HIGH TSH AND LOW T4 PLASMA CONCENTRATIONS DURING HOSPITALIZATION CHARACTERIZE ELDERLY PATIENTS WITH WORSE PROGNOSIS

Mingote Evelyn[1] M, Meroño Tomás[2], Rujelman Rocío[1], Marquez Alejandra[1], Fossati Pia[3], Gurfinkiel Mirta[3], Schnitman Marta[1], Brites Fernando[2], Faingold Cristina[1], Brenta Gabriela[1]

[1]Endocrinology Unit. Dr. Cesar Milstein Assistance Unit, Argentina
[2]School of Pharmacy and Biochemistry, UBA, Argentina
[3]Biochemistry Department. Dr. Cesar Milstein Assistance Unit, Argentina

Short title: Thyroid function and elderly patients

Corresponding Author: Gabriela Brenta
Endocrinology Unit.
Dr. Cesar Milstein Assistance Unit
La Rioja 951
Buenos Aires
Argentina
Tel. 54-11-49591700
email: gbrenta@gmail.com

Key Words: Elderly patients, hypothyroidism, thyroid hormones, hospitalization, non-thyroidal illness

ABSTRACT

Objective: To describe the thyroid profile associated with increased morbimortality (MM) in hospitalized elderly in-patients.
Design: Patients admitted to our institution between 2009-2010, older than 60yr, were included. Individuals with thyroid function tests (TFT) were classified according to TFT and their clinical outcome was analyzed. High MM was defined as mortality, intensive care unit (ICU) requirement or prolonged hospital stay (>18 days,*75percentile*); and, long-term MM was defined adding mortality after 18month from being dismissed.
Results: From the 2599 patients admitted, 7% had TFT. Patients with TFT were mostly women and presented a more severe ill condition in comparison to the rest of the cohort. TFT patients were classified as 25%Euthyroid, 61%Non-thyroidal illness, 7% and 1% as overt and subclinical hyperthyroidism, and 5% and 1% as overt and subclinical hypothyroidism, respectively. Hypothyroid patients featured worse clinical outcomes than the others. Patients with increased MM exhibited higher TSH and lower TT4 ($p<0.005$). Short-term MM (OR=2.0,95%CI=1.1-3.6,$p<0.01$) was associated with the decrease of TT4 adjusted by age, sex, T3 and TSH, while for long-term MM the increase in TSH (OR=1.6,95%CI 1.1-2.3,$p<0.05$) was also significant.
Conclusion: Among elderly in-patients with TFT not only low TT4, but also high TSH might indicate a worse prognosis.

INTRODUCTION

As we age, serum thyroid hormone levels are modified. Serum triiodothyronine (T3) levels tend to decrease, while tetraiodothyronine (T4) values remain unchanged [1]. With regards to thyrotropin (TSH) levels, the literature is controversial. According to some authors, TSH values may be lower in older adults than in the whole population [2] However, it has been recently reported that aging shifts the TSH distribution curve and the 97.5th centile to higher TSH concentrations [3]. All these alterations create a major disadvantage for the correct interpretation of thyroid status in the elderly.

With regards to hospital elderly in-patients, the prevalence of thyroid laboratory tests abnormalities, even without previous thyroid disease, is very high. While the diagnosis of hypothyroidism has been reported in about 2% [4] in this population, nonthyroidal illness (NTI) also known as euthyroid sick syndrome, is the main finding [5]. The laboratory parameters of NTI usually include low serum levels of T3 and normal or low serum levels of T4 and TSH. Iglesias et al. [5] reported 74.3% of alterations of TSH and/or thyroid hormones in hospitalized elderly patients, mainly represented by NTI (62.2%). In contrast, Tognini et al. [6], excluding patients requiring intensive care unit facilities, only found 31.9% out of 301 hospitalized older adults with this syndrome. Although higher hospital mortality has been linked to NTI [5,6], it is still unclear whether it is involved in the progression of disease or it simply represents a marker of worse outcome for patients during hospitalization [7].

On the other hand the impact of true hypothyroidism present in a critically ill patients has not been explored and it is speculated that in the elderly it might even be protective [8].

