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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Subclinical hypothyroidism: A common finding in adult patients with cyanotic congenital heart disease

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Abstract

Objective: Cyanotic congenital heart disease is a systemic disease, with effects on multiple organ systems. A high prevalence of subclinical hypothyroidism (SCH) has been reported in a small cohort of cyanotic congenital heart disease patients. Subclinical hypothyroidism has been associated with various adverse cardiovascular effects, as well as an increased risk of progression to overt hypothyroidism. The aim of this study was to examine the prevalence of SCH in cyanotic congenital heart disease patients, consider possible etiologies, and evaluate thyroid function over time.

Methods: First, 90 clinically stable cyanotic congenital heart disease patients were examined with blood samples (thyroid-stimulating hormone, C-reactive protein, hemoglobin, hematocrit, and N-terminal pro-brain-natriuretic peptide) in a cross-sectional descriptive study. Second, a longitudinal follow-up study of 43 patients originating from the first study part, was carried out. These patients had thyroid function parameters (thyroid-stimulating hormone, thyroid hormones, and thyroid peroxidase antibodies) evaluated biannually.

Results: Elevated thyroid-stimulating hormone was present in 24% of the 90 screened patients. During follow-up (6.5 ± 1.0 years), SCH (defined as ≥2 consecutive elevated thyroid-stimulating hormone values) was present in 26%. Three patients progressed to overt hypothyroidism. Patients with SCH were younger (34 ± 12 vs 42 ± 16 years; $P = .01$) and had a lower oxygen saturation (80 ± 5 vs 84 ± 6%; $P = .03$).

Conclusion: Subclinical hypothyroidism is a very common finding in cyanotic congenital heart disease. This is not associated with increased levels of C-reactive protein, heart failure, or autoimmunity but appears to be associated with cyanosis and age. Since the clinical impact of SCH is uncertain, further studies are needed to determine this. Regular thyroid evaluation is recommended in cyanotic congenital heart disease patients since SCH can develop to overt hypothyroidism.

KEYWORDS

cyanosis, cyanotic congenital heart disease, subclinical hypothyroidism, thyroid-stimulating hormone

1 | INTRODUCTION

Cyanotic congenital heart disease (CCHD) is a multisystem disease with effects on several organ systems due to chronic hypoxemia. Typical findings include secondary erythrocytosis, impaired hemostasis, decreased renal function, cholelithiasis and hypertrophic osteoarthropathy.[1] Despite knowledge about multiorgan impairment little is known about thyroid function in CCHD patients, although Martinez-Quintana et al have reported a high prevalence of subclinical hypothyroidism (SCH) in 24 CCHD patients.[2]

Subclinical hypothyroidism has a prevalence of up to 10% in the general population and is regarded as a mild thyroid failure. It can

hence be interpreted as part of a continuum between an euthyroid state and overt hypothyroidism.[3] SCH is defined as at least two consecutive measurements of elevated thyroid-stimulating hormone (TSH), with thyroid hormones within the normal range. Furthermore, SCH represents an increased risk of progression to overt hypothyroidism in the general population.[3,4]

SCH has clinically been associated with various adverse cardiovascular effects in noncongenital heart disease patients such as increased systemic vascular resistance, heart failure, and increased cardiac mortality.[3–7] Thus, thyroid impairment may add an additional risk to marginal CCHD patients.

The aims of this study were to examine the prevalence of elevated TSH/SCH in a large cohort of CCHD patients, describe the course of SCH over time, as well as examine possible etiologies for an increased prevalence of SCH in CCHD patients compared to the general population.

2 | METHODS

2.1 | Study design

This was a single-center study divided into two parts. The first part (known as Study Part One) was a cross-sectional descriptive study, aiming to determine the overall prevalence of elevated TSH in a large cohort of CCHD patients. TSH elevation was used as an initial screening for SCH in CCHD patients, as Martinez-Quintana et al did in their study. The second part (Study Part Two) was a prospective longitudinal follow-up study in order to confirm the diagnosis of SCH, evaluate thyroid function over time, and examine possible etiologies.

