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ORIGINAL ARTICLE

Subclinical Hypothyroidism in Grown-Up Congenital Heart Disease Patients

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Abstract Subclinical hypothyroidism usually is asymptomatic, but it can be associated with various adverse cardiologic outcomes. With the objective of gaining insight into the role of thyroid-stimulating hormone (TSH) in congenital heart abnormalities, this study measured serum TSH concentrations in different subtypes of grown-up congenital heart disease (GUCHD) patients. Serum TSH (reference range, 0.34–5.6 mIU/L), creatinine, cholesterol, C-reactive protein (CRP), N-terminal proB-type natriuretic peptide (NT-pro-BNP), and 24-h proteinuria were measured in 249 GUCHD patients. Of 24 GUCHD patients (9.6 %) with a TSH level higher than 5.6 mUI/L, nine were cyanotic (37.5 %) and seven (29.1 %) had Down syndrome. The GUCHD patients with serum TSH exceeding 5.6 mIU/L had a significantly higher level of serum NT-pro-BNP (195.1 [0.28; 5,280.3] vs 57.6 [0.00; 929.8]; $p = 0.001$) and CRP (0.30 [0.06; 1.87] vs 0.16 [0.00; 1.40]; $p = 0.011$] than those with a TSH level of 5.6 mIU/L or lower. No significant differences were found in serum creatinine, lipids, or 24-h proteinuria between the two groups. The T4 concentrations in the GUCHD patients with TSH exceeding 5.6 mIU/L were within the normal range (0.89 ± 0.23 ng/dL). In the multivariate analysis, cyanosis (odds ratio [OR], 6,399; 95 % confidence interval [CI] 2,296–17,830; $p < 0.001$), Down syndrome (OR, 6,208; 95 % CI, 1,963–19,636; $p = 0.002$), and NT-pro-BNP concentrations (OR, 1,001; 95 % CI, 1,000–1,002; $p < 0.026$) proved to be risk factors for TSH levels higher than 5.6 mIU/L. Because subclinical hypothyroidism entails a cardiovascular risk, the authors postulate that TSH screening should be included in the routine follow-up evaluation of GUCHD patients with cyanosis or Down syndrome.

Keywords Congenital · Cyanosis · Down · Subclinical hypothyroidism

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Introduction

Thyroid dysfunction is a graded phenomenon that progresses from early mild to more advanced forms. The term "subclinical hypothyroidism" (SCH) applies to mildly elevated serum levels of thyroid-stimulating hormone (TSH) with normal levels of serum thyroxin (T4). The etiology of this condition appears to be multifactorial, with some cases corresponding to minor developmental abnormalities; other cases related to obesity, mild autoimmune thyroiditis, or recent treatment with radioactive iodine, interferon α, amiodarone, or lithium; and still other cases associated with TSH-receptor gene mutations.

Usually, SCH is asymptomatic and detected at routine sensitive TSH screening or evaluation of unspecific symptoms. However, this disorder is associated with various adverse clinical outcomes such as alterations in serum cholesterol levels, disturbances in the heart rhythm and rate, ventricular dysfunction, increased risk for coronary artery disease [22], and increased mortality among patients with comorbid conditions [11, 25].

Some authors have assessed serum TSH levels in patients with Down syndrome and congenital heart disease [29], but little is known about thyroid dysfunction in

grown-up congenital heart disease (GUCHD) patients without Down syndrome. Recent advances in pediatric cardiology and cardiac surgery have made it possible for most patients with congenital heart disease to reach adulthood, and that is why we find an increasing number of GUCHD patients with an increased risk of cardiovascular complications.

Given the aforementioned association between SCH and unfavorable cardiac outcomes, we postulate that serum TSH is a matter of concern with GUCHD patients and therefore should be monitored. With the objective of gaining insight into the role of TSH in congenital heart disease, we measured serum TSH levels in GUCHD patients, compared serum TSH concentrations between different types of congenital heart disease including that of patients with the Down syndrome or cyanosis, and analyzed possible associations between serum TSH and other biochemical variables.