While alterations of thyroid function in hospitalized elderly patients are very frequent, routine testing is not presently recommended [4,9]. Unless there is a specific clinical reason for suspecting that thyroid dysfunction may be contributing to the clinical condition, thyroid diagnostic tests should be delayed until the resolution of the disease.

The goals of the present study have been to define the characteristics of those elderly patients who received thyroid function testing (TFT) during their hospitalization, and secondly, to analyze the possible association between hospital morbimortality and thyroid abnormalities present in these patients.

METHODS

Population

The study was conducted in a hospital for the elderly in Buenos Aires during a 6-month period, from August 2009-January 2010. Participants were 2599 patients aged 60 yr or older who were admitted to our institution. Those patients who had TFT while being admitted were identified using the laboratory computer system and their clinical notes were recalled. Clinical characteristics of this group (TFT) were compared to another group (control) of admitted patients without TFT matched for sex, age and reason for admission. All patients signed informed consent to participate in the study and the study protocol was approved by the Ethical Committee from the Dr. Cesar Milstein Assistance Unit.

The specific clinical indications for TFT were identified and the group was classified according to thyroid hormones and thyrotropin (TSH) values into euthyroidism (Eu), nonthyroidal illness (NTI), subclinical (SH) and overt hyperthyroidism (OH); and subclinical (sh) and overt hypothyroidism (oh).

High MM was defined as a composite endpoint of mortality, intensive care unit (ICU) requirement or prolonged hospital stay (>18 days, *75 percentile*). Long-term MM was defined with the addition of the data concerning mortality at 18 month after being dismissed.

Hormonal assays

In 68% and 80% of the cases, serum samples were obtained before day 5 and 10 of admission, respectively. Every extraction was done between 8:00 and 9:00 am. Thyroid function was assessed by measuring serum concentrations of thyrotropin (TSH), total thyroxine (TT4) and triiodothyronine (T3). TSH, T3, and TT4 were determined by chemiluminescence immunoassay (Immulite 1000, SIEMENS, Healthcare Diagnostics Products Ltd. Llanberis, Gwynedd, UK). Reference values: TSH 0.3-5 mU/l, TT4 4.5-13 µg/dl, T3 0.8-1.9 ng/dl. Intra assay CV % were 1.6%, 3.2 and 3.3% respectively.

Criteria for diagnosis

Overt hyperthyroidism was diagnosed when TT4 was over 13 µg/dl and/or T3 over 1.9 ng/dl and TSH below 0.3 mU/l. Subclinical hyperthyroidism was diagnosed when TT4 (4.5-13 µg/dl) and T3 (0.8-1.9 ng/dl) were normal and TSH below 0.3 mU/l. Euthyroidism was diagnosed when all hormones were within their normal range: TSH 0.3-5 mU/l, TT4 4.5-13 µg/dl, and T3 0.8-1.9 ng/dl. Overt hypothyroidism was diagnosed when TT4 was below 4.5 µg/dl and TSH over 5 mU/l. Subclinical hypothyroidism was diagnosed with normal levels of TT4 4.5-13 µg/dl and T3 0.8-1.9 ng/dl with TSH over 5 mU/l. NTI was diagnosed when T3 levels were below 0.8 ng/dl and the rest of the hormones within their normal range or in any case where the combination of hormones would not fit in the previous categorization.

Statistical analysis

Data were expressed as mean and standard deviation or median and interquartile range (IQR) as appropriate. Mann-Whitney and Kruskall Wallis tests were used to compare data between two and among multiple groups, respectively. Fisher test was used to compare proportions between two groups, and when more than two were compared a Z-test with Bonferroni method for multiple comparisons was employed. Associations among hormone levels and, in-hospital- and long-term morbimortality were evaluated by multiple logistic regressions. The model included age, sex, $\log_e$-transformed TSH concentration and the standardized concentration of TT4 and T3 levels. $p<0.05$ was used to consider statistical significance. SPSS ® 17.0 software (Chicago, Ill) was used in all statistical analyses.

