ORIGINAL ARTICLE

Subclinical hypothyroidism and Down's syndrome; studies on myocardial structure and function

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Background: The management of subclinical hypothyroidism (SH) is still controversial, as the benefit to risk ratio of prolonged L-thyroxine therapy is not clear cut. Some authors have shown abnormalities of myocardial function and structure in adults with SH, which could be reversed by L-thyroxine therapy. As SH frequently affects children with Down's syndrome (DS), and almost one half of these are affected by congenital heart disease, a concomitant SH related impairment of cardiac function might further compromise their clinical condition.
Aims: To establish whether SH influences myocardial structure and function in children with DS.
Methods: Sixteen children with DS and untreated SH and 25 matched euthyroid controls with DS underwent echocardiographic analysis of left ventricular mechanics and tissue characterisation.
Results: None of the 16 patients had myocardial impairment.
Conclusion: Results suggest that children with DS who have SH are not at risk of cardiac disease. Clinicians should consider these data in the management of SH, as the benefit to risk ratio of prolonged L-thyroxine therapy is not clear cut.

Subclinical hypothyroidism (SH) is defined as raised serum thyroid stimulating hormone (TSH) levels associated with normal total or free thyroxine (T4) and triiodothyronine (T3) values. Despite this definition, not all adult subjects with SH are really asymptomatic, sometimes presenting symptoms or signs of hypothyroidism, such as dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramps, cold intolerance, puffy eyes, constipation, and hoarseness.[1] Moreover, some studies in adults showed a correlation between SH and neurobehavioural and neuromuscular abnormalities, increased cardiovascular risk factors (because of increased serum lipid levels), and impairment of myocardial function.[2] McDermott and Ridgway,[2] and Cooper[3] suggested that ''mild hypothyroidism'' may be a more appropriate term for this situation, since SH frequently needs treatment and may progress to overt hypothyroidism. However, others authors suggest that the majority of patients with SH have minimal metabolic and physiological abnormalities and would be unlikely to benefit from L-thyroxine therapy.[4]

The situation is also unclear for children with Down's syndrome (DS), the most frequent cause of genetic mental retardation, in whom an increased prevalence of thyroid disease, particularly of SH, has been reported.[5] A yearly thyroid screening is currently suggested by the American Academy of Paediatrics in the guidelines for the health supervision for children with DS.[6] However, some authors, describing the natural course of SH in DS, concluded that treatment with L-thyroxine is seldom necessary in children with DS,[7 8] as in those of the general population.[9] On the contrary, other investigators suggested that therapy should be encouraged, even in mild cases, because such treatment prevents the development of a more severe hypothyroid state.[10] According to the well known effects of thyroid hormone deficiency on cardiac muscle function, some studies[11 12] showed, in adults with SH, abnormalities of myocardial function and structure, which could be reversed by L-thyroxine therapy. As almost one half of children with DS are affected by congenital heart disease, a possible concomitant, SH related, impairment of cardiac function might worsen their clinical condition and thus influence their life expectancy.

We report the first study of myocardial structure and function in children with DS, aimed at investigating whether SH induces abnormalities of left ventricular (LV) functional and textural properties, and at better defining the need to treat them.

PATIENTS AND METHODS

Study population

From January 1995 to December 2001 we enrolled 330 home reared children with DS, aged 1 month to 19 years (median age 5 years) followed up in our department within a medical care and support programme for individuals with DS. Twenty two patients were excluded because they could not be reviewed regularly and three with cardiac malformations died.

Abbreviations: A, peak of mitral flow velocity at end-diastole; Aa, peak of mitral annular velocity at end-diastole; AbTg, antithyroglobulin antibodies; AbTPO, antiperoxidase antibodies; BSA, body surface area; CVIVS, cyclic variation at interventricular septum; CVPW, cyclic variation at left ventricular posterior wall; DS, Down's syndrome; DT, deceleration time; DTI, Doppler tissue imaging; E, peak of mitral flow velocity at the beginning of diastole; Ea, peak of mitral annular velocity at the beginning of diastole; FS, fractional shortening [(end-diastolic dimension − end-systolic dimension)/end-diastolic dimension]; HR, heart rate; IB, integrated backscatter; INTIVS, averaged intensity at interventricular septum; INTPW, averaged intensity at left ventricular posterior wall; IVRT, isovolumic relaxation time; IVS, interventricular septum; IVSd, end-diastolic interventricular septum thickness; LV, left ventricular; LVEDd, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; PW, posterior wall; PWd, end-diastolic posterior wall thickness; SH, subclinical hypothyroidism; SVI, stress velocity index; σ_{es}, end-systolic meridional wall stress; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; VCFc, rate corrected velocity of circumferential fibre shortening

The remaining 305 patients with DS (157 girls, 148 boys) were followed up for a median of 39 months (range 18–120 months). All patients underwent full clinical examination every 6–12 months by the same paediatrician, who measured height and weight and took a history to establish health status.

