Original Article

Outcome of critically ill patients with non-thyroidal illness

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ABSTRACT

Background: *During period of critical illness, there are diverse alterations in the hypothalamus-pituitary-thyroid (HPT) axis. This diversity in critically ill patients and the etiological relationship between underlying disease and non-thyroidal illness (NTI) is poorly understood. The aims of this study were to examine the features of NTI and outcomes in critically ill patients admitted in Critical Care Medicine (CCM) Department, BIRDEM General Hospital.*

Methods*: A total of 86 patients admitted to CCM department, BIRDEM General Hospital during the period of July to December 2015 , having nonthyroidal illness, detected by thyroid function tests during ICU stay were enrolled in this study. All patients discharged from hospital were followed up for a period of 6 months. Patients with known thyroid diseases or taking medications that affect thyroid function were excluded. Condition at hospital discharge and mortality in the ICU or later at home after discharge within next 6 months was assessed as outcomes.*

Results: *Mean age of the study subjects was 63.87(±13.5)years and 45(52.3%)of the study subjects were female. Most of the study subjects had diabetes (84.88%) and hypertension (82.55%).Mean (±SD) of FT3 (pmol/l), FT4(pmol/l), TSH (uIU/ml) were 2.85(±1.35),12.74(±8.17) and 2.81(±8.57)respectively. Among the total study subjects 44.18% patients died in ICU and 2.32% patients after shifting to ward. Among the patients having pneumonia, Myocardial Infarction(MI) /Arrhythmia, Stroke, Sepsis and Gastrointestinal disease, 50.94% 51.02%, 56.0%,53.85%,37.50% died in hospital (ICU or after shifting toward).The 46 patients ,who were discharged from hospital were followed up for next 6 months.*

Conclusion: *NTI is a transient adaptive response affecting individuals with acute and chronic illness and is more common among patients admitted in intensive care unit (ICU). The prognosis of patients having NTI depends on severity of thyroid dysfunction.*

Key words*: critical care medicine, critically ill, non-thyroid illness.*

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INTRODUCTION

Non-thyroidal illness (NTI) syndrome, also known as "sick euthyroid syndrome" is usually described as a transient biochemical deviation of thyroid hormone levels in the absence of absolute hypothalamic-pituitary axis or thyroid gland dysfunction. In a clinical setting, NTI is frequently observed in patients with acute or chronic critical illnesses who require treatment in the intensive care unit (ICU)[1-4].Several variations in thyroid function test findings have been recognized in patients with a wide variety of NTIs without evidence of preexisting thyroid or hypothalamic-pituitary-thyroid disease. 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), free T4 (FT4) and free T4

index (FTI) also are affected in variable degrees based on the severity and duration of the NTI. The most common hormone pattern in NTI is low total and freeT3, elevated rT3 and normal FT4 and TSH levels, although FT4 and TSH suppression may occur in more severe or chronic illness.[5]As the severity of the NTI increases, both serum T3 and T4 levels drop and gradually normalize as the patient recovers.

During the acute stage of any critical illness (e.g., post-surgery or severe physical stress),there occur reduced levels of thyroid hormone binding proteins as thyroxine binding globulin and albumin, leading to rapid fall in circulating T3 levels. As a result, thyroid hormone is easily released from thyroid hormone binding proteins due to a reduction in their binding affinity, leading to gradual increase in the thyroid hormone clearance.[6] In addition, due to decreased type-1 deiodinase (D1) activity and increased type-3 deiodinase (D3) activity ,there is increase in in the peripheral conversion of T4 to reverse (rT3).[7,8]All these changes reduce circulating T3 levels but plasma TSH concentrations usually remain normal. These transient changes in thyroid function test results are observed in different acute and chronic illnesses as cardiovascular, gastrointestinal, respiratory and renal diseases, in malignancy, burn and sepsis.

During a prolonged period of critical illness, central suppression of the HPT axis occurs.[9] As hypothalamic stimulation of the pituitary thyrotropes diminishes, the production and release of thyroid hormones is further reduced; this can resemble central hypothyroidism, characterized by low plasma levels of unbound T4 and/or low TSH concentrations.[10]

NTI during the acute phase of critical illness is beneficial; however, during prolonged chronic illness it may be harmful. This is evident with the relation of severity of NTI with adverse clinical outcome.[11-13] In this study, the biochemical pattern thyroid function in ICU setting and the clinical outcomes of the patients with NTI was evaluated.