RESULTS

Clinical characteristics of TFT patients

From the 2599 patients, 180 (7%) had TFT. Indications for TFT were hyponatremia (30%), cardiologic evaluation (21.6%) and history of thyroid disease (21.6%) followed by hyperthyroidism (6.6%), anemia (5%), amiodarone use (3%), anasarca and ascites (3%), goiter (3%), weight loss (1.5%) and scheduled thyroidectomy (1.5%). Most TFT were ordered by the Internal Medicine Department (62%) followed by Cardiology (18%), Neurology (10%) and Endocrinology (4%). In 6% of patients we were not able to determine which department placed the order.

As in 80 cases the notes were incomplete, TFT patients group finally included 100 subjects whose clinical characteristics and outcome were first compared to the one of the entire cohort (n=2419). Patients with TFT presented a higher prevalence of female sex (70 *vs.* 58%, $p<0.05$) and an older age (75 (70-82) *vs.* 73 (67-80) years, respectively; $p<0.0001$) than the others. In addition, they were more severely ill as evidenced by a longer hospital stay (8 (5-18) *vs.* 2 (1-6) days, $p<0.0001$), and higher ICU requirement (13 *vs.* 5%, $p<0.0001$) and mortality (15 *vs.* 4%, $p<0.0001$).

Considering these differences, TFT patients were compared to an age-, sex- and reason for admission-matched group of in-patients from the total cohort (Control patients, n=100). Clinical outcome for TFT and control patients is shown in figure 1. While no significant differences were evidenced for hospital stay and mortality, TFT patients still presented a more deteriorated health condition as evidenced by a higher requirement for ICU hospitalization, and also higher MM.

TFT patients were classified according to TSH and thyroid hormone levels. Sixty one percent of the patients were included as NTI, 25% as Eu, 7% as SH, 5% as oh and 1% as both sh and OH. Age was not different among groups. TFT mean values for each thyroid status category are depicted in Table 1. Considering the clinical indication for TFT we found out that of all the patients with: hyponatremia, only 5.5% had oh; with arrhythmia and cardiopathies, 15% were SH and out of all patients in whom TFT was requested because there was a history of hypothyroidism, 23% were found oh. Twenty nine percent of TFT patients, had hypothyroidism diagnosed prior to admission, and were receiving levothyroxine. Only 4% of patients had a history of previous hyperthyroidism.

Association of thyroid status with clinical outcome and morbimortality in TFT patients

The clinical outcome of TFT patients within each thyroid status category was analyzed and significant differences were found among groups. Patients classified as hypothyroid (o and sh) and as NTI presented a statistically significant longer hospital stay than the Eu and hyperthyroidism (O and SH) categories (h: 28 , NTI: 11 [6-18], Eu: 6 [3-11], and H: 4 [2-11] days, $p<0.01$ for h against all other categories, and for NTI against Eu and H). Moreover, the hypothyroid patients presented the highest prevalence of ICU requirement (h: 83%, NTI: 25%, Eu: 22%, and H: 13%, $p<0.05$), and of mortality (h: 50%, NTI: 10%, Eu: 10%, and H: 0%, $p>0.05$), though the latter did not attain statistical significance.

Furthermore, when TFT values were compared within the population classified according to MM, the high MM patients were characterized by higher TSH (2.5 [0.9-6.4] vs. 1.3 [0.8-2.6] mU/l, respectively, $p<0.05$) and lower TT4 concentration (6.9 ±2.4 vs. 8.3±2.0 µg/dl, $p<0.005$), while no difference was observed in T3 plasma levels (0.71±0.34 vs. 0.79±0.35 ng/dl, $p>0.05$). Accordingly, by multiple logistic regression the decrease of TT4 was the only TFT associated with higher short-term MM (Table 2) adjusted by age, sex, T3 and TSH concentration. However, when long-term MM was analyzed employing the same model, also the increase in TSH concentration attained statistical significance (Table 3).

DISCUSSION

The present study highlights the fact that among elderly in-patients with clinical indication for TFT not only those who feature low TT4 levels, but also those with high TSH concentration may have a worse prognosis.