2.2 | Patients

Between 2007 and 2013, all clinically stable adults with CCHD seen at Rigshospitalet, Copenhagen, Denmark, were assessed for inclusion in the study. "Clinically stable" was defined as no hospital admissions or change in medication during the last 3 months before inclusion. CCHD was defined according to Broberg's definition as the presence of a congenital heart defect causing bidirectional or right-to-left shunt with a systemic oxygen saturation at rest of <92% and/or <87% during exercise.[8]

Congenital heart defects were defined as "simple": ventricular septal defect, atrial septal defects and persistent ductus arteriosus, or "complex" congenital heart defects: any defect of greater complexity (univentricular heart, tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries, etc.).

Exclusion criteria were previous thyroid disease or treatment with thyroid altering medicine (amiodarone, levothyroxine, or thiamazol) (Figure 1). Only patients followed biannually with clinical visits and blood samples in the outpatient clinic at Rigshospitalet were included in Study Part Two. At each visit the patients had blood samples taken and were examined with a 6-minute walk test as well as a transcutaneous oxygen saturation measurement after 5 minutes of rest and during/after the 6-minute walk test.

2.3 | Blood samples

Blood samples was drawn from an antecubital vein into Vacutainer tubes containing EDTA for the whole blood count, heparin for the C-reactive peptide (CRP), TSH and thyroid hormones, and clot activator for the thyroid peroxidase antibodies (Anti-TPO). The blood samples in Study Part One included TSH, CRP, hemoglobin (Hgb), N-terminal pro-brain natriuretic peptide (NT-proBNP), and hematocrit (Hct).

The blood samples in Study Part Two included TSH, thyroxine (T4), triiodthyronine (T3), free T4 (fT4), free T3 (fT3), anti-TPO, CRP, NT-proBNP, Hgb, and Hct.

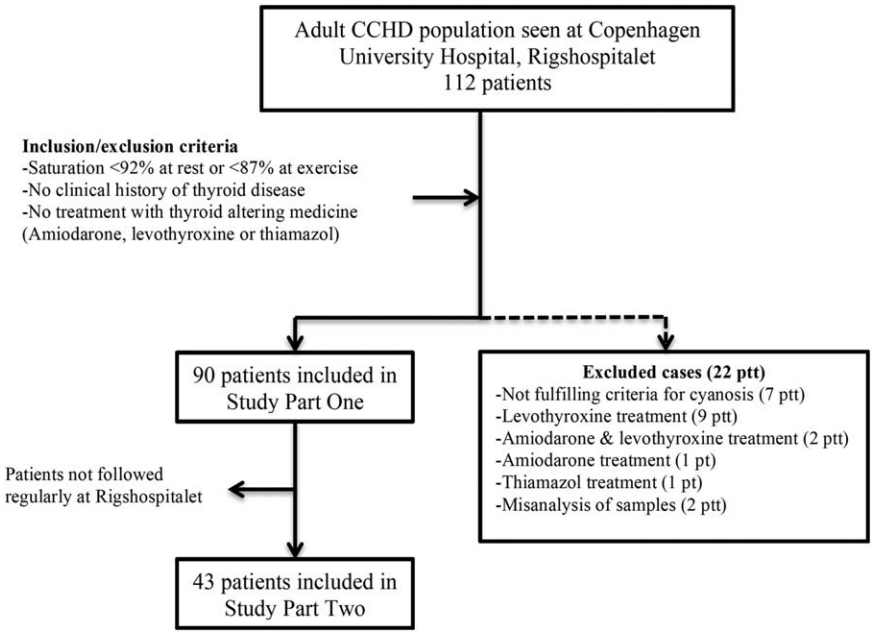

FIGURE 1 Cohort flowchart of adult CCHD population

All samples were analyzed at the institutional laboratory of Rigshospitalet, Copenhagen, Denmark, according to their standards, using commercially available assays. TSH, T3, fT3, T4, and fT4 were analyzed on the Modular E-module with an electrochemiluminescens-immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Anti-TPO was analyzed on the B.R.A.H.M.S. kryptor (B.R.A.H.M.S., GmbH, Hennigsdorf, Germany), CRP was analyzed on the Modular P-module (Roche Diagnostics GmbH), Hgb and Hct were analyzed on the Sysmex XE-2100 system (Sysmex Europe GmbH, Norderstedt, Germany). NT-proBNP was analysed on the Cobas 8000, e602 module (Roche Diagnostics GmbH).