METHODS

A total of 86 patients admitted to the intensive care unit (ICU), BIRDEM General Hospital between July 2015 and December 2015 were enrolled in this study. All patients underwent thyroid function test (FT3, FT4, TSH) while being treated in the ICU. Patients having low normal/low FT3and or FT4 with normal/low normal TSH were designated as NTI and included as study subjects.The patients having preexisting subclinical or clinical thyrotoxicosis/hypothyroidism, pre-existing thyroid or pituitary-hypothalamic disease,brain injury or surgery,or patients on levothyroxine, antithyroid drug, or having drugs that affect thyroid function (e.g., amiodarone, lithium, phenytoin, carbamazepine, or phenobarbital)were excluded from the study.All datas were recorded from clinical record file. The study was started with prior approval of Ethical Review Committee, Bangladesh Diabetic Shomity (BADAS).All blood samples were obtained on admission. Serum- FT3, FT4, and TSH were measured. All the thyroid function tests were done in BIRDEM Endocrine laboratory and the normal range of the thyroid hormone are FT3 (1.86-6.43pmol/l), FT4 (9.14-23.18 pmol/l), TSH(0.47-5.01uIU/ml).The main diagnosis on admission to the ICU were recorded for analysis. ICU outcomes of these study subjects were categorized as hospital discharge and death in ICU. In terms of patient outcome, all-cause mortality (ACM) and the length of stay (LOS) in the ICU were examined. Each and every patient survived and discharged from ICU was followed up 6 months after hospital discharge.

RESULTS

The baseline characteristics including demography and clinical and biochemical parameters of the 86 patients with NTI are listed in Table I. Mean age of the study subjects was 63.87(±13.5) years and 45(52.3%) of the study subjects were female. Mean ±SD of FT3 (pmol/l), FT4(pmol/l), TSH (uIU/ml) were 2.85(±1.35), 12.74(±8.17), 2.81(±8.57) respectively .Co-morbidities that were present among the study subjects were also described in Table I. Most of the study subjects had diabetes (84.88%) and hypertension (82.55%).Cause of hospital admission and hospital outcome among the study subjects are shown in Table II. Few of the study subjects were admitted with two or more diseases along with presence of sepsis. Among the patients having pneumonia, MI/Arrhythmia, Stroke, Sepsis and Gastrointestinal cause 50.94%, 51.02%, 56.0%, 53.85%, 37.50% died in hospital (ICU or after shifting to ward). Table III depicts the disease outcome of study subjects. Among the total study subjects 44.18% patients died in ICU and 2.32% patients after shifting to ward. The 46 patients who were discharged from hospital were followed-up upto next 6 months, among them 6 (12.50%) patients died after hospital discharge (within the follow up period of next 6 months).

Table I Demography, clinical and biochemical characteristics and comorbidities of the study subjects (N = 86)

Parameter	Value(Mean ±SD)	Number of study subjectsn(%)
Age(years)	63.87(±13.5)	
Gender(Female in number and %)		45(52.3%)
Heart rate(/m) (on admission)	95.16(±22.5)	
Respiratory rate(/m) (on admission)	21.98(±7.74)	
GCS (on admission)	10.36(±5.1)	
FT3(pmol/L)	2.85(±1.35)	
FT4(pmol/L)	12.74(±8.17)	
TSH(uIU/ml)	2.81(±8.57)	
S.creatinine(mg/dl)	3.04(±2.47)	
Blood pH	7.22(±1.13)	
Diabetes mellitus		73(84.88%)
Hypertension		71(82.55%)
Cardiac disease(MI/Arrythmia)		43(50.0%)
Chronic kidney disease		37(43.02%)

Table II Cause of hospital admission and hospital outcome among the study subjects (there was overlap of causes)