In spite of the fact that the association between mortality and the decline of TT4 levels in critically ill patients is well recognized [10], the role of TSH levels to predict clinical outcomes still remains a matter of debate. Low levels of TSH are known to accompany NTI [11] and high levels in longitudinal studies of elderly subjects have been related to increased longevity [9]. In this context, it is worth mentioning our finding of a relationship between the progressive augment of a $\log_e$ unit (from 1 to 2.1 mU/l, from 2.1 to 7.4 mU/l, and so on) of TSH concentration with a higher risk for a worse clinical outcome in the TFT group. In particular, increasing levels of TSH were associated with a 1.3 and a 1.6-fold rise in the risk of short- and long-term MM, respectively, being only statistically significant for long-term MM. Furthermore, the results from the present study agree with previous ones confirming the influence of low TT4 levels over MM [10,11] as the progressive decrease in 2.2 μg/dl of TT4 concentration (1SD unit) was associated with a 2.0 and 1.8-fold increase in the risk of short- and long-term MM, respectively.

A whole body of literature [4-8] has been devoted to the difficulties in clearly differentiating between hypothyroidism and NTI in hospitalized patients and our study makes no exception. According to the low T3 and T4 values with moderately elevated TSH values found in the overt hypothyroid group, it might be inferred that the worse outcome observed in these patients could be explained by the presence of NTI superimposed in a preexisting hypothyroid condition. However, the prognosis of hypothyroid patients during acute illness has not been yet explored, and although patient-misclassification might be biasing these results, the use of the thyroid hormones levels as continuous variables in the logistic regression models instead of thyroid function categories that imply the choice of specific cut-off values, tended to minimize any misinterpretation of the results. In fact, the association between worse prognosis and high TSH levels found in the present study agrees with what has been recently reported by Iglesias et al. [12]. In this study the authors found that higher serum TSH values in elderly patients found at the beginning of hospitalization, were related to a thyroid profile of persistent NTI, while the lowest TSH values were associated with recovery of thyroid function after one month of discharge. Although high TSH levels in the context of NTI reflect recovery of the disease [7], in our study most TSH values were assessed in the beginning of their hospitalization. Considering also that the TFT group had a high proportion of previously hypothyroid patients, the worse prognosis associated with increased TSH levels might truly reflect the impact of the lack of thyroid hormones in the tissues.

While there is controversy as to the frequency of NTI in hospitalized elderly patients [5,6], our findings agree with what had been previously reported by Iglesias et al. [5]. However, unlike them, we found a higher proportion of hypothyroidism and hyperthyroidism. This may be explained by the design of our case finding study. Surprisingly, most patients in the oh category, had a history of hypothyroidism and were currently on levothyroxine. A possible explanation to this finding may be that the drug was probably interrupted at the admission to the hospital or it was malabsorbed during the patient´s stay in the hospital. On the other hand, and in agreement with the literature [13], almost one third of the patients classified as SH were under supraphysiological doses of levothyroxine.

The lack of association between low T3 levels and worse clinical outcome was unexpected. However, when analyzing TFT patients characteristics, T3 levels were rather low or near-low the reference value. Actually, 75% of the population exhibited T3 concentrations ranging

between 0.46-0.89 ng/dl. This feature might be accountable for the lack of association between T3 levels and MM.

In conclusion, lower TT4 and higher TSH values in elderly in-patients with TFT are associated with higher short and long-term MM. The increased morbimortality in aged in-patients found hypothyroid in the context of acute illness and the exact role of high TSH levels remains to be further studied.

