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The Relationship Between Hypothyroidism and Cardiac Findings in Children With and Without Down Syndrome

Down Sendromu Olan ve Olmayan Çocuklarda Hipotiroidizm ile Kardiyak Bulgular Arasındaki İlişki

ABSTRACT

Objective: Down syndrome is a genetic syndrome characterized with various dysmorphisms and congenital malformations such as congenital heart diseases. We aimed to evaluate the relationship between Down syndrome, hypothyroidism, and cardiac findings.

Methods: Thyroid hormone profiles and echocardiographic findings were evaluated. Patients with hypothyroidism and Down syndrome were named group 1; patients with hypothyroidism without Down syndrome group 2 and group 3 was control. The echocardiographic parameters (interventricular septum and left ventricular systolic, diastolic posterior wall thickness, left ventricular end-diastolic diameter, ejection fraction) were indexed to body surface area. Left ventricular mass index and relative wall thickness were calculated. Patients with relative wall thickness equal to or below 0.42 were classified as eccentric hypertrophy or normal geometry, while those over 0.42 as concentric remodeling or concentric hypertrophy.

Results: Thyroid stimulating hormone values of groups 1 and 2 were significantly higher than those of group 3. There were no significant differences for fT_4 between the groups. Interventricular septum and left ventricular posterior wall end-diastolic and end-systolic thickness were significantly higher in group 1 than groups 2 and 3. There was no statistically significant difference in left ventricular mass index between groups 1 and 2. In terms of relative wall thickness, 16 out of 29 patients in group 1 were revealed as concentric remodeling, 12 as normal geometry, 1 patient as eccentric hypertrophy. In group 2, 6 patients were revealed as concentric remodeling, 14 as normal geometry. There was no statistically significant difference of left ventricular end-diastolic thickness between 3 groups.

Conclusion: Cardiac morphology and functions were significantly affected by hypothyroidism in patients with Down syndrome. Hypertrophy in Down syndrome may be caused by the cellular changes in myocardium.

Keywords: Cardiac function, cellular and molecular cardiology, echocardiography, genetics

ÖZET

Amaç: Down sendromu, çeşitli dismorfizmler ve doğumsal kalp hastalıkları gibi doğumsal malformasyonlarla karakterize genetik bir sendromdur. Down sendromu, hipotiroidizm ve kardiyak bulgular arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Tiroid hormon profilleri, elektrokardiyografik ve ekokardiyografik bulgular değerlendirildi. Hipotiroidi ve Down sendromlu hastalar Grup 1 olarak adlandırıldı. Down sendromlu olmayan hipotiroidili hastalar Grup 2 ve kontrol grubu Grup 3 olarak adlandırıldı. Ekokardiyografik parametreler (interventriküler septum ve sol ventrikül sistolik-diastolik arka duvar kalınlığı, sol ventrikül diastol sonu çapı, ejeksiyon fraksiyonu) vücut yüzey alanına endekslendi. Sol ventrikül kitle indeksi (SVKİ) ve rölatif duvar kalınlığı (RDK) hesaplandı. RDK'sı 0.42'ye eşit veya altında olan hastalar eksantrik hipertrofi veya normal geometri, 0.42'nin üzerinde olanlar ise konsantrik yeniden şekillenme veya konsantrik hipertrofi olarak sınıflandırıldı.

Bulgular: Grup 1 ve 2'nin TSH değerleri Grup 3'e göre anlamlı olarak yüksekti. Grup 1 ve 2 arasında SVKİ açısından anlamlı fark yoktu. RDK açısından; Grup 1'deki 29 hastanın 16'sında konsantrik yeniden şekillenme, 12'sinde normal geometri, bir hastada eksantrik hipertrofi saptandı. Grup 2'de 6 hastada konsantrik yeniden şekillenme, 14 hastada normal geometri saptandı. Üç grup arasında sol ventrikül diastol sonu kalınlık açısından istatistiksel anlamlı fark yoktu.

Sonuç: Down sendromlu hastalarda kardiyak morfoloji ve fonksiyonların hipotiroidizmden önemli ölçüde etkilendiği belirlendi. Down sedromunda hipertrofi varlığının miyokarttaki hücresel değişikliklerden kaynaklanabileceği düşünülmektedir.