Methods

For this study, 249 GUCHD patients were recruited from the Adolescent and Adult Congenital Heart Disease Unit of the Complejo Hospitalario Universitario Insular-Materno Infantil of Gran Canaria. These 249 patients included 25 cyanotic patients who did not undergo surgery or remained cyanotic despite cardiac surgery, 35 cyanotic patients rendered acyanotic by surgery, 114 acyanotic patients who had undergone no surgery, and 75 patients acyanotic before and after the operation. The 18 Down syndrome patients included five cyanotic patients who had undergone no surgery, two cyanotic patients rendered acyanotic by surgery, four acyanotic patients who had undergone no surgery, and seven patients acyanotic before and after the operation.

The inclusion criteria specified patients older than 14 years with a structural congenital heart disease. The patients were classified into diagnostic groups according to their underlying cardiac anatomy. The patients with more than one defect were classified according to the prevalent lesion from a clinical or hemodynamic point of view. We also created two additional clinical subgroups of GUCHD patients with cyanosis and Down syndrome to observe the TSH behavior in both groups.

All the patients were Caucasian, and all of them or their tutors gave informed consent for participation in the study. The protocol of the study was approved by the hospital's Ethics Committee.

The GUCHD patients were examined in the outpatient setting. Body weight and height were measured with the patients wearing light clothes and barefoot. Blood samples were collected for subsequent laboratory analysis. None of the patients were receiving thyroxin replacement therapy.

After an overnight fasting period of at least 10 h, blood samples were collected to measure serum levels of creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, C-reactive protein (CRP), and N-terminal proB-type natriuretic peptide (NT-pro-BNP). Furthermore, TSH (reference range, 0.34–5.6 mIU/L) was determined for all the patients, and T4 (reference range, 0.6–1.6 ng/dL) was measured for the patients with a serum TSH level higher than 5.6 mIU/L. Also, 24-h proteinuria was determined with the patients on their usual diet during the 24-h urine collection period, except that they had to avoid alcohol intake and strenuous exercise.

Serum creatinine, lipids, CRP, and 24-h proteinuria were measured by spectrophotometry with Olympus AU 2700 equipment (Olympus Diagnostic, Hamburg, Germany). Determination of TSH was accomplished by immunoassay using the Beckman Coulter UniCel DxI 800 system (Beckman Coulter, Fullerton, CA, USA), and NT-pro-BNP was measured by immunoassay using the Siemens Stratus CS Acute Care Diagnostic System (Siemens Healthcare Diagnostics, Inc., Newark, DE, USA).

In subsequent data analysis, biochemical parameters were compared between patients with a serum TSH level of 5.6 mIU/L or lower and those with a serum TSH level exceeding 5.6 mIU/L (our upper normal TSH level). The patients were classified into different subgroups on the basis of their congenital malformations including atrial septal defect (ASD), ventricular septal defect (VSD), partial or complete atrioventricular septal defect (AVSD), coarctation of the aorta (CoAo), pulmonary stenosis (PS), tetralogy of Fallot (TF), and dextro- or levo-transposition of the great arteries (TGA). Two additional subgroups were created corresponding to GUCHD patients with cyanosis and GUCHD patients with Down syndrome.

Patients were identified as cyanotic if their hemoglobin oxygen saturation was 93 % or less. Oxygen hemoglobin saturation was measured with a digital oximeter (Model 512 Handheld Pulse Oximeter; Novametrix Medical Systems Inc., Wallingford, CT, USA).

Quantitative variables were expressed as mean ± standard deviation or median and quartiles (5; 95). Qualitative variables were expressed as percentages. Possible associations between categorical variables were evaluated using the Pearson chi-square test or Student's *t* test for continuous data. The nonparametric Mann-Whitney U test was used to compare two independent samples when the assumption of normality or homogeneity of variance was not met.

Serum TSH concentrations in the different subgroups of congenital heart diseases were evaluated using a univariate general lineal model adjusted for a p value level of 0.05 and the Bonferroni correction. Binary logistic regression multivariate analysis was performed to compare the TSH

dichotomous variable (concentrations of ≤5.6 and >5.6 mIU/L) with those independent variables that had a p value inferior to 0.10 in the univariate analysis (Table 1). Age also was included in the multivariate analysis, although its p value was 0.204. The results were expressed as odds ratios (ORs) with their 95 % confidence intervals (CIs). Data analysis was carried out using SPSS 15.0 (SPSS, Chicago, IL, USA).

Results

Between September 2008 and July 2011, 249 GUCHD patients were consecutively evaluated in the Adolescent and Adult Congenital Heart Disease Unit of the Complejo Hospitalario Universitario Insular-Materno Infantil of Gran Canaria.