2.4 | Study Part One—TSH

An initial screening of elevated TSH in a large cohort of CCHD patients, including patients not seen regularly at Rigshospitalet, was deemed appropriate. A TSH elevation was defined as a concentration above 4.5 mU/L, independently of age and gender, according to local laboratory guidelines.

2.5 | Study Part Two—SCH

The CCHD patients who were followed biannually with blood samples in the outpatient clinic at Rigshospitalet were monitored according to their thyroid function. SCH was based on the first three blood samples taken after inclusion and was defined as at least two consecutive blood samples with elevated TSH ($4.5 < \text{TSH} < 10$ mU/L) in the presence of thyroid hormones within their normal ranges (T4 70–140 nmol/L; T3 1.4–2.8 nmol/L; fT4 14–23 pmol/L; fT3 4.1–6.9 pmol/L). Patients were considered positive for anti-TPO with values $>60 \times 10^3$ U/L. Overt hypothyroidism was defined as TSH >10 mU/L and decreased thyroid hormones.

2.6 | Statistical analysis

Categorical variables were compared by a chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using Student's *t* test for unpaired observations. 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. Correlations between variables were analyzed using linear regression and Pearson's coefficient of correlation (*r*). All statistical analyses were conducted with IBM SPSS version 23.0. All tests were two-sided, and differences were considered significant with a *P* value less than .05.

2.7 | Ethics

The study was conducted according to the most recent amendments to the Declaration of Helsinki and in adherence to good clinical practice. The study was part of a descriptive study examining the prevalence of thrombosis in CCHD. The Danish Ethical Committee approved the protocol, and written informed consent was obtained from all patients.

3 | RESULTS

A total of 112 patients were assessed for inclusion. Of these, 22 were excluded (Figure 1). The number of patients included in Study Part One was therefore 90 patients, with a slightly over-representation of female patients (54%). Twenty-four percent of these patients had elevated TSH. None of the included patients had had recent cardiac/noncardiac surgery done (defined as surgery within the last 12 months before inclusion), and no genetic disorders were present beside Down syndrome and DiGeorge (Tables 1 and 2).

Study Part Two consisted of 43 patients (Figure 1). At the initial examination, the mean age was 40 years (18–77 years) and the mean follow-up period was 6.5 years (interquartile range 6.0–7.5 years). Twenty-six percent of the patients had SCH, and 36% of those were positive for anti-TPO (Table 3). Of the patients with SCH ($n = 11$), two patients normalized over time and three patients (27%)—one Down syndrome patient and two anti-TPO positive—progressed to overt hypothyroidism. The persistency of SCH was 55%, and 16% of the initially euthyroid patients developed SCH during follow-up (Figures 2 and 3).

The patients with SCH were younger, and had a lower oxygen saturation (80% [73;86] vs 84% [72;93], $P = .03$). There was no difference in gender, presence of Down syndrome, complex vs simple heart disease, anti-TPO or NT-proBNP (Table 3). Correlating individual values of Hct and Hgb with their corresponding values of TSH, fT3, and fT4, showed a correlation coefficient of $r = 0.24$ (Pearson's *r*, $P < .05$) for TSH, a correlation coefficient of $r = -0.11$ (Pearson's *r*, $P < .05$) for fT3 and $r = -0.16$ (Pearson's *r*, $P < .05$) for fT4. NT-proBNP and TSH had a correlation coefficient of $r = -0.05$ (Pearson's *r*, $P = .64$) and a linear regression of TSH and NT-proBNP revealed no coherency.