Anahtar Kelimeler: Ekokardiyografi, genetik, hücresel ve moleküler kardiyoloji, kardiyak fonksiyon

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Down syndrome (DS) is a genetic syndrome complex with neurophysiologic and neuropsychologic features, characterized by various dysmorphisms and congenital malformations. Most frequently seen system anomaly in DS is congenital heart disease. Subclinical hypothyroidism, which often accompanies DS, and impairment of cardiac function leads to clinical worsening and shortened life expectancy. The aim of this study was to evaluate the relationship between Down syndrome, hypothyroidism, and cardiac findings.

Materials and Methods

Study Population

Clinical Research Ethical Committee approved the study (decree no: 2018-066). The families of the patients younger than 16 years of age provided their written informed consents.

We included 29 patients, genetically diagnosed with DS, who were also diagnosed with hypothyroidism (group 1) and 20 hypothyroidism patients without DS (group 2) referred from endocrinology department in order to be investigated for cardiac pathologies and 20 healthy children who presented with palpitations or murmur but have normal cardiac findings (group 3). All of the referred patients were aged 0 to 14 years.

Patients who were over 15 years old, have a congenital anomaly other than DS, congenital or acquired heart disease (e.g., cardiomyopathy, rheumatic heart disease, myocarditis, hypertension), underwent surgeries related to heart or thyroid gland, have autoimmune thyroiditis, other comorbidities not related to DS or any other pathology that can affect electrocardiographic (ECG) and echocardiographic (ECHO) findings were excluded from the study.

Laboratory Analysis

Computerized blood count parameters [hemoglobin (HGB), hematocrit (HCT), red blood cell count (RBC), mean corpuscular volume (MCV), and erythrocyte distribution width (RDW)] were analyzed using 2 mL of patient blood in K3EDTA containing tubes with Beckman Coulter LH 780 Analyzer (Beckman Coulter, California, USA). Serum thyroid stimulating hormone (TSH), free fT_4, anti-TPO, and anti-thyroglobulin (anti-TG) levels were obtained using chemiluminescence immunoassay method with Beckman Coulter Unicel DxI 800 Immunoassay System (Beckman Coulter).

Electrocardiographic Examination

Nihon Kohden cardiofax M (Nihon Kohden Corporation, Tokyo, Japan) 12 derivation ECG was used with recording speed set to 25 mm/s and amplitude 10 mm/mV. Electrocardiograms were evaluated for rhythm, PR, QT, QTc segments, QRS waves, and axis. Any rhythm or conduction defect was documented.

Echocardiographic Examination

Echocardiography (2 dimensions, M-mode) was performed using Philips IE33 ultrasound system (Philips,Eindhoven, The Netherlands) and 3-MHz transducer. Each participant underwent ECG examination in accordance with the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[1] Left ventricle ejection fraction (EF), fractional shortening (FS), end-diastolic and end-systolic diameters (LVEDD), interventricular septum (IVS), and left ventricle posterior wall end-diastolic and end-systolic thickness (IVSD, IVSS, LVPWD, LVPWS, respectively) were measured using standard M-mode ECHO. Left ventricular mass index (LVMI) and RWT were calculated to evaluate hypertrophy. Left ventricular mass was estimated with $0.8\{1.04[([LVEDD+IVSd+PWd]^3 - LVEDD^3)]\}+0.6$ formula and divided by body surface area to calculate the LVMI. The RWT was measured as 2 times posterior wall thickness divided by LV end-diastolic diameter. Patients with RWT equal to or below 0.42 were classified as eccentric hypertrophy or normal geometry, while those over 0.42 as concentric remodeling or concentric hypertrophy.

Statistically Analysis

Data were analyzed with Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL). Kolmogorov–Smirnov test, means, and standard deviations were used to assess the distribution of parametric data. Medians were used for nonparametric data. Categorical variables were demonstrated using case numbers and percentages. Nonparametric and categorical variables were analyzed using Kruskal–Wallis and Mann–Whitney *U* tests. Chi-square test was used to evaluate categorical variables. $P < 0.05$ was considered statistically significant.

Results

Demographics, including age and sex, are demonstrated in Table 1. Age and sex were not different between groups ($P > 0.05$).