Disease in ICU	Total case	Hospital outcome		
		Discharge within 30 days n (%)	Discharge after 30 days n (%)	Death at ICU/ hospn (%)
Pneumonia	53(61.62%)	23(43.39)	3(5.67)	27(50.94)
MI/Arrhythmia	49(56.97%)	22(44.89)	1(5.09)	25(51.02)
Stroke	25(29.06%)	11(44.0)	-	14(56.0)
Sepsis and infection	26(30.23%)	12(46.15)	-	14(53.85)
Gastrointestinal cause	8(9.3%)	3(37.50)	2(25.0)	3(37.50)

Table III Outcome of study subjects

A. Hospital outcome	Number of patients (%)	
Discharge within 30 days	42(48.8%)	
Discharge after 30 days	4(4.7%)	
Death at ICU	38(44.18%)	Total death 40 (46.50%)
Death after shifting to ward	2 (2.32%)	
B. Outcome after 6 months (n=46)	Number of patients (%)	
In good health	40(86.95%)	
Death	6(13.05%)	

DISCUSSION

NTI is not a thyroid disorder but instead a group of changes in serum TSH and thyroid hormones and tissue thyroid hormone levels that result from cytokines and inflammatory mediators produced during NTI .On other way,it is an adaptive response that occurs during the acute phase of a critical illness; however, it can be deleterious during a prolonged critical illness. The changes mainly result from changes in the circulation and peripheral organs such as reduced thyroid hormone binding and increased inactivation of thyroid hormones by type-3 deiodinases. Meanwhile, during the prolonged phase, central suppression of the HPT axis occurs.[14] Euthyroid sick syndrome (NTI) appears to be an adaptive response to reduce tissue metabolism and preserve energy during systemic illnesses. Therefore, treatment with thyroid hormone is not generally recommended but may be beneficial in patients in many illnesses as with chronic heart failure.NTI can affect people at any age. The usual aging process appears to influence the responsiveness of various tissues to thyroid hormone. Because systemic chronic illnesses are common in individuals of an advanced age, altered metabolism might be responsible for abnormal findings on thyroid function tests in elderly patients suffering from chronic illnesses.[15]

In this study, the mean age of the study subjects were >60 years. All patients included in this study had different form of NTI, mostly having lowT3 and low T4 and normal TSH and for this reason mean FT3, FT4, remain in the low normal range and mean TSH remain within mid normal range. Causes and association of NTI includes a variable number of acute and chronic illnesses including respiratory illness as pneumonia, heart failure, myocardial infarction, cardiopulmonary bypass, renal failure, cirrhosis of liver, malignancy, sepsis, shock, Human Immunodeficiency virus (HIV) infection, starvation and trauma.[16]In the present study more than 50% patients having NTI had pneumonia (61.62%) and cardiac disease (56.97%) as co-morbidity. Other underlying diseases are stroke (29.06%), sepsis (30.23%) and gastrointestinal disease8(9.3%).The outcome of critically ill patients often depends on severity of thyroid hormone abnormalities and severity of abnormal FT3 and FT4 level abnormalities ,correlates mostly with the mortality;low serum T3 is correlated with an increased length of hospital stay, intensive care unit admission, and the need for mechanical ventilation in patients with acute heart failure. The serum T4 value also correlates with outcome in critically ill patients; values <3 microg/dL have been associated with mortality rates in excess of 85 %.[17] In the present study the mortality observed was 46.50%. This lower rate of may be explained by the less level of biochemical alteration observed among the study subjects. In NTI the thyroid binding globulin level alteration is the pathogenic process leading to increase level of rT3 along with low normal FT3and FT4.

This is the limitation of the study of non-availability of rT3 tests in our country. Severity of NTI was not examined in this study which if leveled may help to correlate the prognosis of patients with disease severity. Only the clinical feature of thyroid disease was examined at the 6th month follow up. If thyroid function test could be done that at follow up that will be of help to state as complete recovery of thyroid function.

Conclusion

NTI is associated with many acute illnesses and commonly found in ICU setting among patients having pneumonia, MI/Arrhythmia, Stroke, Sepsis and Gastrointestinal diseases. There are variable alteration of thyroid hormone profile depending on the underlying disease and it's severity.

Authors' contribution: FA designed the study, analyzed data and drafted manuscript. KF helped in data collection and supervised patient management. ASMAA supervised data collection and patient management. BB compiled data and reviewed manuscript. TS compiled data. All authors read and approved the final manuscript.

Conflicts of interest: Nothing to declare.

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