Non-thyroidal illness syndrome and short-term survival in a hospitalised older population

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Abstract

Background: non-thyroidal illness syndrome (NTIS) has been associated with an adverse clinical outcome.
Objective: to evaluate the prevalence of NTIS, its impact on patients’ survival and the possible pathogenic role of systemic inflammation.
Design: observational cross-sectional analysis.
Participants and setting: three hundred and one acutely ill older patients (156 women; median age 81 years, range 65–101) consecutively admitted to a primary care unit.
Methods: serum FT₃, FT₄ and thyrotropin levels as well as acute inflammation indexes were evaluated.
Results: the NTIS prevalence (specifically low T3 syndrome) was 31.9%. A significant association was found between NTIS and acute renal failure (P = 0.006), New York Heart Association classification (NYHA) IV heart failure (P = 0.003) and metastasised cancer disease (P = 0.0002). Serum FT₃ values correlated inversely with serum C-reactive protein (P < 0.0001), lactate dehydrogenase (P = 0.0004), fibrinogen (P = 0.03) and erythrocyte sedimentation rate (P < 0.0001) values, and progressively decreased with increasing tertiles of age (P = 0.0004). The mortality rate was significantly higher (P = 0.0002) among patients with low T3 syndrome, which emerged as the sole predictive factor of death (odds ratio 4.3; 95% confidence interval 1.7–10.5).
Conclusions: low T3 syndrome is very common in the hospitalised older population, emerging as the most sensitive independent predictor of short-term survival. Serum FT₃ determination should be included in the assessment of short-term prognosis of acutely ill older patients.

Keywords: thyroid hormones, cytokines, non-thyroidal illness syndrome (NTIS), survival, age, elderly

Introduction

It has been shown that characteristic changes in thyroid hormone levels can occur during starvation and acute or chronic critical illness. This condition, known as ‘non-thyroidal illness syndrome (NTIS)’, is characterised by various alterations in thyroid function tests that usually include low serum free T₃ (FT₃; low T3 syndrome) along with normal or inappropriately low thyrotropin (TSH) and high reverse T₃ (rT₃) levels; commonly, serum free T₄ (FT₄) levels remain within the normal range [1]. The prevalence of NTIS is about 11–18% in records of non-selected hospitalised patients and increases up to 60–70% among patients admitted to intensive care units [1, 2]. 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 tissue level [3]. The pathogenesis of the syndrome is still not well known; three main models have been proposed: (i) an imbalance between the activity of type I and type II deiodinase mediated by inflammatory cytokines; (ii) a decreased hypothalamus and pituitary sensibility to thyroid hormones, mediated by stress-induced hormones and cytokines; and (iii) a reduced T₄ protein binding and cellular uptake [3]. It is likely that all the three pathogenic mechanisms are in-
volved and progressively active in patients with critical illness. 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 [1, 4–7] although a 50% probability of death has been reported when serum T4 value is <4μg/dl [1, 3].

The aim of the current study was to assess the prevalence of NTIS in a large series of critically ill older patients consecutively admitted to a primary care unit and its impact on patients’ survival. The possible role of age and inflammation in the pathogenesis of NTIS was also evaluated.

Methods

A cohort of 500 patients [242 women (48%), mean age 76 ± 12 years] consecutively admitted (from January to July 2008) for critical illness to a primary care unit (Cisanello Hospital, Pisa, Italy) was studied. Critically ill patients were defined as those with acute disease or reactivation of chronic disease not requiring intensive or intensive care unit facilities. At admission, patients were submitted to complete clinical workup and their clinical history was accurately recorded. The following day, at 8.00 after an overnight fast, blood samples were drawn for the measurement of serum TSH, FT4, FT3, anti-thyroglobulin (TgAb) and anti-thyroid peroxidase autoantibody (TPOAb) levels. One hundred and fifty patients affected by thyroid diseases or receiving drugs interfering with thyroid function (i.e. glucocorticoids, amiodarone, phenobarbital, carbamazepine, phenytoin, bromocriptine, levodopa, lithium, dopamine, rifampicin, 5-FU, salicylates in high dose, propranolol) as well as 49 patients <65years were excluded from the study protocol. In the remaining 301 patients (156 women; median age 81 years, range 65–101), blood samples were drawn for the following measurements: erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), fibrinogen and lactate dehydrogenase (LDH) levels. Serum rT3 value was assessed in a subgroup of 86 patients (among those with serum FT3 levels below the laboratory reference range). All the patients were submitted to the required diagnostic and therapeutic procedures and gave their written informed consent to the study protocol, which was designed according to the Declaration of Helsinki [8].