4 | DISCUSSION

4.1 | Prevalence of elevated TSH and SCH

This study showed a prevalence of elevated TSH of 24% in the baseline cohort, which corresponds well with the findings of Martinez-Quintana et al.[2] According to current guidelines regarding the diagnosis of SCH, an initial elevated TSH should be reassessed after 3–6 months to rule out a transient increase or laboratory error, before SCH can be diagnosed.[3] However, most studies evaluating the prevalence of SCH have made the diagnosis by only a single measurement of TSH, including the study of Martinez-Quintana et al.[2,9]

In our study, the diagnosis of SCH was ascertained by the follow-up study, which showed that 26% of the cohort had persistent TSH elevation with thyroid hormones in normal range. The prevalence of SCH in our cohort of CCHD patients is markedly increased compared to an observed prevalence of up to 10% in the general population.[4]

4.2 | Course of SCH in follow-up

During a mean follow-up of 6.5 years, the persistence of SCH in this study was 55%, and three patients (27%) progressed to overt

TABLE 1 Baseline demographic and clinical characteristics of the 90 CCHD patients participating in Study Part One

	Study population (n = 90)	Reference
Age (years), mean ± SD	40 ± 15	
Female gender, *n* (%)	49 (54)	
Transcutaneous oxygen saturation at rest, % (range)	83 (66–94)	
Transcutaneous oxygen saturation at exercise, % (range)	68 (40–88)[a]	
6-Minute walk test distance, m (range)	400 [184;566][b]	
Cardiac surgery, *n* (%)	16 (17.8)	
Diagnoses		
Simple heart defects, *n* (%)	60 (66.7)	
• Simple heart defect with Eisenmenger's syndrome, *n*	57	
• Ventricular septal defect, *n* (%)	37 (41.1)	
• Atrial septal defect, *n* (%)	16 (17.8)	
• Atrioventricular septal defect, *n* (%)	4 (4.4)	
• Aortopulmonary window, *n* (%)	1 (1.1)	
• Persistent ductus arteriosus, *n* (%)	2 (2.2)	
Complex heart defects, *n* (%)	30 (33.3)	
• Complex heart defect with Eisenmenger's syndrome, *n*	5	
• Univentricular heart, *n* (%)	16 (15.6)	
• Hemitruncus, *n* (%)	2 (2.2)	
• Pulmonary atresia, ventricular septal defect, and major aortopulmonary collateral arteries, *n* (%)	9 (10)	
• Pulmonary arteriovenous malformation, *n* (%)	2 (2.2)	
• Ebstein malformation with atrial septal defect, *n* (%)	1 (1.1)	
Genetic disorders		
• Down syndrome, *n* (%)	10 (11)	
• DiGeorge syndrome, *n* (%)	5 (5.5)	
Blood samples		
Thyroid-stimulating hormone (mU/L)	2.5 [1.0;7.4]	0.35-4.50
C-reactive protein (mg/L)	2 [1;22][c]	<10
Hemoglobin (g/dL)	18.7 ± 2.7	11.8–16.9
Hematocrit (%)	56 ± 9	35–50
NT-proBNP (pmol/L)	45 [7;724][d]	<45

Quantitative variables are expressed as mean ± standard deviation or median and quartiles [5;95], and qualitative variables are expressed as percentages of total.
[a]Data missing in 12 patients.
[b]Data missing in 14 patients.
[c]Data missing in 16 patients.
[d]Data missing in three patients.

hypothyroidism (Figures 2 and 3). In comparison, other studies have reported similar persistencies of SCH of 68% and 56% over mean follow-up periods of 9.2 and 4 years, respectively.[10,11]

Three female patients (two anti-TPO positive and one with Down syndrome) progressed to overt hypothyroidism after 1.5, 4, and 5 years of diagnosis of SCH, respectively. This corresponds with a reported annual rate of progression in women with raised serum TSH of 3%, and 4% if also positive for antithyroid antibodies. Thus, it seems the patients with SCH in our cohort follow the same rate of progression to overt hypothyroidism as in the general population, with female gender, positive anti-TPO status, TSH values >10 mU/L and Down syndrome being independent risk factors.[9,12–14] Nevertheless it is worth noting that 10% of the patients assessed for inclusion were already excluded due to preexisting overt hypothyroidism—a significantly higher percentage than in other population based studies (Figure 1).[14,15]

4.3 | Laboratory analytical problem: hemoconcentration

Considering the high Hct of CCHD patients, a concern of this study was that hemoconcentration could cause falsely high concentrations of TSH due to a relatively low plasma volume in the sample. To address this issue, values of TSH and thyroid hormones were correlated with their corresponding levels of Hct/Hgb, yielding only a weak correlation for TSH and no correlation for thyroid hormones. The high prevalence observed in this study was therefore not interpreted to be due to hemoconcentration.