Hemoglobin, HCT, MCV, RBC, TSH, fT_4, anti-TG, and anti-TPO levels of each group are shown in Table 2. Thyroid stimulating hormone levels were significantly different between groups. Group 3 had lower TSH levels than groups 2 and 1 ($P < 0.001$, $P=0.001$ respectively). Groups 1 and 2 did not have statistically different TSH levels ($P=0.583$). Free fT_4 levels were not different between groups ($P=0.052$).

Interventricular septum end-diastolic thickness indexed, IVSSi, LVEDDi, LVPWDi, LVPWSi, EF, and FS values of each group are demonstrated in Table 3. Interventricular septum end-diastolic thickness indexed and IVSSi were significantly different between groups ($P=0.001$, $P=0.003$). Interventricular septum end-diastolic thickness indexed value of group 1 was significantly higher than groups 2 and 3 ($P=0.016$, $P=0.001$, respectively). Group 1 had a higher IVSSi compared to groups 2 and 3 ($P=0.010$ and $P=0.013$, respectively). Groups 2 and 3 were not different in terms of IVSDi and IVSSi ($P=0.081$, $P=0.214$). Left ventricle end-diastolic diameter indexed values were not statistically different between groups ($P=0.111$). Differences in LVPWDi

Table 1. Comparison of Age and Sexuality Between Groups

	Group 1 (n = 29) Mean ± SD/(%)	Group 2 (n = 20) Mean ± SD/(%)	Group 3 (n = 20) Mean ± SD/(%)	*P*
Age	4.6 ± 4.2	6.4 ± 3.8	6.2 ± 3.7	0.150
Sex				
Male	12 (41.4)	12 (60)	10 (50)	0.439
Female	17 (58.6)	8 (40)	10 (50)	

Table 2. Comparison of Laboratory Findings

	Group 1 (n = 29)	Group 2 (n = 20)	Group 3 (n = 20)	
	Mean ± SD	Mean ± SD	Mean ± SD	*P*
TSH	5.6 ± 2.8	4.2 ± 2.3	2.2 ± 0.9	**<0.001**
fT_4	1 ± 0.4	1.2 ± 0.7	1.1 ± 0.6	0.052
Anti-TG	0.9 ± 0.0	0.9 ± 0.3	0.9 ± 0	0.782
Anti-TPO	2.5 ± 2.8	1.4 ± 1.4	2.4 ± 1.1	0.072
HGB (g/dL)	12.7 ± 1	12.6 ± 0.9	12.3 ± 1.5	0.604
HCT (%)	37.8 ± 3	36.7 ± 2.6	36.5 ± 4.3	0.166
MCV (fL)	82.3 ± 7	78.2 ± 4.5	77 ± 6.3	**0.002**
RDW (%)	15.7 ± 1.4	14.3 ± 3	15.1 ± 1.9	0.069
RBC ($\times 10^6$/μL)	4.6 ± 0.5	4.7 ± 0.3	4.7 ± 0.4	0.334

Anti-TG, anti-thyroglobulin; fT_4, free T_4, HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; RBC, red blood cell count; RDW, erythrocyte distribution width; SD, standard deviation; TSH, thyroid stimulating hormone.
Bold values in the table indicate that the difference is statistically significant.

Table 3. Comparison of Echocardiographic Findings

	Group 1 (n = 29)	Group 2 (n = 20)	Group 3 (n = 20)	
	Mean ± SD	Mean ± SD	Mean ± SD	*P*
IVSD (mm)	5.5 ± 1.2	5.8 ± 2.2	5.5 ± 1.6	0.972
IVSDi (mm/m²)	8.7 ± 2.6	6.8 ± 2.1	5.8 ± 2.2	**0.001**
IVSS (mm)	7.6 ± 1.2	8 ± 2.4	8.2 ± 2.2	0.597
IVSSi (mm/m²)	12 ± 3.4	9.4 ± 2.6	8.8 ± 3	**0.003**
LVEDD (mm)	25.4 ± 5	30.5 ± 4.9	31.7 ± 5.5	**<0.001**
LVEDDi (mm/m²)	42 ± 12.9	37.7 ± 8.1	35.2 ± 10.7	0.111
LVPWD (mm)	5.1 ± 1.8	5.6 ± 2.3	5.2 ± 1.5	0.900
LVPWDi (mm/m²)	8.3 ± 3	6.5 ± 2.1	5.6 ± 1.9	**0.004**
LVPWS (mm)	7.4 ± 1.5	8.2 ± 2.2	8.3 ± 2.3	0.900
LVPWSi (mm/m²)	12 ± 3.4	9.8 ± 2.7	8.9 ± 2.9	**0.004**
EF (%)	69.8 ± 4.2	70.8 ± 5.9	72.4 ± 4.4	0.188
FS (%)	37.8 ± 4.3	39.3 ± 4.7	40.9 ± 3.9	**0.015**
LV mass index (gr/m²)	41.3 ± 10.6	46.1 ± 19.5	38.4 ± 11.4	0.813
RWT	0.42 ± 0.12	0.34 ± 0.11	0.33 ± 0.07	**0.021**