Table 2 shows the different types of congenital abnormalities and the number and type of congenital abnormalities that had associated cyanosis or Down syndrome. Five cyanotic patients (20 %) had a basal hemoglobin oxygen saturation of 91 and 93 %, and the remaining cyanotic GUCHD patients had basal hemoglobin oxygen saturation levels below 90 %. No patient was receiving amiodarone or thyroid treatment.

Table 3 shows the demographic data and the TSH concentrations for the different types of congenital heart abnormalities, patients with cyanosis, and patients with the Down syndrome. No significant differences were seen between the TSH concentrations and the different types of congenital heart diseases except for AVSD, which differed significantly from the remaining congenital heart diseases ($p < 0.05$) except for ASD.

Table 1 summarizes the demographic data and laboratory test results for the GUCHD patients with serum TSH levels of 5.6 mIU/L or lower and those with levels exceeding 5.6 mIU/L. Whereas 24 GUCHD patients (9.6 %) had TSH concentrations higher than 5.6 mUI/L, 5 GUCHD patients (2 %) had TSH levels above 10 mUI/L (3 patients with the Down syndrome including 1 patient with associated cyanosis), and 2 patients had cyanosis (including 1 patient with the Down syndrome).

Cyanotic and Down syndrome groups had a significantly higher percentage of patients with a TSH concentration above 5.6 mIU/L ($p < 0.001$). Similarly, higher serum concentrations of NT-pro-BNP ($p = 0.001$) and CRP ($p = 0.011$) were found in those patients with TSH levels higher than 5.6 mIU/L. No significant differences were found in serum creatinine, lipid levels, or 24-h proteinuria between the two groups. Concentrations of T4 in the patients with a TSH higher than 5.6 mUI/L was of 0.86 ± 0.22 ng/dL, whereas in the five patients with a TSH higher than 10 mUI/L, the T4 levels were 0.90 ± 0.23 ng/dL.

Table 1 Demographic data and laboratory test results from grown-up congenital heart disease (GUCHD) patients with TSH levels of 5.6 mIU/L or lower and those with levels higher than 5.6 mIU/L

	TSH ≤5.6 mIU/L (225)	TSH >5.6 mIU/L (24)	p value
Age (years)	25.6 (17.4; 61.2)	29.5 (17.6; 64.6)	0.204
Gender (male)	142 (63.1)	13 (54.1)	0.098
Height (cm)	168.7 ± 11.9	164.1 ± 13.3	0.099
Weight (kg)	69.3 ± 17.	74.8 ± 23.2	0.192
Down syndrome	11 (4.9)	7 (29.1)[a]	<0.000
Cyanosis	16 (7.1)	9 (37.5)[b]	<0.000
Creatinine (mg/dL)	1.0 (0.7; 1.3)	1.0 (0.8; 1.7)	0.180
Total cholesterol (mg/dL)	164.2 ± 36.0	172.9 ± 47.1	0.391
LDL cholesterol (mg/dL)	96.9 ± 30.1	98.4 ± 30.0	0.816
HDL cholesterol (mg/dL)	48.9 ± 11.6	49.3 ± 7.9	0.673
Triglycerides (mg/dL)	84.0 (43.0; 191.2)	97.0 (39.2; 315.2)	0.113
TSH (mIU/L)	2.04 (0.73; 4.2)	6.85 (5.7; 29.5)	0.000
CRP (mg/dL)	0.16 (0.00; 1.40)	0.30 (0.06; 1.87)	0.011
NT-pro-BNP (pg/mL)	57.6 (0.00; 929.8)	195.1 (0.28; 5280.3)	0.001
Proteinuria (g/24 h)	0.08 (0.04; 0.36)	0.07 (0.03; 3.83)	0.833

Quantitative variables are expressed as mean ± standard deviation or median and quartiles (5; 95); qualitative variables are expressed as percentages of total LDL, HDL, TSH, CRP, NT-pro-BNP

LDL low-density lipoprotein, *HDL* high-density lipoprotein, *CRP* C-reactive protein, *NT-pro-BNP* N-terminal pro-brain natriuretic peptide

[a] Three GUCHD patients with Down syndrome (one with associated cyanosis) had a TSH level higher than 10 mIU/L

[b] Two GUCHD patients with cyanosis (one with Down syndrome) had a TSH level higher than 10 mIU/L