4.4 | Autoimmunity

A decreased secretion of thyroid hormones with TSH elevation/SCH is often associated with autoimmune disease. In non-CCHD patients,

TABLE 2 Study Part One: demographic data, relevant clinical characteristics and blood sample test results in subjects with elevated TSH and with TSH within normal range

	TSH ≤4.50 mU/L (*n* = 68)	TSH >4.50 mU/L (*n* = 22)
Age (years)	43 ± 16	33 ± 11
Female gender, *n* (%)	35 (51)	14 (64)
Down syndrome, *n* (%)	7 (10)	3 (14)
DiGeorge syndrome, *n* (%)	2 (3)	3 (14)
Complex heart disease, *n* (%)	18 (27)	12 (55)
Oxygen saturation at rest, % (range)	84 [71;93]	82 [74;92]
6-Minute walk test distance (m)	390 [190;535][a]	437 [150;574][b]
Hemoglobin (g/dL)	18.5 ± 2.9	19.2 ± 2.3
Hematocrit (%)	55 ± 9	57 ± 8
Thyroid-stimulating hormone (mU/L)	2.3 [1.0;4.2]	5.4 [4.5;11.3]
C-reactive protein (mg/L)	2 [1; 19][c]	2,5 [1;38][b]
NT-proBNP (pmol/L)	45 [6;724]	48 [9;1046][d]

Quantitative variables are expressed as mean ± standard deviation or median and quartiles [5;95] and compared with nonparametric Mann-Whitney *U* test or Student's *t* test. Qualitative variables are expressed as percentages of total and compared with chi-square or Fisher's exact test.
[a]Data missing in nine patients.
[b]Data missing in six patients.
[c]Data missing in 10 patients.
[d]Data missing in two patients.

60%-80% of SCH cases are associated with markedly elevated thyroid peroxidase antibodies (anti-TPO).[3] This autoimmune etiology may explain why SCH is more prevalent in both women and Down syndrome patients.[12,13] In this study, despite an overrepresentation of both females and Down syndrome patients, anti-TPO was only associated with 36% of the cases with SCH. There was no difference in anti-TPO status between the two groups with SCH and non-SCH (Table 3).

4.5 | Low-grade inflammation

SCH can result from a persistent TSH increase after an episode of thyroiditis, and Kvetny et al have shown SCH to be associated with increased CRP and low-grade inflammation.[16] In our study, there was no significant difference in the mean values of CRP in the group of patients with TSH within normal range and those patients with elevated TSH (Table 2). Since no association with increased levels of CRP was found, low-grade inflammation of the thyroid gland or persistent TSH elevation after an episode of thyroiditis was therefore not considered a plausible etiology for the high prevalence of SCH observed in our study.

4.6 | Chronic hypoxemia

The degree of cyanosis observed at examination was shown to be associated with SCH. Similar findings have been reported in an animal

TABLE 3 Anti-TPO status, relevant clinical characteristics, and demographic data in patients from Study Part Two

	TSH ≤4.50 mU/L (*n* = 32)	TSH >4.50 mU/L (*n* = 11)	*P* value
Age (years)	43 ± 14	33 ± 11	.027
Female gender, *n* (%)	19 (59)	7 (64)	.803
Down syndrome, *n* (%)	7 (22)	2 (18)	.795
DiGeorge syndrome, *n* (%)	1 (3)	2 (18)	.156
Complex heart disease, *n* (%)	5 (16)	5 (45)	.092
Anti-TPO positive, *n* (%)	3 (9)[a]	4 (36)[b]	.103
Saturation at rest (%)	84 [73;93]	80 [73;86]	.031
NT-proBNP (pmol/L)	34 [6;431]	25 [9;267]	.656

Quantitative variables are expressed as mean ± standard deviation or median and quartiles [5;95] and compared with nonparametric Mann-Whitney *U* test or Student's *t* test. Qualitative variables are expressed as percentages of total and compared with chi-square or Fisher's exact test.
[a]Data missing from three patients.
[b]Data missing from one patient.