ECHO, EF, ejection fraction; FS, fractional shortening; IVSDi, interventricular septum end-diastolic thickness indexed; IVSSi, interventricular septum end-systolic thickness indexed; LVEDDi, left ventricle end-diastolic diameter indexed; LVPWDi, left ventricle posterior wall end-diastolic thickness indexed; LVPWSi: Left ventricle posterior wall end-systolic thickness indexed; RWT, relative wall thickness.

and LVPWSi values between groups were statistically significant ($P=0.004$, $P=0.004$). The values of LVPWDi group 1 were significantly higher than those of groups 2 and 3 ($P=0.047$ and $P=0.002$, respectively). Group 1 had higher values of LVPWSi than those of groups 2 and 3 ($P=0.047$, $P=0.005$, respectively). Groups 2 and 3 were not statistically different in terms of LVPWDi and LVPWSi ($P=0.102$, $P=0.204$).

There was no statistical difference for EF between groups but there was a significant difference in FS between groups ($P=0.036$). Group 1 had a significantly lower FS than group 3 ($P=0.015$). There were no significant differences between groups 1 and 2 or groups 2 and 3 ($P=0.146$, $P=0.565$, respectively).

Left ventricle mass index and relative wall thickness data are demonstrated in Table 3. There was no significant difference between groups in terms of LV mass index but groups 1 and 2 were significantly different in terms of RWT ($P=0.021$). Of 29 patients in group 1, 16 had concentric remodeling, 12 had normal geometry, and 1 had eccentric hypertrophy. Six patients in group 2 were found to have concentric remodeling and the remaining 14 patients had normal geometry.

PR, QTc, and QRS intervals were not statistically different between groups (Table 4).

Discussion

Down syndrome is one of the common chromosomal abnormalities. It is seen once in approximately 800 live births. The phenotype of DS is composed of intellectual disorders, short stature, heart diseases, digestive disorders, and orthopedic anomalies accompanied by abnormal physical and neurological findings.[2,3]

There is a well-known relationship between DS and thyroid dysfunction, but it is not clear how exactly this dysfunction occurs. The prevalence of hypothyroidism in Down syndrome has been reported as 13.7%-51% in various studies.[4-6] In another study, 55% of DS patients had thyroid dysfunction.[7] Hatipoğlu et al[8] stated that fT_4 may be normal and TSH may be high in DS, and this indicates subclinical hypothyroidism. In our study, there was no significant difference in TSH levels between patients with Down Syndrome-Hypothyroidism (DS-HT) and non-DS-HT, whereas TSH levels of both groups were higher than the control group. There was no significant difference between the groups in terms of fT4 levels.

It has been reported that hyperthyroidism and hypothyroidism cause alterations in cardiac contractility, oxygen consumption of myocardium, stroke volume, blood pressure, and systemic

Table 4. Comparison of ECG Findings

	Group 1 (n = 29)	Group 2 (n = 20)	Group 3 (n = 20)	
	Mean ± SD	Mean ± SD	Mean ± SD	*P*
HR (bpm)	121.2 ± 28	110.9 ± 27.5	104.2 ± 20.1	0.053
PR (ms)	120 ± 14.1	111.9 ± 13.7	126 ± 13.4	0.108
QTc (ms)	398.86 ± 33.32	404.6 ± 23.5	393.75 ± 18.04	0.360
QRS (ms)	85.5 ± 10.5	85.5 ± 8.9	80 ± 6.5	0.096

HR, heart rate; SD, standard deviation.