A blood sample was obtained for TSH, free T4, free T3, and antithyroglobulin (AbTg) and antiperoxidase (AbTPO) antibodies; all were evaluated using routine immunochemiluminometric assays (Architect, Abbott, USA; Immulite, DPC, UK). The TSH assay had a functional sensitivity $\leqslant 0.01$ mIU/l, an analytical sensitivity $\leqslant 0.0025$ mIU/l, an intra-assay precision of 1.9% at 0.17 mIU/l and 0.9% at 36.1 mIU/l, and an inter-assay precision of 5.1% at 0.17 mIU/l and 2.2% at 36.8 mIU/l. Normal values were: TSH 0.5–4.7 mU/l; free T4 7.0–14.8 pg/ml; free T3 1.7–3.7 pg/ml; AbTg up to 40 IU/ml; AbTPO up to 35 IU/ml.

Participants

The 16 children recruited for the echocardiographic analysis of LV mechanics and tissue characterisation were all those defined as affected by SH. Criteria of inclusion were: (1) no medication at the time of the study; (2) TSH levels above 6.5 mU/l for 12 months or more (we focused on subjects with a persistent and more severe SH in whom the risk of cardiac involvement was presumably higher); and (3) absence of congenital or acquired heart disease. In addition 25 age, body surface area, and living area matched euthyroid DS subjects were studied as control group.

Patients and controls were recruited only after parents' informed consent, considered sufficient by the Ethical Committee of the Federico II University due to the non-invasive procedures used.

Echocardiographic analysis

Each patient underwent complete baseline echocardiographic examination (Sonos5500, Agilent Technologies, Andover, MA, USA) in the supine position with transducer frequencies appropriate for body size. Measurements of the LV internal dimension, and interventricular septal and posterior wall thickness were assessed at end-diastole and end-systole according to methods established by the American Society of Echocardiography.[13] Left ventricular ejection time was measured from the Doppler aortic valve flow velocity envelope and rate corrected to a heart rate of 60 beats/minute by dividing by the square root of the RR interval on the electrocardiogram. During the echocardiographic examination, peak systolic and diastolic blood pressures were measured for each patient with a Dinamap 845-XT Vital Signs Monitor (Critikon Inc., Tampa, Florida). End-systolic pressure was estimated from peak systolic and diastolic blood pressures based on a previously validated equation.[14]

Measurements

Indexes of LV pump function

Fractional shortening (FS), defined as [(end-diastolic dimension − end-systolic dimension)/end-diastolic dimension] and rate corrected velocity of circumferential fibre shortening (VCFc), assessed as fractional shortening divided by rate corrected ejection time, were calculated and used as the measures of global LV performance.

Indexes of afterload

We used end-systolic meridional wall stress (σ_{es}), that incorporates both blood pressure and LV geometry, as an index of afterload. It was calculated by the method described by Grossman and colleagues,[15] assessing LV systolic pressure as arterial systolic blood pressure.

Indexes of myocardial contractility

A load independent index of contractility at the endocardium, the relation between VCFc and σ_{es}, was measured as previously described.[16] The VCFc-σ_{es}, relation for each patient was expressed as a Z score (SVI-Z) based on the distribution of this index in normal subjects.

Indexes of diastolic function

LV diastolic function was evaluated using pulsed wave Doppler recordings of mitral valve inflow. From the apical four chamber view, the Doppler beam was aligned perpendicular to the plane of the mitral annulus with the sample volume positioned inside the left ventricle at the level of the edges of the mitral valvar leaflets. For each subject, the mitral Doppler time-velocity curves from at least three representative beats were analysed for peak early (E) and atrial (A) flow velocities as well as their ratio (E/A), and the results were averaged. Deceleration time (DT) was calculated by measuring the time from the peak velocity of early flow (E) to an extension of the rate decline of velocity to baseline. Isovolumic relaxation time (IVRT) was identified as the interval between closure of the aortic valve and opening of the mitral valve. In addition, diastolic mitral annular velocities during rapid filling (Ea) and atrial contraction (Aa), which are relatively preload independent indexes of LV diastolic function, were measured by Doppler tissue imaging (DTI) as previously described.[17] Finally, transmitral peak E to annular Ea ratio was calculated as an index of LV filling pressure.[18]

Integrated backscatter (IB)

Two-dimensional IB images were acquired and stored by means of acoustic densitometry (Hewlett-Packard Sonos 5500). Methodological findings have been previously reported.[19] From the time intensity curve, both at the interventricular septum (IVS) and the posterior wall (PW), we measured two IB parameters: (1) the magnitude of cyclic variation of IB (CV_{IB}), determined as the difference between the minimum and maximum peaks, which reflects the myocardial contractile function; and (2) the averaged myocardial IB intensity (calibrated by subtracting the IB intensity of the pericardium from the raw values), which is directly related to the myocardial collagen content.[20]

Statistical analysis

All data were expressed as mean (SD). Between-group differences were tested by the unpaired Student's *t* test. A p value less than 0.05 was considered significant.