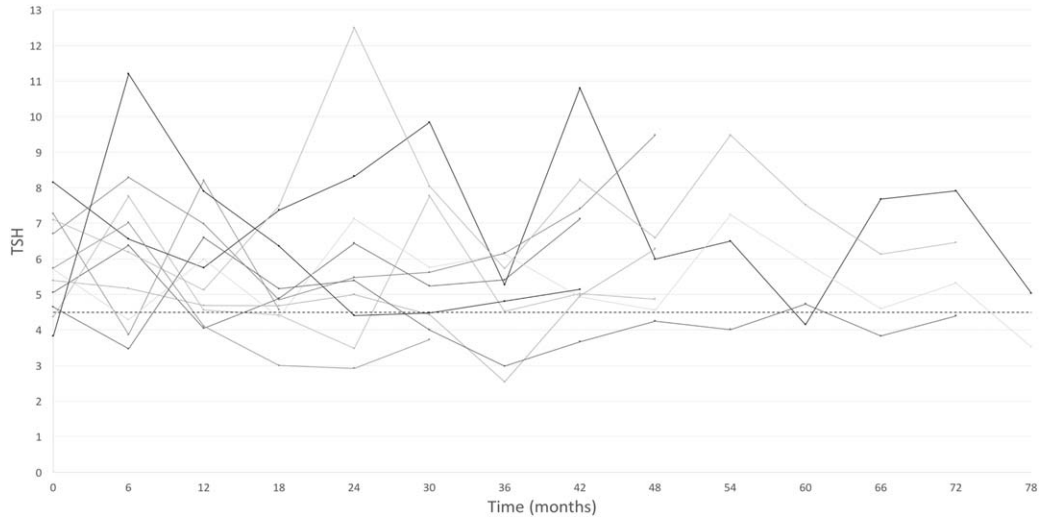

FIGURE 2 Study Part Two: Spaghetti plot showing values of individual TSH values over time for the patients with SCH. Dashed line represents the cutoff value of TSH for SCH

study from 1972, where hypoxemia decreased thyroid function in rats.[17] Hypoxia of the thyroid gland could therefore be a plausible explanation of the high prevalence of SCH in CCHD.

4.7 | Heart failure and SCH

Thyroid dysfunction is a common finding in patients with heart failure.[7,18,19] NT-proBNP and 6-minute walk test distance were used as clinical surrogate-markers of cardiac function during the follow-up, besides regular clinical evaluation. There was no difference in mean NT-proBNP or 6-minute walking distance between the patients with or without SCH, and no correlation was found between TSH and NT-proBNP.

It seems therefore unlikely that heart failure alone could explain the high prevalence of SCH in CCHD.

4.8 | Chronic disease and nonthyroidal illness syndrome

A small study by Moshang et al indicated CCHD to be associated with an altered peripheral metabolism of thyroid hormones, a phenomenon also seen in nonthyroidal illness syndrome.[20] Nonthyroidal illness syndrome is often observed in hospitalized patients and in critical illness, but is also seen in chronic disease.[21] The hallmark of nonthyroidal illness syndrome is a low T3 and a paradoxically normal TSH, although TSH can be elevated in some cases.[21,22] Given the chronic illness of CCHD patients, nonthyroidal illness syndrome could be a factor for the high prevalence of elevated TSH observed. However, the prerequisite for this syndrome is low levels of thyroid hormones and, in the present study, all the patients with persistent TSH elevation had thyroid hormones within normal range.