vascular resistance.[9] Studies on adults with subclinical hypothyroidism stated that thyroid hormone deficiency may lead to abnormalities in both myocardial structure and function.[10-12] In children with subclinical hypothyroidism, IVS thickness and LV diameter were significantly higher compared to the control group, while other parameters were not different.[10-12] Iqbal et al[13] found that adult patients with subclinical hypothyroidism had higher LV diameter than the control group but reported no statistical significance. Franzoni et al[14] reported that septal myocardium was the most affected area of LV in subclinical hypothyroidism. In a study by Varma et al.[15] it was shown that the IVS thickness increased in subclinical and overt hypothyroidism, whereas left ventricular posterior wall thickness increased only in overt hypothyroidism. In our study, we demonstrated that IVS and LVPW thickness increased significantly in DS-HT group compared to non-DS-HT group, conversely there was no significant difference between non-DS-HT group and control group. This suggests that subclinical hypothyroidism has no significant effect on cardiac morphology while DS has an effect on myocardial structure. In our study, it was considered that there was no significant difference in terms of ECHO findings between the patients with or without hypothyroidism because of the fact that non-DS-HT cases were all subclinical, all of them received treatment and there was not enough time to cause structural changes in the heart due to their short duration of hypothyroidism. In cases with DS, the fact that their cardiac pathologies and hypothyroidism start probably at birth or shortly after it leads to changes in cardiac morphology. Myocyte enhancer factor-2 (Mef2) gene takes role in morphogenesis and especially myogenesis of musculoskeletal system and various other tissues. Myocyte enhancer factor-2 mutation, which frequently accompanies DS, may be responsible for myocardial hypertrophy. Studies relating Mef2 gene to regulation of alpha-actin and alpha-myosin heavy chain in the heart support this theory.[16] We think that, in addition to the effects of Mef2 mutation, 20-50 other mutations which may be present in DS may lead to changes in the myocardium, especially concentric changes in the left ventricle posterior wall and IVS, as we demonstrated in our study. Toscano et al[10] demonstrated that DS patients with or without subclinical hypothyroidism did not have abnormalities of myocardial structure or function. Özdemir et al[17] stated that morphological parameters such as LVPW and IVS thickness or left ventricular FS which represents myocardial contractility did not change with treatment in patients with congenital hypothyroidism. Conversely, they found that LVEDD, cardiac output, and LVMI changed significantly. In our study, we found no significant differences between DS-HT and non-DS-HT patients in terms of LVMI.

Although hypothyroidism has different pathological mechanisms than DS, the result is myocardial dysfunction.[18] Left ventricular systolic and diastolic functions were demonstrated to be impaired in a study on adults with overt hypothyroidism.[19] Even though not as prominent as overt hypothyroidism, it has been reported that subclinical hypothyroidism leads to left ventricular systolic and diastolic dysfunction. Mishra et al[20] stated that patients with subclinical hypothyroidism had impaired left ventricular function. Some studies indicate that left ventricular EF may be lower in patients with hypothyroidism.[21,22] In subclinical hypothyroidism, left ventricular diastolic diameter was found to be affected and left ventricular EF was reduced.[23] Özdemir et al[17] reported that patients with congenital hypothyroidism had low EF. In our study, we found that DS-HT patients had significantly impaired FS but normal EF. The fact that we found no significant difference between the DS-HT and non-DS-HT groups in terms of EF and FS, but hypothyroidism groups were different than the control group in terms of FS, leads us to think that DS does not have any negative effects on cardiac systolic functions while hypothyroidism does; in accordance with the literature.

In severe hypothyroidism, ECG findings including sinus bradycardia, low voltage, flattened or negative T wave, prolongation of PR and QT segments, right bundle branch block, rarely ventricular arrhythmia, torsades de pointes and widened QRS complex may be seen.[9,24] Although hypothyroidism is known to cause prolongation of QT distance, we found no significant changes. This may be due to the fact that patients in our study were under treatment.

Study Limitations

The most important limitation of our study was the low number of cases. The lack of data on disease duration in hypothyroid patients made clear clinical discrimination difficult. There was no information about cardiologic disease history of hypothyroid patients and control group. Another limitation was the lack of data on detected cardiac pathologies of DS patients at birth and interventions, if any. In addition, the lack of long-term follow-up data may have not allowed us to detect some changes that occur in a long time.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Health Sciences, (Approval No: 2018-066).

Informed Consent: The families of the patients younger than 16 years of age provided their written informed consents.

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