Evaluation of congenital heart diseases and thyroid abnormalities in children with Down syndrome

Down sendromlu çocuklarda konjenital kalp hastalıkları ve tiroid anormalliklerinin değerlendirilmesi

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Abstract

Objective: Congenital heart disease (CHD) associated with thyroid disease has been reported in Down syndrome (DS). The purpose of this work was to assess abnormalities of the thyroid in relation to the frequency and type of CHD on admission among children with DS.
Methods: This retrospective study included 187 children with DS between August 1993- December 2005. Karyotype analysis, thyroid function tests and echocardiographic studies were performed in all children with DS. If necessary, hemodynamic study by catheterization was carried out. Thyrotropin releasing hormone (TRH) stimulation test was performed in patients having elevated thyroid stimulating hormone (TSH) level. Statistical analyses were performed using Chi-square, "t" test for independent samples or Mann-Whitney U test.
Results: It was found that 136 (72.73%) patients with DS had CHD. The age difference at the time of admission was statistically significant for these two groups ($p<0.001$) in children with /without CHD. There were 12 (11.88%) patients with congenital hypothyroidism and DS, of whom 11 had CHD. There were statistically significant differences in the levels of TSH and total thyroxine (tT4) between congenital and subclinical hypothyroid and euthyroid groups ($p<0.001$ for TSH and $p< 0.001$ for tT4). But there was no significant relationship between having any kind of CHD and levels of TSH and tT4.
Conclusion: Our data suggest that all patients with DS should be evaluated with careful physical and echocardiographic examination on admission. In addition, congenital or subclinical hypothyroidism should also be kept in mind in children with DS and monitored accordingly. *(Anadolu Kardiyol Derg 2010; 10: 440-5)*
Key words: Down syndrome, congenital heart disease, congenital hypothyroidism, subclinical hypothyroidism

Özet

Amaç: Down sendromunda (DS), konjenital kalp hastalığı (KKH) ve tiroid hastalığı (TH) birlikteliği bildirilmiştir. Bu çalışmanın amacı, başvuru sırasında DS'lu çocuklardaki konjenital kalp hastalığının tipi ve sıklığı ile tiroid bozukluğu arasındaki ilişkiyi belirlemektir.
Yöntemler: Bu retrospektif çalışma, Ağustos 1993 ile Aralık 2005 arasındaki DS'lu 187 çocuğu içermekteydi. DS'lu tüm hastalara karyotip analizi, tiroid fonksiyon testi ve ekokardiyografik çalışmalar yapıldı. Gereken hastalara kalp kateterizasyonu uygulanarak hemodinamik çalışmalar yapıldı. Tiroidi uyarıcı hormon (TSH) düzeyi yüksek olanlara tirotropin salgılatıcı hormon uyarı testi yapıldı. İstatistiksel analizlerde Ki-kare, bağımsız örneklem "t" veya Mann-Whitney U testleri kullanıldı.
Bulgular: DS'lu 136 (%72.73) hasta konjenital kalp hastalığına sahipti. KKH'lığı olan ve olmayan DS'lu hastalardan oluşan iki grup arasında, başvuru zamanlarındaki yaşlara göre istatistiksel anlamlılık ($p<0.001$) vardı. DS'lu konjenital hipotiroidisi olan 12 (%11.88) hasta vardı, bunların 11'inin KKH'lıklıydı. Konjenital, subklinik hipotiroidi ile ötiroidler arasında TSH düzeyi ve total tiroksin (tT4) düzeyi arasında istatistiksel (TSH için $p< 0.001$ ve tT4 için $p< 0.001$) anlamlı fark vardı. Ancak TSH ve total tT4 düzeyi ile KKH'nın bulunma durumunun istatistiksel anlamlığı yoktu.
Sonuçlar: Çalışmamız, DS'lu tüm hastalar başvurularında dikkatli bir şekilde fizik ve ekokardiyografik muayene yapılması gerekli olduğu göstermektedir. Buna ek olarak, DS'lu çocuklarda konjenital ve subklinik hipotiroidinin akılda tutulması ve takibi de gereklidir. *(Anadolu Kardiyol Derg 2010; 10: 440-5)*
Anahtar kelimeler: Down sendromu, konjenital kalp hastalığı, konjenital hipotiroidi, subklinik hipotiroidi

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Introduction

Down Syndrome (DS) is the most common chromosomal abnormality that is compatible with life, with reported incidences ranging from 1/700-1/800 live births (1-3). Although there is a wide variation among individuals in the clinical manifestations, particularly in neonates, diagnosis of DS is based on its characteristic features and associated systemic and functional malformations. Congenital heart disease (CHD), which is the most frequent systemic malformation, is present in 16-62% of individuals with DS (3-5). Although DS remains one of the most common causes of mental retardation, the quality of life and mortality of an individual with DS depends on the seriousness of the CHD (6-8).

An increased prevalence of thyroid disease, particularly subclinical hypothyroidism (SH), has been reported in DS. In children with DS, a possible concomitant SH-related impairment of cardiac function may worsen their clinical condition and can ultimately affect their life expectancy (9). For this reason, a yearly thyroid screening is suggested in the guidelines of the American Academy of Pediatrics for the health supervision of children with DS (10).

The aim of this study was to assess the reasons for visiting the clinic, thyroid function tests and the frequency and type of CHD among children with DS at the time they were admitted to the health center.

