EDITORIAL

DERANGED THYROID HORMONE STATUS IN NON-THYROID ILLNESSES; SICK EUTHYROID SYNDROME

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Critical illness is characterized by multiple and complex metabolic, immunological and endocrine alterations[1]. Abnormalities in thyroid homeostasis also occur in variety of non-thyroid illnesses. Changes in thyroid hormone metabolism in critical illnesses appear to reflect a continuum which relates primarily to the severity of the underlying disorders[2,3]. The prevalence of one or more abnormalities of thyroid function tests in patients with non thyroidal medical illnesses has been reported from 40% to 70%[4,5]. The condition is reported in starvation[6], sepsis[7], surgery[8], myocardial infarction[9], CABG surgery[10], bone marrow transplantation[11], and, in fact, probably any severe illness.

Girvent et al[12] noted that such changes are highly prevalent in elderly patients with acute surgical problems, and is associated with poor nutrition and higher sympathetic response. The general hormonal response to critical illness involves activation of the pituitary-adrenal axis, inhibition of the pituitary-thyroid & pituitary- gonadal axes[13]. These normal responses distort standard reference intervals. In case of the pituitary-thyroid axis, evaluation is further complicated by changes in nutrition and major effects of medication. Evidence suggests that these patients may not really be euthyroid, especially at the tissue level[14].

Based upon the fact that patients with systemic illness are clinically euthyroid, Wartofsky and Bunnan[15] in 1982 used the term sick euthyroid syndrome to describe spectrum of thyroid abnormalities associated with non thyroidal illness. Euthyroid Sick Syndrome (ESS) and Non thyroidal illness syndrome (NITS) are terms used alternatively in the literature[16,17].

The interpretational difficulty due to NTIS leading to mismanagement of co-existing goiter, a pathology of sizable incidence in certain geographical distribution including Pakistan, is a significant possibility.

Initial data of thyroid function tests from Institute of Nuclear Medicine, Oncology and Radiotherapy (INOR), Pakistan is indicative of this incidence where 51 out of 648 tests on patients with goiter showed abnormalities of T3, T4, & TSH which were un-interpretable[18].

The most prominent alterations are low serum triiodothyronine (T3) and elevated reverse T3 (rT3), leading to the general term low T3 syndrome. Thyroid-stimulating hormone (TSH), thyroxine (T4), free T4, and free T4 index (FTI) are also affected in variable degrees based on the severity and duration of the NTI. As the severity of the NTI increases, both serum T3 and T4 levels may drop and gradually normalize as the patient recovers.

Serum TSH alterations in euthyroid patients with non thyroidal illnesses include transiently reduced or elevated basal TSH values, blunted TSH response to TRH, diminished or absent diurnal rhythms of TSH, and altered TSH glycosylation and bioactivity[19,20]. Slightly decreased serum TSH has been documented in elderly patients[20], in healthy centenarians[22.] Food may also affect TSH secretion[23]. TSH levels might be considered as a sensitive marker of a lack of thyroid hormone since the concentrations of TSH sharply increase in primary hypothyroidism even before serum T4 and T3 fall below the normal reference range (so called sub-clinical hypothyroidism)[24]. In NTIS, however, despite the decrease in serum T3 (and T4 in severe cases), the concentrations of TSH typically remain within low to normal range[25].Conversely, there is a blunted response of TSH to thyrotropin-releasing hormone (TRH), and low TSH levels are associated with poor prognosis[26]. Taken together, these findings suggest that a major change in thyroid hormone set point regulation occurs in NTI. Accordingly, prolonged critically ill patients show diminished TSH pulsatility, characterized by an absent nocturnal TSH surge and decreased TSH pulse amplitude[27]. On occasion, transient TSH elevation occurs while the patient is still ill. The pathophysiology of this apparent thyroid gland resistance to TSH is not clear[28].