Table 2 Type and number of congenital heart disease, cyanosis, and Down syndrome in the grown-up congenital heart disease (GUCHD) patients

Type of congenital malformations	*n* (%)	Cyanosis	Down syndrome
VSD	41 (16)	5	5[a]
Atrial septal defect	24 (9.6)	1	1
Coarctation of the aorta	23 (9.2)	0	0
Tetralogy of Fallot	19 (7.6)	0	0
Pulmonary stenosis	19 (7.6)	0	0
Atrioventricular septal defect	18 (7.2)	3	11[b]
Transposition of the great arteries	16 (6.4)	4	0
Bicuspid aortic valve	12 (4.8)	0	0
Aortic stenosis	11 (4.4)	0	0
Double-outlet right ventricle	7 (2.8)	4	0
Univentricular heart	6 (2.)	4	0
Pulmonary atresia	5 (2)	3	0
Ebstein anomaly	4 (1.6)	1	0
Ductus	4 (1.6)	0	0
Other types of cardiopathies	40 (16)	0	1
Total	249 (100)	25	18

n number of patients

[a] Two Down syndrome patients with VSD had cyanosis

[b] Three Down syndrome patients with AVSD had cyanosis. The patients with AVSD included 12 patients with partial and six patients with complete defect. The patients with transposition of the great arteries included eight patients with dextro- transposition and eight patients with levo-transposition of the great arteries

Table 3 Demographic data and TSH levels in the different types of congenital heart abnormalities[a]

Patients (*n*)	Age (years)	Males *n* (%)	TSH (mIU/L)
Total congenital (249)	31.3 (30.0–32.6)	149 (60)	2.89 (2.52–3.27)
VSD (41)	27.7 (25.1–30.3)	27 (66)	2.95 (2.06–3.83)
ASD (24)	38.1 (32.4–43.8)	8 (33)	3.25 (0.50–6.01)
CoAo (23)	31.7 (26.5–368)	16 (70)	2.68 (2.02–2.35)
ToF (19)	31.3 (27.4–35.2)	12 (63)	2.24 (1.81–2.67)
PS (19)	31.8 (26.5–37.0)	14 (74)	1.79 (1.35–2.10)
ASVD (18)	28.8 (23.0–34.7)	6 (33)	6.01 (4.06–7.96)
TGA (16)	32.8 (23.9–41.8)	12 (75)	2.74 (1.78–3.70)
Cyanotic (25)	34.6 (29.8–39.3)	15 (60)	5.93 (3.93–7.92)
Down syndrome (18)	28.4 (23.3–33.5)	8 (44)	6.59 (4.01–9.17)

n number of patients

VSD ventricular septal defect, *ASD* atrial septal defect, *CoAo* coarctation of the aorta, *ToF* tetralogy of Fallot, *PS* pulmonary stenosis, *AVSD* atrioventricular septal defect, *TGA* transposition of the great arteries

[a] TSH and age values correspond to the mean and 95 % confidence interval

In the multivariate analysis, cyanosis (OR, 6,399; 95 % CI, 2,296–17,830; $p < 0.001$), Down syndrome (OR, 6,208; 95 % CI, 1,963–19,636; $p = 0.002$), and NT-pro-BNP concentrations (OR, 1,001; 95 % CI, 1,000–1,002; $p < 0.026$] proved to be risk factors for a TSH level higher than 5.6 mIU/L, whereas age, gender, and PCR concentration did not.

Discussion

Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3–8 % in the population without known thyroid disease and increasing with age and in women [12, 14]. In our series, the percentage of patients with SCH was higher than the prevalence reported in previous studies, reaching 9.6 % of our GUCHD patients and without existing differences between the sexes.

Different etiologies have been shown to cause hypothyroidism such as inflammation, proteinuria, and autoimmune diseases [7]. Tuzcu et al. [30] reported that high-sensitivity CRP levels were higher in patients with SCH than in control subjects, indicating that a low-grade inflammation might be related to altered TSH concentrations. However, other authors have failed to find a relationship between CRP levels and SCH [13].

In relation to proteinuria, a relatively frequent finding in cyanotic GUCHD patients [18], it is known that urinary excretion of thyroid hormones may lead to low serum levels of free thyroid hormones unless their production is increased under the influence of TSH [10, 21]. However, we found no significant differences in 24-h proteinuria between GUCHD patients with TSH concentrations of 5.6 mIU/L or lower and GUCHD patients with TSH levels higher than 5.6 mIU/L.