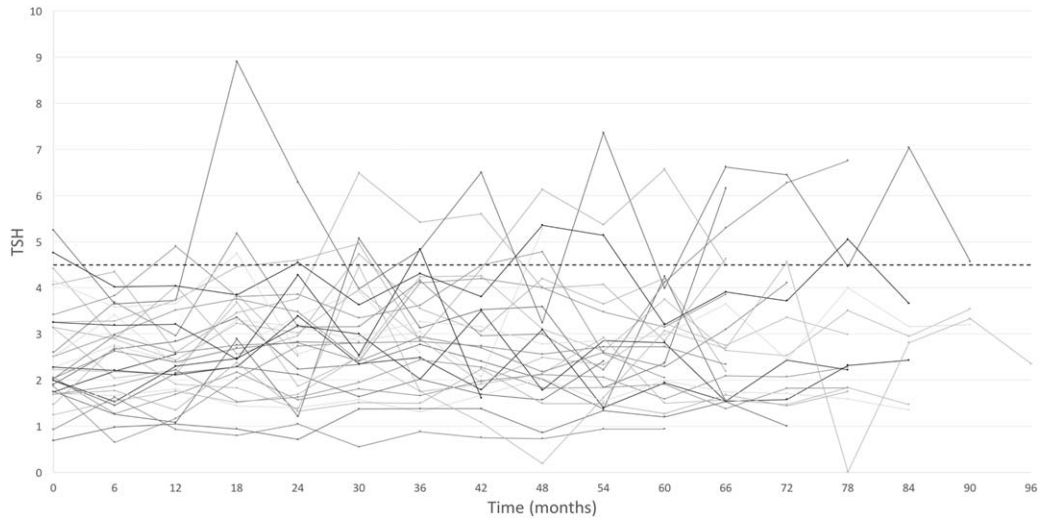

FIGURE 3 Study Part Two: Spaghetti plot showing individual values of TSH values over time for the patients with normal TSH. Dashed line represents the cutoff value of TSH for SCH

4.9 | SCH is more common in the younger CCHD patients

The prevalence of SCH increases with increasing age in the normal population, but this does not seem to be the case in CCHD. The patients with SCH in this study were significantly younger than subjects with normal TSH (Table 3). A possible explanation could be the introduction of national iodine supplementation in Denmark from 1998. The younger patients in this cohort have hence been iodine-replete most of their life, compared with the older patients. Iodine-repletion is shown to cause a higher prevalence of subclinical and overt hypothyroidism, particularly in young women.[23,24]

Another possible explanation relates to the patients with complex heart disease being younger and more cyanotic. Lower oxygen saturation was shown to be associated with elevated TSH and SCH, why this might explain the association of SCH with lower age. Though due to the limited sample size, this was not possible to show in this study, why this remains speculative.

5 | LIMITATIONS

Due to geographical limitations and the fact that some patients were followed up elsewhere, not all patients were available for ongoing evaluation of thyroid function, which would have been desirable and strengthened our work. Regarding low-grade inflammation, although we did not find any difference in CRP levels between patients with elevated and normal TSH, a measurement of high-sensitivity CRP might have shown a difference. Finally, thyroid gland imaging and radioiodine uptake were not conducted to assess composition and vitality of thyroid gland tissue but could possibly have contributed to a clarification of possible etiologies.

6 | CONCLUSION

Patients with CCHD have a high prevalence of SCH compared to the general population, which we confirmed in our patient cohort. In the present study the high prevalence was not associated with autoimmunity, increased CRP or heart failure, but an association with the degree of cyanosis and age was found. Although difficult to extrapolate to CCHD patients in general, this study has provided relevant insight and background for further investigation. Since SCH can progress to overt hypothyroidism, regularly monitoring of the thyroid function in CCHD patients should be considered. Although the cohort of the present study is larger than previous studies of SCH in CCHD, the clinical impact of SCH in CCHD patients is still unknown, why further studies are needed in order to determine this.

CONFLICT OF INTEREST

None.

DISCLOSURE OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Data collection, data analysis/interpretation, statistics, drafting article, approval of article: Bak

Concept/design, data collection, data analysis/interpretation, statistics, critical revision of article, approval of article: Hjortshøj

Data analysis/interpretation, critical revision of article, approval of article: Gæde

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