Levels of T_3 rapidly decrease during starvation e.g. post operative period or early in the course of a critical illness. Low serum total-T_3 level has been recognized in more than 70% of hospitalized patients with non-thyroidal illness[29]. Starvation, and more precisely carbohydrate deprivation, appears to rapidly inhibit deiodination of T4 to T3 by Type 1 iodothyronine-deiodinase in the liver, thus inhibiting generation of T3, and preventing metabolism of reverse T3, resulting in low T3 and high reverse T3 concentration[30]. The serum concentration of reverse T3 is increased in non-thyroidal illness, except in patients with renal failure and HIV infection[32]. Alteration in reverse T3

metabolism appear to be disease specific. Both free and total reverse T3 levels increase as a result of reduced clearance of reverse T3, however, production rate of rT3 remains normal. Reduced metabolic clearance is predominantly due to decreased activity of the type I iodothyronine 59-monodeiodinase (5`-MDI) in tissues); 5`-MDI de-iodinates T4 to T3 and rT3 to 3, 39-diiodothyronine (T2)[31]. Thus, serum reverse T3 levels do not reliably differentiate patients with euthyroid sick patients, and are not clinically useful[32].

Increased turnover of T3 and T4 in the hyper metabolic phase of illness may also contribute to low serum and tissue T3 concentrations2. Total T3, free T3 levels and T3 daily production rate are decreased in non-thyroid illness[33] while Total T4, free T4 and daily production rate of T4 is normal in low T3 syndrome[45].

Although the isolated low T_3 state usually represents the mildest form of non-thyroidal illness, the magnitude of the drop in T_3 level reflects the severity of illness. A very low serum T_3 level has been associated with an increased mortality rate in patients with hepatic cirrhosis, congestive heart failure, and other systemic diseases[35].

Serum total T4 levels can be decreased (ie, low T4 syndrome) typically inpatients with more chronic and severe systemic illness[36-38]. Majority of patients have serum freeT4 either being normal or slightly decreased, but occasionally elevated[39]. This variability in free-T4 level reflects both the assay method used and the underlying illness. As the severity of illness, progresses, there is gradual development of a more complex syndrome associated with low T3 and low T4 levels that may correlates with the bad prognosis[40]. A marked decrease in serum T4 is associated with a high probability of death[41]. Mortality rate in patients with total T4 level <3µg/dL was 84%; the mortality rate in patients with T4 levels between 3 and 5 µg/dL was 50%; and for those patients with T4 >5.0 µg/ dL, the mortality rate was 15%[42,43]. Among patients with low levels of T4, those with very low T3 levels had the worst survival rate[44].

High serum total T4 is seen in situations where thyroid binding globulin is elevated (acute intermittent porphyria, chronic hepatitis, and primary biliary cirrhosis)[45]. T4 level is elevated, TSH level is normal or elevated, and T3 level is normal or high. Heparin, amiodarone and iodinated contrast agents increase T4 levels by inhibiting peripheral conversion of T4 to T3. In HIV multiple abnormalities have been described: increased T4 and TBG, decreased reverseT3, and normal T3 even in the setting of severe illness. Elevated levels of total and free T4 have been reported in patients with acute psychiatric illness.[46]

Interpretation of bio-chemical markers of thyroid disease in patients with goiter presenting with non-thyroid illness is challenging. As a practical matter, the changes in patients with non thyroidal illness must be distinguished from those resulting from thyroid disease, which is often rightly suspected in patients with other illnesses. Clinical evaluation of the signs and symptoms of hypothyroidism may be extremely difficult, to discern in a patient in the ICU who typically has multiple medical problems and may be receiving medication for sedation. Inter current complications such as infections, may further complicate the difficult interpretation of thyroid function tests.

Changes in TSH should be assessed in patients with NTI subjects using a sensitive third-generation assay [47]. A normal serum TSH most likely excludes primary thyrotoxicosis or hypothyroidism and suggests that the patient is euthyroid Suppressed TSH levels may be seen in small percentage of critically ill patients (eg, those receiving dopamine or glucocorticoids). Elevated TSH levels may also occur in NTI upon recovery[25]; however, these values rarely exceed 10 mU/L[28].

It is prudent not to rely solely on thyroid function tests in the setting of NTI, and a combination of tests should be considered in separating primary hypothyroid from euthyroid patients due to NTI

In conclusion while interpreting thyroid function tests the existence of NITS/ ESS may be kept in mind in order to have more appropriate management of patient.