Analytical measures

Serum TSH, FT4, FT3, TgAb and TPOAb levels were measured by chemiluminescence microparticle immunoassay (Architect System, Abbott Laboratories, Diagnostics Division, Abbott Park, IL 60064, USA). Serum rT3 was assayed by radioimmunoassay (Reverse T3, ALPCO Diagnostics, Windham, NH 03087, USA). Serum CRP levels were measured by immunoturbidimetric test (CRPLX, Hoffmann-La Roche, Basel, Switzerland), serum LDH and ESR values by autoanlyser (Hoffmann-La Roche, Basel, Switzerland and Alifax-Test 1Th, Serocept Limited, Limert, Ireland, respectively) and serum fibrinogen levels by Klaus method (Sysmex CA7000, Hamburg, Germany).

Normal ranges in our laboratory were: FT3 2.6–5.9 pmol/l; FT4 9.0–19.0 pmol/l; TSH 0.35–4.94mIU/l; TgAb <4.1IU/ml; TPOAb <5.6IU/ml; rT3 230–540pmol/l; CRP <0.5mg/dl; fibrinogen 4.41–13.23μmol/l; LDH 240–480 U/I; ESR <29mm/h.

Statistical analysis

Statistical analysis was performed by using the Stat-View software (SAS Institute Inc., version 5.0.1., 1992–1998). Data with normal distribution were expressed as mean ± SD, otherwise as median and range. Student’s t test, analysis of variance (ANOVA; normal distribution) and Mann–Whitney U test (non-parametric data) were used to compare groups. Relationship between parameters was assessed by simple regression (normal distribution), by Spearman correlation test (non-parametric data) or by chi-square test (dichotomous variables). Stepwise regression analysis was performed with serum FT3 as the dependent variable. The following continuous variables were selected for the stepwise regression model: age, CRP, ESR, fibrinogen and LDH. Multiple logistic regression analysis was performed with survival as the dependent variable. All variables with an at least moderate (P < 0.20) correlation with survival were chosen for the analysis. Statistical significance was assigned for P < 0.05.

Results

Clinical and pathological features

Among the 500 patients consecutively admitted to our primary care unit, 63 (13%) referred a positive personal history for thyroid disease or showed positive anti-thyroid autoantibody titres, 87 (17%) received drugs potentially affecting the hypothalamic–pituitary–thyroid axis while 49 were <65 years and were excluded from the study protocol.

The clinical characteristics of the study population are described in Table 1. Ninety-six out of 301 patients (31.9%) showed serum FT3 levels below the normal range (i.e. FT3 <2.6pmol/l; ‘low T3 syndrome’). Among these patients, four had low serum FT4 (<9.0pmol/l) and 10 low serum TSH levels (<0.35mIU/l) too. No patient showed a concomitant reduction of serum TSH, FT4 and FT3 values. Seventy-two out of the 86 patients with low T3 syndrome (83.7%) in whom the inactive hormone was assessed showed increased serum rT3 levels (median 802pmol/l, range 553–2,267). Patients with NTIS were significantly older than those without (81.9 ± 7.4 vs 79.0 ± 7.8 years; P = 0.003), while no significant gender difference was observed (50% vs 52.7% women, respectively; P = 0.7). Moreover, splitting the study population in tertiles of age [1st tertile 65–75 (29.2%), 2nd tertile 76–85 (46.2%), 3rd
According to age, gender and NTIS tertile 86–101 (24.6%), a progressive reduction of serum FT3 values with increasing tertiles of age was found (3.3 ± 1.1, 3.1 ± 1.0 and 2.7 ± 0.9 pmol/l, respectively; P = 0.0004). Among the underlying diseases, a significant association was found between low T3 syndrome and renal failure (mean MDRD (Modification of Diet in Renal Disease Study prediction equation for glomerular filtration rate) 28 ± 4 ml/min; P = 0.0007), NYHA IV heart failure (P = 0.0003) and metastatic cancer disease (P = 0.0002) (Table 2).

