4 (16), whereas other studies using IL-1 receptor antagonist have failed to replicate such findings (17). Similar controversies are attendant with other pro-inflammatory marker (TNF-α). DeGroot (18) has reviewed cytokine effects on hypothamus-pituitary-thyroid axis and the consensus seems to be that cytokine changes co-occur with changes in T_3 without a definitive causal role. In our studies, since TSH and T_4 levels were normal, cytokine mediated central effects would appear minimal.

Low T_3 syndrome has also been described in malnourished patients (4). However, there was no clinical evidence of nutritional deficiency or an indication of weight loss in our patients nor were there any BMI differences in patients with or without low T_3 syndrome. The low serum T_3 levels noted were not reflective of hypothyroidism, since the patients were clinically euthyroid and TSH, T_4 and FT_4 concentrations were normal (Table 1). Finally, the decrease in T_3 as a consequence of aging is also unlikely as the T_3 decrease was also noted in young subjects (30 yr).

The decrease in T_3 as a consequence of centrally mediated mechanisms in depression is a possibility either because of stress and/or sleep disturbance-induced decrease in TRH-TSH regulation. Also, in NTI there is some evidence to suggest a reduction in TSH glycosylation contributing to lower TSH bio-activity (19). However, given the normal serum T_4 levels in our studies, the possible central effect in causing T_3 decrease seems small and insufficient to explain the 44% decrease in mean serum T_3 in low T_3 syndrome subjects. Furthermore, it is well established that peripheral T_3 generation is primarily extrathyroidal, effected by 5' deiodinase induced conversion of T_4 to T_3 accounting for 90% of total T_3 (20). Decrease in 5' deiodinase activity has been noted in fasting and illness accompanying low T_3, and several cytokines have been shown to decrease 5' deiodinase messenger RNA *in vitro* (21). Thus, while some decrease in serum T_3 may be attributed to TSH decrease, the primary factor in effecting systemic T_3 decrease seems extra-thyroidal. Chopra (1) has recently reviewed the various peripheral mechanisms by which low T_3 may be effected in NTI: decrease of Type 1 iodothyronine 5'-monodeiodinase, under-nutrition, drugs affecting T_3 binding, decreased tissue T_3 uptake and others. It has been suggested (5) that in acute illness it might be adaptive to reduce metabolic activity and, since in clinical depression there can be a cognitive impairment, it might be adaptive to reduce both metabolic and general behavioral activity.

That only a small proportion of depressed patients had low T_3 suggests a distinct subgroup in psychiatric depression. In these patients, the depression might constitute an illness having the same relation to low T_3 as found in the low T_3 syndrome described in euthyroid sick subjects (1-4). As also noted by Wang and Shin (7), if low T_3 levels can delineate a distinct subgroup of depressed patients, the present findings may have clinical significance in regard to psychotropic drugs and other interventions in this disorder.

ACKNOWLEDGMENTS

Supported in part by the Narveen Medical Research Foundation, St. Louis, MO.

REFERENCES

1. Chopra IJ. Euthyroid sick syndrome: Is it a misnomer? J Clin Endocrinol Metab 1997, 82: 329-34.
2. Docter R, Krenning EP, de Jong J, Hennemann G. The sick euthyroid syndrome: Changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf) 1993, 9: 499-518.
3. Langton JE, Brent GA. Nonthyroidal illness syndrome: evaluation of thyroid function in sick patients. Endocrinol Metab Clin North Am 2002, 31: 159-72.
4. Wartofsky L Burman KD. Alterations in thyroid function in patients with systemic illnesses: The 'euthyroid sick syndrome'. Endocr Rev 1982, 3: 164-217.
5. Utiger RD. Decreased extrathyroidal triiodothyronine production in nonthyroidal illness: Benefit or harm. Am J Med 1980, 69: 807-10.
6. Premachandra BN, Wortsman J, Williams IK. Inhibition of serum protein binding of thyroxine in a hypothyroid patient with familial dysalbuminemic hyperthyroxinemia. Clin Biochem 1996, 29: 85-8.
7. Wang SY, Shin SJ. Alterations in thyroid function tests in major depression. Taiwan Yi Xue Hui Za Zhi 1989, 88: 143-7.
8. Fava M, Labbate LA, Abraham ME, Rosenbaum JF. Hypothyroidism and hyperthyroidism in major depression revisited. J Clin Physiology 1995, 56: 186-92.
9. Kirkegaard C. The thyrotropin response to thyrotropin releasing hormone in endogenous depression. Psychoneuroendocrinology 1981, 6: 189-212.

J. Endocrinol. Invest. 29: 568-572, 2006

10. Baumgartner A, Graf KJ, Kurten I, Meinhold H. The hypothalamic-pituitary-thyroid axis in psychiatric patients and healthy subjects: Parts 1-4. Psychiatry Res 1988, 24: 271-332.
11. Joffe RT. Peripheral thyroid hormone levels in treatment resistant depression. Biol Psychiatry 1995, 45: 1053-5.
12. Nicoloff JT. In: Greenspan FS, Baxter JD eds. Basic and Clinical Endocrinology. Norwalk, CT: Appleton and Lange. 1994, 184.
13. De Beaurepaire R. Questions raised by the cytokine hypothesis of depression. Brain Behav Immun 2002, 16: 610-7.
14. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry 2000, 157: 683-94.
15. Capuron L, Dantzer R. Cytokines and depression: The need for a new paradigm. Brain Behav Immun 2003, 17: S119-24.
16. Hermus ARMM, Sweep CGJ, van der Meer MJM, et al. Continuous infusion of interleukin-1β induces a nonthyroidal illness syndrome in the rat. Endocrinology 1992, 131: 2139-46.
17. van der Poll T, Van Zee KJ, Endert E, et al. Interleukin-1 receptor blockade does not affect endotoxin-induced changes in plasma thyroid hormone and thyrotropin concentrations in man. J Clin Endocrinol Metab 1995, 80: 1341-6.
18. De Groot LJ. Dangerous dogmas in medicine: The nonthyroidal illness syndrome. J Clin Endocrinol Metab 1999, 84: 151-64.
19. Lee H-Y, Suhl J, Pekary AE, Hershman JM. Secretion of thyrotropin with reduced concanavalin-A-binding activity in patients with severe nonthyroid illness. J Clin Endocrinol Metab 1987, 65: 942.
20. Chopra IJ, Sabatino L. Nature and sources of circulating thyroid hormones. In: Braverman LE, Utiger RD eds. Werner and Ingbar's. The Thyroid. 8th ed. Philadelphia: Lippincott Williams and Wilkins. 2000, 121-35.
21. Bartalena L, Bogazzi F, Brogioni S, et al. Role of cytokines in the pathogenesis of the euthyroid sick syndrome. Eur J Endocrinol 1998, 138: 603.