RESULTS

In 16 children with DS and SH we performed comparative evaluations of characteristics and echocardiographic parameters of LV morphology and compared them to similar evaluations carried out in 25 controls matched for age and body surface area (table 1). Heart rate, and measurements of LV dimensions, wall thickness, and LV mass were comparable.

As summarised in table 2, LV systolic function, expressed both as global pump function (FS and VCFc) and myocardial contractility (SVI Z score) were not significantly different in the two groups. Likewise, no clear evidence of LV diastolic dysfunction, evaluated both by Doppler mitral flow indices and PW-DTI annular velocities, was found in patients with DS and SH. Compared to normal subjects,[16] low values of afterload index (σ_{es}) were detected in both groups with DS. Finally, ultrasonic textural data (table 3), both at IVS and PW, showed no differences between the two groups.

Table 1 Comparative evaluations of characteristics and echocardiographic parameters of left ventricular morphology in children with Down's syndrome with and without (control group) subclinical hypothyroidism

	DS and SH n=16	Control group with DS n=25
Age (months)	65.5 (40.8)	70.3 (27.4)
M/F	7/9	11/14
BSA (m^2)	0.62 (0.3)	0.67 (0.2)
TSH values (mU/l)	Above 6.5 (mean 7.8)	Range 0.5–4.7 (mean 3.2)
FT3/FT4 values (mean)	3.0/11.8	2.7/12.0
AbTg and/or AbTPO positive/negative	4/12	1/25
HR (beats/min)	87.3 (18.9)	84.2 (16.9)
LVEDd (mm)	31.4 (4)	32.6 (3)
IVSd (mm)	5.4 (0.7)	6 (0.6)
PWd (mm)	4.9 (1.1)	5.2 (0.7)
LVMI (g/m^2)	58.3 (10.4)	54.3 (7.7)

No differences between the two groups were statistically significant. DS, Down's syndrome; SH, subclinical hypothyroidism; BSA, body surface area; HR, heart rate; LVEDd, left ventricular end-diastolic diameter; IVSd, end-diastolic interventricular septum thickness; PWd, end-diastolic posterior wall thickness; LVMI, left ventricular mass index.

DISCUSSION

The current practice of treating children with an increased TSH level appears to be based on the data obtained from studies in adults,[9] although the management of cases without overt signs or symptoms of hypothyroidism and with TSH serum levels of less than 10 mU/l is controversial both for adults and for children. However, in DS, some signs and symptoms of hypothyroidism, such as slow thinking, poor memory, muscle weakness, fatigue, muscle cramps, constipation, and, in some cases, weight gain and dry skin, can be difficult to discriminate from similar signs and symptoms found in the natural course of the Down's syndrome itself.[10 21] Thus, in some cases the evaluation of biochemical data alone may be misleading about the possible progression to an overt hypothyroidism and the need for treatment.

It has long been recognised that thyroid diseases exert profound effects on the cardiovascular system and heart, the latter being one of the most thyroid hormone responsive tissues in the body.[22] In particular, thyroid hormone deficiency can induce impairment of both ventricular systolic and diastolic functions by alterations in calcium uptake and release.[23] Nevertheless, previous studies dealing with myocardial function in patients with SH reported conflicting results,[11 12 24–27] probably related to differences in patient selection (age, sex, ethnic extraction, inclusion of patients with acute or unstable SH), criteria of diagnosis (range of TSH levels), and particularly in terms of methodological approach (use of different functional indexes). Thus, in order to avoid a potential bias in the functional analysis of patients with subclinical hypothyroidism, for the first time we used heart rate and load independent indexes of ventricular function.

Previous studies on systolic function in SH patients reported discordant data. Indeed, Biondi and colleagues[11] showed in adults with SH normal values of indexes of global LV pump function (FS, VCFc, and cardiac output); Arem and colleagues,[28] who studied eight patients with SH, at rest and during exercise, found normal cardiac structure and function with just a slightly reduced LV diastolic dimension at rest. On the contrary, Di Bello and colleagues,[24] in 16 patients with SH (TSH >3.6 mIU/l), described subtle abnormalities of systolic function, with increased rate corrected pre-ejection period, even though FS was normal. In our patients with Down's syndrome we found increased pump function indexes (FS and VCFc) with lower afterload (σ_{es}) compared to the values reported in the normal subjects[16]; these data are concordant with our previous results showing that in patients with Down's syndrome the afterload is reduced owing to a low end-systolic pressure.[29] As a consequence, in these patients it is more crucial to utilise for functional analysis load independent indexes of myocardial contractility—that is, stress-velocity index, which were within the normal range in all our study population.