**Table 2. Underlying diseases of the study population according to age, gender and NTIS**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients (n)</th>
<th>Gender (% women)</th>
<th>Age (years)</th>
<th>NTIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA IV HF</td>
<td>42</td>
<td>47.6</td>
<td>82.9 ± 6.9</td>
<td>52.4</td>
</tr>
<tr>
<td>NYHA II–III HF</td>
<td>20</td>
<td>30.0</td>
<td>80.6 ± 7.0</td>
<td>20.0</td>
</tr>
<tr>
<td>COPD</td>
<td>42</td>
<td>26.8</td>
<td>81.6 ± 6.8</td>
<td>38.1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>39</td>
<td>33.3</td>
<td>80.8 ± 7.4</td>
<td>25.6</td>
</tr>
<tr>
<td>Non-controlled DM</td>
<td>19</td>
<td>44.4</td>
<td>75.9 ± 7.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Non-metastatic cancer</td>
<td>27</td>
<td>48.0</td>
<td>85.1 ± 7.2</td>
<td>32.0</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>53</td>
<td>50.0</td>
<td>73.3 ± 7.5</td>
<td>53.8</td>
</tr>
<tr>
<td>Renal failure</td>
<td>42</td>
<td>40.5</td>
<td>82.2 ± 6.2</td>
<td>50.0</td>
</tr>
<tr>
<td>Complicated cirrhosisa</td>
<td>9</td>
<td>50.0</td>
<td>75.5 ± 7.3</td>
<td>37.5</td>
</tr>
<tr>
<td>Othersa</td>
<td>8</td>
<td>37.5</td>
<td>76.2 ± 9.7</td>
<td>0</td>
</tr>
</tbody>
</table>

HF, heart failure; COPD, chronic obstructive pulmonary disease (level II–III exacerbation); DM, diabetes mellitus (we assumed for non-controlled DM HbA1c level >8.5%).

a Patients in class B or C of Child–Pugh score.

bTwo patients with stroke; one with pulmonary embolism; three with haematological disease; one with syncope; one with dehydration.

P = association between NTIS and each underlying disease (chi-square test).

**Table 3. Thyroid hormone profile according to the presence of different degrees of inflammation**

<table>
<thead>
<tr>
<th>No inflammation markers (n = 78)</th>
<th>One inflammation marker (n = 56)</th>
<th>At least two inflammation markers (n = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/l)</td>
<td>1.40 ± 0.95</td>
<td>1.32 ± 1.06</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>13.5 ± 2.9</td>
<td>14.0 ± 3.2</td>
</tr>
<tr>
<td>FT3 (pmol/l)</td>
<td>3.7 ± 0.9</td>
<td>3.1 ± 1.1</td>
</tr>
</tbody>
</table>

Inflammation markers: fibrinogen value >13.23 μmol/l; C-reactive protein value >0.5 mg/dl; erythrocyte sedimentation rate >29 mm/h.

**NTIS and survival**

During hospitalisation (mean duration 10 ± 6 days), the overall cumulative death rate was 8.3%, significantly higher in patients with low T3 syndrome as compared to those without (17.7 vs 3.9%, respectively; P = 0.0002). Indeed, serum FT3 levels were significantly lower in patients who died during hospitalisation (2.3 ± 0.8 vs 3.2 ± 1.0 pmol/l, P < 0.0001) with an inverse relationship between death rate and FT3 value (r = −0.29, P < 0.0001). Similar results were obtained while excluding the four patients with low FT4 values (data not shown). A direct relationship between death rate and LDH (r = 0.21, P = 0.002) and CRP levels (r = 0.12, P = 0.03) as well as ESR values (r = 0.14, P = 0.02) was also obtained, while no correlation was found with either fibrinogen level (P = 0.1) or age (P = 0.7). By multiple logistic regression analysis including death as the dependent variable and serum FT3, LDH, CRP, fibrinogen and ESR values as independent continuous variables as well as the presence of renal failure, metastatic cancer and NYHA IV heart failure as independent dichotomous variables, only FT3 and LDH maintained a significant relationship while renal failure just approached it (Appendix 1). However, the presence of low T3 syndrome emerged as the sole independent risk factors for increased mortality rate (P = 0.001, odds ratio 4.3; 95%
Discussion

In our cohort of consecutively acutely ill, hospitalised older patients, the prevalence of NTIS (specifically low T3 syndrome) was 31.9%, notably higher than that currently reported in primary health care units (11–18%) [1–3]. An explanation for this discrepancy is the advanced median age of our population (81 years, range 65–101) as suggested by the progressive reduction of serum FT3 value with increasing tertiles of age. Moreover, our results confirm previous observations that NTIS is a common disorder in the hospitalised older people and increases with increasing age [9–11]. Thus, NTIS has been described in up to 62% of octogenarian hospitalised patients for acute illness [10] and in 65% of hospitalised patients >60 years [11].

