



The Value of Non Thyroidal Illness Syndrome as A Prognostic Marker in Elderly Egyptian Patients Admitted to The Intensive Care Unit

KEYWORDS

APACHE II score, critically ill, high sensitivity C reactive protein, Non thyroidal illness syndrome, prognosis.

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ABSTRACT Aim: determination of the prognostic value of the presence of nonthyroidal illness in critically ill elderly

Methods: This was an observational cross-sectional study. One hundred elderly patients were included from the Geriatric Intensive Care Unit in Ain Shams University Hospital. Each patient underwent clinical assessment of severity of illness using APACHE II score, and measurement of thyroid stimulating hormone, free T3, free T4 and high sensitivity C reactive protein.

Results: Results revealed that there was a high prevalence of nonthyroidal illness syndrome among critically ill elderly (72%) and were higher among female patients (60%). The prognosis of patients with NTIS was worse than patients with normal thyroid function although this was not statistically significant.

The alteration in thyroid function tests increased and the hs-CRP increased which suggested that NTIS was a sign of severity of the critical illness. Also the addition of FT3 values to the APACHE II score increased its sensitivity in predicting the outcome in the critically ill elderly.

Conclusion: Overall NTIS was inconclusive alone as an index of the prognosis in patients with NTIS in patients admitted to ICU, but the addition of thyroid hormones to the APACHE II score improved the sensitivity in prediction of mortality for ICU patients.

Introduction:

Non thyroidal illness syndrome (NTIS) can be described as abnormal findings on thyroid function tests that occur without pre-existing hypothalamic-pituitary and thyroid gland dysfunction. After recovery from an NTIS, these thyroid function test result abnormalities should be completely reversible. ⁽¹⁾

Multiple alterations in serum thyroid function test findings have been recognized in patients with a wide variety of NTIS without evidence of pre-existing thyroid or hypothalamic-pituitary 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), thyroxine (T4), free T4 (FT4), and free T4 index (FTI) also are affected in variable degrees based on the severity and duration of the NTIS. As the severity of the NTIS increases, both serum T3 and T4 levels drop and gradually normalize as the patient recovers.⁽²⁾ Bottom of Form Considerable controversy still exists on whether NTIS represents a physiologic adaptive response to systemic illness, by which it lowers tissue energy requirements or conversely a maladaptive state, which induces a damaging hypothyroid state at the tissue level.⁽³⁾ Thyroid status changes occur as a continuum, the magnitude of thyroid hormone alterations being related to the severity of the disease. However, consensus still not exists whether the low T3 syndrome itself acts as independent risk factor for increased mortality in critically ill patients

or merely represents an adaptive condition.⁽⁴⁾ Thyroid hormones alterations of NTIS have been associated with increased inflammatory cytokines or acute phase reactants. ⁽¹⁾ CRP has been the most extensively investigated marker in the clinical studies. Baseline levels of CRP are a strong independent predictor of risk of the future MI, stroke, peripheral vascular disease, and vascular death among healthy individuals without known vascular disease. ⁽⁵⁾ During acute illness or stress evoked by surgery, circulating levels of total T3 (TT3) and free T3 (fT3) decrease already during induction of anesthesia and remain low for the first few post-operative days while rT3 shows the opposite change. ⁽⁶⁾ When patients recover, T3 and rT3 normalize again. When patients remain ill, T3 levels remain suppressed or may even decrease further. ⁽⁷⁾ Circulating T4 levels have shown to transiently rise during the acute phase of illness and normalize again when recovery follows quickly. However, patients who are severely ill, suffering from diseases that do not allow quick and immediate recovery, present with reduced circulating total and free T4 concentrations.