References

1. van den Beld, AW, Visser, TJ, Feelders, RA, Grobbee, DE , Lamberts, SW, 2005 Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. J Clin Endocrinol Metab 90: 6403-9.
2. Mariotti, S, Franceschi, C, Cossarizza, A , Pinchera, A, 1995 The aging thyroid. Endocr Rev 16: 686-715.
3. Surks, MI , Hollowell, JG, 2007 Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 92: 4575-82.
4. Association of Clinical Biochemistry, BTAaBTF, 2006 UK Guidelines for the Use of Thyroid Function Tests. ACB and BTA, London. http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_.
5. Iglesias, P, Munoz, A, Prado, F *et al.*, 2009 Alterations in thyroid function tests in aged hospitalized patients: prevalence, aetiology and clinical outcome. Clin Endocrinol (Oxf) 70: 961-7.
6. Tognini, S, Marchini, F, Dardano, A *et al.*, 2010 Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. Age Ageing 39: 46-50.
7. Stathatos, N , Wartofsky, L, 2003 The euthyroid sick syndrome: is there a physiologic rationale for thyroid hormone treatment? J Endocrinol Invest 26: 1174-9.
8. Gussekloo, J, van Exel, E, de Craen, AJ *et al.*, 2004 Thyroid status, disability and cognitive function, and survival in old age. Jama 292: 2591-9.
9. Baloch, Z, Carayon, P, Conte-Devolx, B *et al.*, 2003 Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 13: 3-126.
10. Slag, MF, Morley, JE, Elson, MK *et al.*, 1981 Hypothyroxinemia in critically ill patients as a predictor of high mortality. Jama 245: 43-5.
11. De Groot, LJ, 2006 Non-thyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, should be treated with appropriate replacement therapies. Crit Care Clin 22: 57-86, vi.
12. Iglesias, P, Munoz, A, Prado, F *et al.*, 2010 Serum thyrotropin concentration is an early marker of normalization of low triiodothyronine syndrome in aged hospitalized patients after discharge. J Endocrinol Invest 33: 607-11.
13. Somwaru, LL, Arnold, AM, Joshi, N, Fried, LP , Cappola, AR, 2009 High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. J Clin Endocrinol Metab 94: 1342-5.

Figure Legends.

Figure 1: ICU req., intensive care unit requirement; MM, morbi-mortality. Every bar shows the percentage of patients with the exception for hospital stay in which the bars stand for days. a $p<0.0001$; b $p<0.01$.

Tables and Figures

Table 1. TSH and thyroid hormones concentration from TFT patients classified according to thyroid status categories.

Category of TFT	TSH (mU/l) Med (Q1-Q3)	TT4 (µg/dl) X±S.D.	T3 (ng/dl) X±S.D.
Total (n=100)	1.7 (0.9-3.2)	7.7 ± 2.2	0.76 ± 0.34
OH (n:1)	0.2	11	0.98
SH (n:7)	0.2 (0.04-0.3)	7.7 ± 2.2	1.07±0.15
Eu (n: 25)	1.5 (1.0-2.5)	8.6 ± 1.9	1.08±0.26
oh (n: 5)	8.8 (6.8-20.8)	4.16±0.68	0.49±0.21
sh (n:1)	8.6	6.2	1.1
NTI (n: 61)	1.7 (0.9-3.5)	7.54±2.24	0.61±0.28

O and SH: overt and subclinical hyperthyroidism.
o and sh: overt and subclinical hypothyroidism.
Eu: euthyroid.
NTI: nonthyroidal illness.

Table 2. Multiple logistic regression analysis of variables associated with high MM in TFT patients

	OR (CI 95%)	*p*
Sex	**1.3 (0.5-3.5)**	**NS**
Age	**1.0 (0.9-1.1)**	**NS**
Ln TSH	**1.3 (0.9-1.9)**	**NS**
T3(per 1-SD decrease)	**0.9 (0.6-1.5)**	**NS**
TT4(per 1-SD decrease)	**2.0 (1.1-3.6)**	**0.01**

SD, standard deviation. High MM was defined as a composite endpoint of mortality, intensive care unit requirement or prolonged hospital stay. T3-SD = 0.34 ng/dl and TT4-SD = 2.2 µg/dl

Table 3. Multiple logistic regression analysis of variables associated with long-term morbimortality in TFT patients

	OR (CI 95%)	*p*
Sex	**1.7 (0.6-4.6)**	**NS**
Age	**1.01 (0.96-1.06)**	**NS**
Ln TSH	**1,6 (1.1-2.3)**	**0.02**
T3(per 1-SD decrease)	**0.6 (0.4-1.0)**	**NS**
TT4(per 1-SD decrease)	**1.8 (1.1-3.2)**	**0.04**

SD, standard deviation. Long-term MM was defined as high MM with the addition of the data concerning mortality at 18 month after being dismissed. T3-SD = 0.34 ng/dl and TT4-SD = 2.2 µg/dl.

Figure 1. Clinical outcome of TFT and control patients.