Table 2 Doppler echocardiographic parameters of left ventricular function in children with Down's syndrome with and without (control group) subclinical hypothyroidism

	DS and SH n=16	Control group with DS n=25
Systolic function		
FS (%)	40 (3.8)	39.3 (4.5)
VCFc (circ/sec)	1.35 (0.3)	1.31 (0.3)
σ_{es} (g/cm^2)	32 (13)	30.7 (6.3)
SVI Z score	0.78 (0.34)	0.34 (0.11)
Diastolic function		
Mitral peak E (m/s)	1 (0.1)	1.1 (0.2)
Mitral peak A (m/s)	0.6 (0.1)	0.7 (0.1)
E/A ratio	1.66 (0.2)	1.42 (0.2)
DT (ms)	102.8 (22)	107.5 (30)
IVRT (ms)	51.6 (8.4)	53.6 (8.1)
Mitral annulus peak Ea (m/s)	0.19 (0.03)	0.20 (0.03)
Mitral annulus peak Aa (m/s)	0.14 (0.04)	0.12 (0.04)
E/Ea	5.26 (0.8)	5.5 (1.27)

No differences between the two groups were statistically significant. DS, Down's syndrome; SH, subclinical hypothyroidism; FS, fractional shortening; VCFc, rate corrected velocity of circumferential fibre shortening; σ_{es}, end-systolic meridional wall stress; SVI, stress velocity index; DT, deceleration time; IVRT, isovolumic relaxation time.

Data on diastolic function in SH are also conflicting. Biondi and colleagues,[11] studying 26 patients with stable SH, showed abnormal diastolic relaxation (prolonged IVRT and increased A wave), which may be reversed by L-thyroxine therapy. Although Di Bello and colleagues[24] seem to confirm these data, only four of 16 patients showed clear cut LV diastolic dysfunction (that is, above the 95% confidence limit of the control group). Nevertheless, Doppler derived mitral flow indexes are the results of a complex interplay of several factors (heart rate, loading condition) other than intrinsic diastolic properties. Thus, we also included in our study the analysis by DTI of the velocity of the mitral annulus displacement, which is relatively load independent, and calculated the mitral E/Ea ratio, that has been shown to closely correlate with LV filling pressure.[18] Our results, showing that Doppler mitral flow and DTI myocardial

Table 3 Ultrasonic textural data at interventricular septum and posterior wall in children with Down's syndrome with and without (control group) subclinical hypothyroidism

	DS and SH n=16	Control group with DS n=25
CV_{IVS}	9.8 (1.5)	10.2 (2.2)
CV_{PW}	11.3 (3.7)	12 (2.4)
INT_{IVS}(dB)	−35 (4)	−33.6 (5.5)
INT_{PW}(dB)	−31 (3.8)	−30.7 (5.9)

No differences between the two groups were statistically significant. DS, Down's syndrome; SH, subclinical hypothyroidism; CV_{IVS}, cyclic variation at interventricular septum; CV_{PW}, cyclic variation at left ventricular posterior wall; INT_{IVS}, averaged intensity at interventricular septum; INT_{PW}, averaged intensity at left ventricular posterior wall.

velocities were not significantly different from those of the control group, seem to suggest normal LV diastolic properties. Shan and colleagues[30] have recently reported a significant relation of mitral annulus DTI velocities to myocardial structure (interstitial fibrosis), confirming the advantages of DTI over conventional ultrasound techniques.

Finally, we performed in our population a myocardial ultrasonic tissue characterisation, which also showed results comparable to the control group (with DS). Our data are not consistent with previous results[24] reporting a significant decrease of both cyclic variations, suggestive of impaired intrinsic contractility, and absolute diastolic mean grey level, probably due to an increase in capillary permeability and thus in myocardial water content. The apparent discrepancies of our textural analysis of LV myocardium compared to those of previous studies in adults with subclinical hypothyroidism might be related to the lower mean age of our study population. Although our cases were selected on the basis of an SH lasting 12 months or more and with TSH values above 6.5 mU/l, the shorter time of exposure to SH of our study population might not be sufficient to provoke detectable textural abnormalities.

In conclusion, our results show, for the first time in children, the absence of abnormalities of myocardial structure and function in children with DS and SH, suggesting that thyroid function and health status should be monitored carefully, and L-thyroxine treatment only given when clinical signs and symptoms of hormone deficiency have been clearly shown. We also suggest that the use of load independent indexes is mandatory to warrant an adequate LV functional analysis.

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