Regarding autoimmunity, the susceptibility of the thyroid to autoimmune thyroid diseases may result from the complexity of hormonal synthesis, peculiar oligoelement requirements, specific capabilities of the thyroid cell's defense system, and the loss of immunologic tolerance for

self-antigens [26]. Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis or chronic lymphocytic thyroiditis, is by far the most frequent autoimmune disease affecting Down syndrome patients [4] and the most common cause of primary hypothyroidism in the normal population. Hashimoto's thyroiditis is related to the presence of antithyroid peroxidase antibodies (TPO-Ab), which work against thyroid peroxidase, an enzyme that plays a part in the T4-to-T3 conversion and synthesis process. The fact that the most frequent congenital heart disease in Down syndrome patients is AVSD [5] explains that AVSD patients had higher TSH concentrations than patients with the remaining congenital heart abnormalities.

In relation to adverse cardiac outcomes, a recently published large metaanalysis of 11 prospective cohort studies showed that SCH was associated with an increased risk of cardiovascular events and coronary heart disease mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater [24]. On the contrary, a Cochrane review regarding the effect of T4 replacement therapy in SCH based on randomized clinical studies could not demonstrate consistent evidence of reduced cardiovascular morbidity, improved quality of life, or a reduction of symptoms in the treated groups [31]. However, mildly altered thyroid function has been strongly associated with a poor prognosis and an increase in the hospitalization rates [27] of patients with heart failure [8, 23], contributing to a progressive activation of the hormonal and immunologic systems [9, 17] and inducing remarkable changes in the heart function and structure [29, 32]. This is particularly relevant for GUCHD cyanotic patients because they usually have the poorest exercise capacity [28] and the worst systemic ventricular function [2].

Also, hypercholesterolemia has been associated as a risk factor for coronary events. Alterations of serum cholesterol in SCH is characterized by an increase in the serum cholesterol levels that runs parallel to an increase in serum TSH concentrations [3]. A possible mechanism that attempts to explain this finding is a decrease in fractional LDL clearance due to the small number of hepatic LDL receptors [6] and their reduced activity seen in SCH patients.

Although we earlier reported lower serum total cholesterol and LDL cholesterol concentrations in GUCHD patients than in patients randomized from a general population [19], the current study failed to find significant differences in total or LDL cholesterol levels between GUCHD patients with serum TSH levels of 5.6 mIU/L or lower and GUCHD patients with TSH concentrations higher than 5.6 mIU/L. Similarly, Meier et al. [20] reported that although high serum lipids levels were found in patients with mild thyroid failure as a group, the results could not be extended to most patients with SCH and TSH levels between 5 and 10 mIU/L, as seen in most of our patients.

Measurement of serum TSH and T4 is the cornerstone in monitoring SCH. However, the initial diagnosis of SCH should be confirmed 8 to 12 weeks later due to the considerable circadian rhythm and the small seasonal variation in TSH secretion [1] by the measurement of TSH, T4, and TPO-Ab. If positive, thyroid function should be evaluated every 6 months during the first 2 years and every year after the two initial years. If normal, no further evaluation is needed. If TSH, T4, and TPO-Ab levels become normal, control conditions can be stopped after 3 years because they are necessary only if the patient gets pregnant or experiences hypothyroid symptoms [15].

Although available data are considered insufficient and uncertain to support a benefit for levothyroxine therapy in patients with SCH, particularly for the group with TSH less than 10 mIU/L [16], the higher rate of progression to clinically overt hypothyroidism and the possibility that SCH is a cardiovascular risk factor should alert us. Congenital heart disease patients with cyanosis or Down syndrome should be closely followed up with TSH screening because their congenital abnormalities make their hearts more vulnerable. Meanwhile, therapy for this group of patients should be individualized by taking into account patients' symptoms, age, lipid concentrations, NT-pro-BNP levels and associated medical conditions such as ventricular dysfunction or heart failure.

Despite our awareness of the study's limitations (e.g., antithyroid peroxidase antibodies were not measured, and SCH was diagnosed on the basis of a single TSH determination), we postulate that TSH screening should be included in the routine follow-up assessment of GUCHD patients with cyanosis or Down syndrome.

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