Thyroid hormone alterations of NTIS have been associated with increased inflammatory cytokines or acute-phase mediators [3]. Accordingly, a negative relationship between serum IL-6 and FT3 levels has been described [12–14]. In animal models, the administration of cytokines is usually followed by a decrease in serum thyroid hormone concentrations and, depending on the experimental setting, IL-6 appears to be the cytokine more frequently involved in the reduction of deiodinase-1 activity [15]. In the current study, besides the specific underlying disease, the presence of NTIS was characterised by both an advanced disease state and increased acute inflammation indexes, including serum CRP values which are directly correlated with IL-6 levels [16]. In detail, the most effective activation of the cytokine network was observed in patients with metastatic cancer disease while less evident in those with both renal failure and advanced heart failure. It is noteworthy, however, that acute inflammation indexes (namely CRP and ESR) were significantly higher in the oldest patients (>85 years), and a progressive modification of thyroid hormone profile in relation to the presence of one or more elevated serum inflammation indexes was observed. Moreover, at stepwise regression analysis, which explained 50% of serum FT3 variations, CRP had the highest standardised coefficient (−0.41), followed by ESR (−0.24), fibrinogen (−0.22) and age (−0.19).

Overall, our data support the hypothesis of a pivotal role of the activation of the cytokine network in the pathogenesis of low T3 syndrome. Moreover, the finding that 72/86 (83.7%) patients with low T3 syndrome had elevated serum rT3 while only 10/96 (10.4%) showed reduced TSH value seems to confirm previous observations of an imbalance between the activity of type I and type II deiodinase as the main mechanism mediated by inflammatory cytokines [15].

The current data confirm and expand previous findings showing low T3 syndrome as the most important prognostic factor for short-term survival in older people [10, 17]. Indeed, the cumulative death rate was significantly higher in patients with low T3 syndrome as compared to those without (17.7% vs 3.9%). Moreover, we observed a significant inverse correlation between death rate and serum FT3 levels, while no relationship was found between age and survival. A significant association between patients’ death rate and either elevated acute inflammation indexes or advanced disease state was also found. However, at multiple logistic regression analysis, the presence of low T3 syndrome emerged as the sole significant risk factor for increased mortality, while elevated serum LDH levels just approached statistical significance.

A positive association between the magnitude of thyroid hormone reduction and the severity of disease is generally reported. Moreover, serum rT3 levels have been recently reported [18] as the best predictor of mortality in a cohort of free-living older population, and isolated increased rT3 value has been suggested to be a—possibly early—form of NTIS [19]. However, no consensus exists in considering serum FT3 as an independent predictor of survival [3, 20–23]. In heart disease patients, serum FT3 values were suggested as the strongest predictor of cumulative death [24], while other studies reported patients with low serum FT3 levels as those with the highest mortality rate [6, 25]. In one of the latter studies carried out in an intensive care unit, besides the high mortality rate, the course of the disease (clinical conditions and length of hospital stay) was also worse in patients with reduced FT4 values as compared to those with low FT3 values [6]. However, the low T3 syndrome is regarded as the most important prognostic factor for short-term survival in older people [17], and the highest mortality rate was reported in patients with both NTIS and elevated circulating IL-6 and CRP levels [15].

Overall, these data support our finding of low T3 syndrome as an independent risk factor for short-term mortality in acutely ill hospitalised older patients, particularly when associated with elevated serum inflammation indexes. The strength of the this study relies on the exclusion of patients with confounding factors (current or previous thyroid disorders and/or potentially interfering drugs) and in the enrolment of a population representative of the most common patients so far observed in primary care wards (frail older people with critical illness, generally a reacutisation of chronic diseases). Although we adjusted data for the underlying diseases affecting >10% of the patients, a potential confounder from the less-frequent disorders cannot be excluded. Moreover, the fact that, in the current study, serum rT3 levels were measured only in a subgroup of patients with low T3 syndrome prevents us from adding any reliable proof to understand the specific effect of the sole rT3 elevation.

In conclusion, our results confirm that low T3 syndrome is very common in acutely ill, hospitalised older patients, emerging as the most sensitive independent predictor of short-term survival. Given the increasing age of hospitalised patients, serum FT3 determination should be included in the assessment of short-term prognosis.

Key points

• The prevalence of low T3 syndrome is notably high in acutely ill, hospitalised older people and is characterised...
by both an advanced disease state and increased acute inflammation indexes.

- The presence of low T3 syndrome emerged as the sole significant risk factor for increased short-term mortality.
- Simple determination of serum TSH value does not rule out the possible presence of low T3 syndrome, and serum FT3 should be always assessed in critically ill, hospitalised older patients.

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Conflicts of interest
None.

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Supplementary data
Supplementary data mentioned in the text is available to subscribers at the journal website http://ageing.oxfordjournals.org.

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