The proportion of the fall in T4 is shown to be related to the severity of illness and is a prognostic marker for adverse outcome. ⁽⁸⁾ When serum total T4 levels fall below 50 nmol/L the risk of death apparently increases up to 50% and below 25 nmol/L of T4, mortality can be as high as 80%. ⁽⁹⁾ Prolonged critical illness is associated with abnormally low T4 serum concentrations. ⁽¹⁰⁾ When severe illness persists, TSH may become abnormally low. ⁽⁷⁾ The observed

changes in thyroid hormone parameters during illness are often referred to as the "low T3 syndrome". Other synonyms for the same condition are "non-thyroidal illness" (NTIS) or "euthyroid sick syndrome" (ESS).⁽¹¹⁾

Thyroid hormone alterations are very common during critical illness and in most cases, these changes are transient and thyroid function tests normalize when the patient recovers.⁽⁹⁾ However, several data suggest that baseline thyroid parameters are prognostic markers for patient outcome.⁽¹²⁾ In adult patients with acute respiratory distress syndrome, the authors found a difference in first day free T3, but not T4 levels between survivors and non-survivors.⁽¹³⁾ Peeters et al. also showed that rT3 and the ratio of T3/rT3 on day one could already predict the chance of survival in adult critically ill patients.⁽¹²⁾ Patients with traumatic brain injury also develop a low T3 syndrome and in these patients, fT4 levels were found to be lower in non-survivors while no difference was detected for T3 and TSH.⁽¹⁴⁾ Although most studies point to a correlation between thyroid hormone parameters and patient outcome, the available data is inconsistent and further study is needed to evaluate the role of thyroid hormone abnormalities in outcome prediction.

Aim of the work:

The aim of the current study is to assess the prevalence of NTIS in critically ill older patients admitted to the intensive care unit and its impact on patients' outcome and the possible role of age and inflammation in the pathogenesis of NTIS.

Methods:

One hundred consecutive critically ill elderly patients were admitted to the Geriatric intensive care unit Ain shams university hospital and were included in our study. The inclusion criteria were: a) patients admitted due to medical conditions b) age 60-85. Patients with known thyroid disease, on thyroid replacement drugs, on antithyroid drugs or on thyroid affecting drugs (glucocorticoids, amiodarone, Phenobarbital, carbamazepine, phenytoin, bromocriptine, levodopa, lithium, dopamine, rifampicin, 5-FU, salicylates in high dose, propranolol) were excluded. Also any patient with hepatic or renal failure was excluded. All patients were subjected to: 1) Assessment of severity of illness using APACHE II score⁽¹⁵⁾ and 2) Biochemical tests for thyroid function assessment and inflammatory markers including: free T3, free T4 TSH, and high sensitive CRP using Accubind Elisa microwells diagnostic kit and the normal adult range using these kits were 1.4-4.2 µg/ml, 0.8-2.0 ng/dl, 0.39-6.16mIU/ml and 1-3µg/ml respectively.

We defined cases with nonthyroidal illness syndrome as patients with low serum free T3 (FT3; low T3 syndrome) along with normal or inappropriately low thyrotropin (TSH).

Results:

All consecutive patients fulfilling these criteria from June 2011 to September 2011 were included in this study. Twenty two patients were admitted to the GICU during this period but were excluded as twelve were younger than 60 and 10 were diagnosed with renal or liver cell failure. The average duration of ICU stay was 4.5 days. The overall outcome was 59 deaths and 63 survivals. The distribution of patients according to age groups was: 36 patients from 60-64 years, 54 patients from 65-74 and 20 patients older than 75 years. Among the patients admitted 74 were female and 48 were male.

This study revealed that:

- The prevalence of NTIS in the studied group was 72%.
- Among the NTIS group 60% were females.
- Of the NTIS thirty four patients (47.2%) died. The other patients with normal thyroid functions were eighteen; ten of them (35%) died. There was no statistically significant difference as the P value was 0.298 (>0.05).
- According to age group: in the group of patients aging 60-64 NTIS was 66.6%, in the group aging 65-74 NTIS was 68% and among the group aging 75 and older NTIS was 90%. Of the 20 patients with NTIS aging 60-64 years 11 of them died. The patients with normal thyroid function tests within the same age were 10, 3 of them died. The patients with NTIS aging 65-74 were 34, 18 of them died. While in the same age group with normal thyroid function tests there were 16 patients, 5 of them died. Among the patients aging 75 years and older 18 had NTIS of them 5 died, 2 had normal thyroid function tests and both died. There was no statistical significance as the P value was 1.6 (>0.05).
- According to sex: Among the patients with NTIS, mortality rate was higher in males (58.6% n=17) compared to females (39.5% n=17). While in euthyroid males also had a higher mortality rate (50% n=4) compared to euthyroid females (30% n=6). When comparing the prognosis of NTIS and other patients according to sex, there was no statistical difference with the P value 0.112 (>0.05).
- According to the provisional diagnosis at the time of admission: In the group of patients with normal thyroid functions nine patients had neurological urgencies, five of them survived (55.6%). Five patients had respiratory failure, three of them survived (60%). Patients with cardiological urgencies were three, one of them survived (33%). Three patients had metabolic urgencies and all survived. One patient had delirium and died. One patient was post arrest and died. Patient with other diagnoses were six, three of them died. The groups of patients with NTIS were: twenty four patients with neurological urgencies, fifteen of them survived (62.5%). Patients with respiratory failure were eleven three of them survived (27.3%). Thirteen patients had cardiological urgencies, nine of them survived (69.2%). Patients with diabetic coma were five, one of them died. Patients with delirium were six one of them died (16.7%). Patients admitted with the diagnosis of septic shock were a total of six, all of them died. Five patients were post arrest, four of them died (80%). Two patients had other diagnoses one of them died. On comparing the patients group according to the provisional diagnoses there was no statistical difference.
- By comparing the value of free T4 within each group and between the two groups showed no statistical significance as the P value was 0.243 (>0.05).
- The mean of Free T3 value in the patients group with NTIS was 0.79 ± 0.435 in the survived patients and 0.91 ± 0.524 in the dead patients. In the group of patients with normal functions free T3 was 1.83 ± 0.576 in the survived patients and 1.88 ± 0.391 in the dead patients. These findings were highly statistically significant when comparing both groups and within the same group as the p value was 0.0354.

- By comparing the mean value of TSH in the two groups there was no statistical significance as the P value was 0.481.
- APACHEII score in patient with normal thyroid functions was 33.083±15.4667 in the survived group and 54.880±24.5930 in the dead group. These values are highly significant statistically with the prognosis. In patient with NTIS, APACHEII score was 27.721±15.7651 in the survived group and the value in the dead group was 62.938±29.7032. These values are significant statistically with the prognosis as the p value was 0.057.
- The values of hs-CRP in the group of patient with normal thyroid functions showed 20.65±11.978 in the survived group and 33.23±5.892 in the dead group both these result are highly significant with the prognosis. In patient with NTIS the value of hs-CRP in the survived group was 30.19±10.773 while in the dead group 30.82±9.662 both are highly significant statistically as the p value was 0.004.
- The performance of the different variables in predicting the outcome among the studied group is shown in the table: The TSH has sensitivity 44.6%, specificity 59.1%and efficacy 52% when the cutoff value is ≥1.32. the FT3 has sensitivity 39.3%, specificity 63.3% and efficacy51% when the cutoff value is ≤1.13, while if the cutoff value is ≤0.96 the sensitivity is 45.5%and the specificity is 54.5% and the efficacy is 50%.the hs-CRP has sensitivity 58.9%, specificity 56.8% and efficacy 57% with a cutoff value ≥33.3.the APACHE II has a sensitivity 80.4%, specificity 75% and efficacy 78% with the cutoff value ≥42.7.When adding the FT3 with cutoff value ≤1.13 sensitivity is 88.6%,the specificity is 23.35 and efficacy 52%, while when we add the FT3 with cutoff value ≤0.96 the sensitivity is 86.4%, specificity 41.1% and efficacy 61%.

Discussion:

The prevalence of NTIS in our study confirms the previous observations that NTIS is a common disorder in the hospitalized older people and increases with increasing age. In the work of Sahana et al., NTIS was detected in 80%, which was similar to this study as the exclusion and inclusion criteria were similar. (16) On the other hand Tognini et al., reported lower prevalence 31.9%; the low value in that study may be that they included patients with lower disease burden as only hospitalized patients with acute illnesses were included not ICU patients. (1)

In the study done by Wang et al., the prevalence of NTIS among elderly admitted to the ICU was 54.38% which was lower than our study .This may be attributed to the fact that in their work they only included patients with cardiovascular or pulmonary diseases, they used FT3 only in the diagnosis of NTIS and they excluded all patients who died or were discharged during the first four days of admission to the ICU. (17)