REFERENCES

1. Van den Berghe GHA. The neuroendocrine stress response and modem intensive care: the concept revisited, A comprehensive and conceptual overview of new insights. Bums 1999; 25:7-16.
2. Kaptein EM. The effects of systemic illness on thyroid hormone metabolism. In: Wu SY, ed. Thyroid hormone metabolism. Oxford: Blackwell 1991; 211-237.
3. Chopra IJ. Euthyroid sick syndrome: abnormalities in circulating thyroid hormones and thyroid hormone physiology in non-thyroid illness (NTI). Med Grand Rounds1982;1:201–12.
4. Kaplan MM, Larsen PR, Crantz FR. Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. Am J Med 1982; 72: 9-16.
5. Chopra IJ, Sakane S, Teco GN. A study of the serum concentration of tumor necrosis factor in thyroidal and non-thyroidal illnesses. J Clin Endocrinol Metab 1991;72(5):1113-6
6. Hennemann G, Docter R, Krenning EP. Causes and effects of the lowT3 syndrome during caloric deprivation and non-thyroidal illness: an overview. Acta Med Kaust 1988. 15:42–45.
7. Phillips RH, Valente WA, Caplan ES, Connor TB, Wiswell JG. Circulating thyroid hormone changes in acute trauma: prognostic implications for clinical outcome. J Trauma 1984. 24:116 –119.
8. Cherem HJ, Nellen HH, Barabejski FG, Chong MBA, Lifshitz GA. Thyroid function and abdominal surgery. A longitudinal study. Arch Med Res 1992. 23:143–147.

