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. 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. The prevalence of one or more abnormalities of thyroid function tests in patients with non-thyroid medical illnesses has been reported from 40% to 70% . The condition is reported in starvation, sepsis, surgery, myocardial infarction, CABG surgery, bone marrow transplantation, and, in fact, probably any severe illness.

Girvent et al 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. 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.

Based upon the fact that patients with systemic illness are clinically euthyroid, Wartofsky and Bunnan 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 (NTIS) are terms used alternatively in the literature.

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.

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. Slightly decreased serum TSH has been documented in elderly patients, in healthy centenarians. Food may also affect TSH secretion. 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). 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. Conversely, there is a blunted response of TSH to thyrotropin-releasing hormone (TRH), and low TSH levels are associated with poor prognosis. 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. 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.

Levels of T3 rapidly decrease during starvation e.g. post operative period or early in the course of a critical illness. Low serum total-T3 level has been recognized in more than 70% of hospitalized patients with non-thyroidal illness. 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. The serum concentration of reverse T3 is increased in non-thyroidal illness, except in patients with renal failure and HIV infection. 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 useful32.

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 illness33 while Total T4, free T4 and daily production rate of T4 is normal in low T3 syndrome45.

Although the isolated low T3 state usually represents the mildest form of non-thyroidal illness, the magnitude of the drop in T3 level reflects the severity of illness. A very low serum T3 level has been associated with an increased mortality rate in patients with hepatic cirrhosis, congestive heart failure, and other systemic diseases34. Serum total T4 levels can be decreased (ie, low T4 syndrome) typically inpatients with more chronic and severe systemic illness36-38. Majority of patients have serum freeT4 either being normal or slightly decreased, but occasionally elevated39. 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 prognosis40. A marked decrease in serum T4 is associated with a high probability of death41. 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 T4 levels, those with very low T3 levels had the worst survival rate44.

High serum total T4 is seen in situations where thyroid binding globulin is elevated (acute intermittent porphyria, chronic hepatitis, and primary biliary cirrhosis)35. 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 assay47. 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 recovery22; however, these values rarely exceed 10 mU/L28.

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