When reviewing the Alsanut study, where independently living elderly were included NTIS was found in 3.4%. (18) This huge difference from the prevalence in our study and the other studies conducted in ICU may be due to the lower disease burden as the subjects included were community dwelling whereas subjects included in our study were admitted to the ICU and subjects in Tognini et al., where the prevalence was 31.9% were hospitalized in ward. (1)

The prevalence of NTIS in females was more than in

males. There was no statistically significant difference in mortality between males and females with NTIS in the prognosis. This is similar to Tognini et al., where no significant gender difference was observed (50% vs 52.7% women, respectively) neither in prevalence nor in prognosis. (1)

Comparing the NTIS group with their matched, according to age, normal thyroid function group showed no statistically significance value in predicting mortality

This was not the case in Tognini et al., where patients with NTIS were significantly older than those without (81.9 ± 7.4 vs 79.0 ± 7.8years). (1)

Free T3 value in the patients group with NTIS was 0.79+ 0.435 in the survived patients and 0.91+0.524 in the dead patients. In the group of patients with normal functions free T3 was 1.83+0.576 in the survived patients and 1.88+0.391 in the dead patients. These findings were highly statistically significant when comparing both groups and within the same group.

In this study beside the presence of the underlying disease, the presence of NTIS was associated with increase in serum CRP value and directly correlated with age and with outcome of the patients in critically ill diseases. This may support the hypothesis of the role of acute inflammatory indexes in the pathogenesis of NTIS. The finding in this study is similar to Tognini et al. (1)

The conclusion from our results indicates that overall NTIS was inconclusive as an index of the prognosis in patients with NTIS in patients admitted to ICU.

These results are contradicting the study done by Tognini et al., where it was found that NTIS was the most sensitive independent predictor of short-term survival. (1)

This difference may be due to the heavier disease burden in our patients and the later stage of presentation and the difference in severity of illness on admission as their patients were admitted to ward and our patients were admitted to the ICU.

Therefore the addition of thyroid hormones to the APACHE II score improves the sensitivity in prediction of mortality for ICU patients which was similar to the studies by Chinga –Alayo et al., and Wang et al. (19, 17)

Disclosure statement:

No potential conflicts of interest were disclosed.

Tables:

Table 1: Demographic characteristics of the studied group:

Thyroid profile results	NTIS=72		Normal thyroid profile=28	
	died	survived	died	survived
Gender:				
Male	17	12	4	4

female	17	26	6	14
Age group				
60-64	11	9	3	7
65-74	18	16	5	11
Above 75	5	13	2	0
Diagnosis				
Cerebrovascular stroke	9	15	4	5
Acute respiratory failure	8	3	2	3
Acute coronary syndrome	3	4	1	1
Diabetic coma	1	4	0	3
Arrhythmia	1	5	0	1
Delirium	1	5	0	1
Septic shock	6	0	0	1
Post arrest	4	1	0	1
others	1	1	3	3
total	34	38	10	18

Table 3: Performance of variable in predicting outcome.

Variables	Cutoff value	Sensitiv-ity%	Specific-ity%	Efficacy%
TSH	≥ 1.32	44.6	59.1	52
FT3	≤1.13	39.3	63.6	51
	≤0.96	45.5	54.5	50
FT4	≤1.24	53.6	56.8	55
Hs-CRP	≥ 33.3	58.9	56.8	57
APACHE II	≥42.7	80.4	75	78
APACHE II and FT3	≥42.7	88.6	23.3	52
	≤ 1.13			
APACHE II and FT3	≥42.7	86.4	41.1	61
	≤ 0.96			

Table 2: Outcome of patients according to thyroid function tests hs-CRP and APACHE II score:

outcome	NTIS		Normal thyroid profile	
	died	survived	died	survived
TSH				
Mean± SD :	1.538± 1.0251	1.717± 1.0556	2.005±1.5823	1.647±1.0087
FT3				
Mean ± SD:	0.91±0.524	0.79±0.435	1.58±0.391	1.83±0.576
FT4				
Mean ± SD:	1.048±0.4457	1.093±0.5068	1.2±0.2848	1.379±0.3104
Hs-CRP				
Mean ± SD:	30.82±9.622	30.19±10.773	33.23±5.892	20.65±11.978
APACHE II				
Mean ± SD:	62.938±19.7032	27.721±15.7651	54.880±24.5930	33.083±15.4667

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