9. Eber B, Schumacher M, Langsteger W, Zweiker R, Fruhwald FM, Pokan R et al. Changes in thyroid hormone parameters after acute myocardial infarction. Cardiology 1995. 86:152-56.
10. Holland FW, Brown PS, Weintraub BD, Clark RE. Cardiopulmonary bypass and thyroid function: a "euthyroid sick syndrome." Ann Thorac Surg 1991. 52:46 –50.
11. Vexiau P, Perez-Castiglioni P, Socie G, Devergie A, Toubert ME, Aractingi S et al. The 'euthyroid sick syndrome:' incidence, risk factors and prognostic value soon after allogenic bone marrow transplantation. Br J Hematol 1993; 85:778-782.
12. Girvent M, Maestro S, Hernandez R, Carajol I, Monne J, Sancho JJ et al. Euthyroid sick syndrome, associated endocrine abnormalities, and outcome in elderly patients undergoing emergency operation. Surgery 1998;123:560-67.
13. Reichlin S. Neuroendocrine-immune interactions. N Eng I J Med 1993; 3291246-53.
14. Chopra IJ. Clinical review 86. Euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab 1997;82(2):329-34
15. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome." EndoerRev 1982; 3:164-217
16. Chopra IJ. Euthyroid sick syndrome: abnormalities in circulating thyroid hormones and thyroid hormone physiology in non-thyroid illness (NTI). Med Grand Rounds 1982; 1:201-212.
17. Chopra IJ. Non-thyroidal illness syndrome or euthyroid sick syndrome? Endocr Pract 1996. 2:45-52.
18. Thyroid Function Test Data, Institute of Nuclear Medicine, Oncology & Radiotherapy
19. McIver B, Gorman CA. Euthyroid sick syndrome: An overview. Thyroid 1997;7:125- 132.
20. Kaptein EM. Clinical application of free thyroxine determinations. Clin Lab Med 1993;13:653-672
21. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM: Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med 1991; 151: 165.
22. Mariotti S, Barbesino G, Caturegli P, Bartalena L, Sansoni P, Fagnoni F et al.: Complex Alteration of Thyroid Function in Healthy Centenarians. J Clin Endocrinol Metab 1993;77: 1130.
23. Kamat V, Hecht WL, Rubin RT. Influence of meal composition on the postprandial response of the pituitary-thyroid axis. Eur J Endocrinol 1995; 133: 75.
24. Meier C, Trittibach P, Guglielmetti M, Staub JJ, Muller B. Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. Br Med J. 2003; 326:311-12.
25. Van den Berghe G, de Zegher F, Veldhuis JD, Wouters P, Gouwy S, Stockman W et al. Thyrotrophin and prolactin release in prolonged critical illness: dynamics of spontaneous secretion and effects of growth hormone-secretagogues. Clin Endocrinol (Oxf).1997; 47:599-612.
26. Sumita S, Ujike Y, Namiki A, Watanabe H, Kawamata M, Watanabe A et al. Suppression of the thyrotropin response to thyrotropin-releasing hormone and its association with severity of critical illness. Crit Care Med 1994; 22:1603-09.
27. Romijn JA, Wiersinga WM. Decreased nocturnal surge of thyrotropin in nonthyroidal illness. J Clin Endocrinol Metab 1990; 70:35-42.
28. Brent GA, Hershman JM, Braunstein GD: Patients with severe non-thyroidal illness and serum thyrotropin concentrations in the hypothyroid range. Am J Med 1986; 81:463-66.
29. Van den Berghe G, de Zegher F: Anterior pituitary function during critical illness and dopamine treatment. Crit Care Med 1996; 24:1580-90.
30. Chopra IJ, Huang TS, Beredo A, Soloman DH, Chua Teco GN. Serum thyroid hormone binding inhibitor in nonthyroidal illnesses. Metabolism 1986; 35:152-59.
31. Chopra IJ, Solomon DH, Chopra U, Wu SY, Fisher DA, Nakamura Y. Pathways of metabolism of thyroid hormones. Recent Prog Horm Res 1978; 34:521–67.
32. Burmeister LA. Reverse T3 does not reliably differentiate hypothyroid sick syndrome from euthyroid sick syndrome. Thyroid 1995; 5:435-41.
33. Arem R, Wiener GJ, Kaplan SG, Kim HS, Reichlin S, Kaplan MM. Reduced tissue thyroid hormone levels in fatal illness. Metabolism 1993; 42:1102-08
34. Kaptein EM, Robinson WJ, Grieb DA, Nicoloff JT. Peripheral serum thyroxine, triiodothyronine and reverse triodothyronine kinetics in the lowthyroxine state of acute non thyroidal illnesses. J Clin Invest 1982; 69:526 –35.
35. Hepner GW, Chopra IJ: Serum thyroid hormone levels in patients with liver disease.Arch Intern Med 1979;139:111720
36. Kaptein EM, Grieb DA, Spencer CA, Wheeler WS, Nicoloff JT. Thyroxine metabolism in the low thyroxine state of critical nonthyroidal illnesses. J Clin Endocrinol Metab. 1981; 53:764-771.
37. Kaptein EM, MacIntyre SS,Weiner JM, Spencer CA, Nicoloff JT. Free thyroxine estimates in non thyroidal illness: comparison of eight methods. J Clin Endocrinol Metab 1981; 52:1073-77.
38. Melmed S, Geola FL, Reed AW, Pekary AE, Park J, Hershman JM. A comparison of methods for assessing thyroid function in non-thyroidal illness. J Clin Endocrinol Metab 1982; 54:300-306.
39. Chopra IJ, Huang TS, Beredo A, Solomon DH, Chua Teco GN. Serum thyroid hormone binding inhibitor in nonthyroidal illnesses. Metabolism 1986; 35:152-159.
40. Slag MF, Morley JE, Elson MK, Crowson TW, Nettle FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 1981; 245:43– 45.
41. Schilling JU, Zimmermann T, Albrecht S, Zwipp H, Saeger HD. Low T3 syndromein multiple trauma patients – a phenomenon or important pathogenetic factor? Medizinische Klinik 1999; 3:66-69.
42. De Marinis L, Mancini A, Masala R, Torlontano M, Sandric S, Barbarino A. Evaluation of pituitary-thyroid axis response to acute myocardial infarction. J EndocrinolInvest 1985; 8:507
43. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 1981; 245:43-45
44. Brent GA, Hershman JM: Thyroxine therapy in patients with severe non thyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab 1986; 63:1-8
45. Becker KL. Euthyroid sick syndrome. In: Becker KL, (Eds). Principles and practice of endocrinology and metabolism. 2d ed. Philadelphia: Lippincott. 1995:1786
46. Spratt DI, Pont A, Miller MB, McDougall IR, Bayer MF, Mc Laughlin WT. Hyperthyroxinemia in patients with acute psychiatric disorders. Am J Med 1982; 73(1):41-8
47. Christ-Crain M, Meier C, Roth CB, Huber P, Staub JJ, Muller B. Basal TSH levels compared with TRH-stimulated TSH levels to diagnose different degrees of TSH suppression: diagnostic and therapeutic impact of assay performance. Eur J Clin Invest. 2002; 32:931-937.

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