Methods

The medical records of children with DS who were admitted to either our outpatient or inpatient departments between August 1993 and December 2005 were reviewed. The study was carried out in the Akdeniz University Department of Pediatrics. Our department is the only tertiary care unit for children with genetic problems in the Western Mediterranean region of Turkey. It serves as both a referral center and also as a walk-in clinic which provides health care to children at their families' request without the need for referral from another health center.

At the time of being diagnosed with DS, the sex, age, and reason for visiting the health center were recorded for all of the patients involved in this study. Each patient then underwent thyroid function assessment, screening for CHD, and cytogenetic analysis. Only these retrospective data are discussed in this article. The inclusion criteria for DS were based on karyotype analysis and, in order to screen for the presence of CHD, echocardiographic evaluation was used. In order to determine age in terms of years, the formula [(admission date-birth date)/365] was used.

Chromosomal analyses were performed on blood lymphocytes with the Giemsa-Trypsin banding method at the medical genetics laboratory. Thyroid function tests were carried out as a routine procedure on all of the patients with DS. A thyrotrophin-releasing hormone (TRH) stimulation test was performed on the children who had both clinical signs of hypothyroidism and thyroid stimulating hormone (TSH) levels greater than 5 µIU/ml. The presence of SH was confirmed by levels of TSH exceeding based on the results of the TRH stimulation test.

All patients were evaluated for CHD by electrocardiography (ECG) and underwent a two-dimensional (2D) echocardiographic examination and Doppler studies, using a "General Electric Vingmed Vivid 7 Pro" model ultrasound scanner. The presence and severity of any cardiac malformation was determined according to the recommendations of the American Society of Echocardiography (10).

Congenital heart defects were classified as either "isolated", if there was only one anatomic heart defect or a well-known combination of defects, such as tetralogy of Fallot (TF), or "associated", if there was more than one anatomic heart defect. The presence of an atrioventricular canal defect (AV) was defined as "complete" if a single common atrioventricular valve was present, and "partial" if both atrioventricular valves (mitral and tricuspid) were seen with either a primum atrial septal defect, an inlet ventricular septal defect or a cleft anterior leaflet of the mitral valve.

After the diagnosis of CHD, a hemodynamic study by catheterization was carried out if necessary.

Statistical analyses

All statistical analyses were carried out using the Med Calc version 8.01 computer program (Med Calc Software, Mariakerke, Belgium). Data were expressed as the mean±standard deviation (SD). If the SD was greater than half the mean due to a wide range between minimum and maximum values, the data were expressed as the median (range: minimum, maximum values of the series and lower, upper values of 95% confidence interval of the mean). Comparisons of the data between the different groups were performed using Chi-square test, the "t" test for independent samples or the Mann-Whitney U test, where appropriate. A "p" value of <0.05 was considered statistically significant.

Results

During the review period, 187 children with DS who fulfilled the inclusion criteria were identified. The female-to-male ratio was 1.08. The mean age of all the DS patients at the time of admission to the health center was 1.57 years (1 day-14.63 years; 1.10-2.03 95% CI of the mean). Of these patients, 164 (87.70%) were younger than 5 years old, 14 (7.49%) were between 6-10 years old, and 9 (4.81%) were between 11-15 years old (Fig. 1).

Karyotype analysis was performed in all children with DS (Table 1). Table 2 shows the clinical presentation characteristics of 149 (79.7%) patients with DS.

Table 3 shows the distribution of the characteristics of 101 patients with DS according to thyroid function status. There were 12 (11.88%) cases of congenital hypothyroidism with DS, of which, 11 had CHD. At the time of admission to the health center,

the mean age and the mean TSH and tT4 levels among the DS cases with congenital hypothyroidism were 0.23 years, 48.37 µIU/mL and 6.91 µg/dL, respectively.

Although their clinical signs and thyroid function tests were normal at the time of admission, clinical signs of hypothyroidism later developed in 38 (37.62%) cases during the follow-up period (3.25 years, 0.085-14.92, 1.84-4, 65 95% CI of mean). Of these 38 patients, the presence of any type of CHD was detected in 28 of them. At the time the hypothyroidism was diagnosed, the mean age of this group of patients was 1.28 years and the mean TSH and tT4 levels were 18.46 µIU/ml and 9.87 µg/dl, respectively. Thyroid hormone replacement therapy was administered to all of the hypothyroid cases as soon as the diagnosis was established.

Table 1. The distribution of karyotype analysis of patients with Down syndrome

Type of karyotype	n	%
Trisomy +21	172	91.98
Translocation	7	3.74
Mosaicism	7	3.74
21 del 19p	1	0.53
Total	187	100

Data are presented as proportions/percentages
Descriptive statistics

Table 2. The clinical presentation characteristics of 149 patients with Down syndrome

Variables	DS	HD	I	GIS	HB	MMR
Age, years	1.2 (0.4-1.9)	0.7 (-0.2-1.3)	1.8 (0.6-3.1)	1.4 (-0.1-2.8)	0.1 (-0.0-0.3)	3.2 (1.1-5.3)
F/M ratio	1.0	0.8	1.8	1.1	2.8	1.8
TF[a] CH, n	5	3	0	1	3	0
SH, n	16	7	6	2	3	4
ET, n	13	16	5	6	6	5
CHD (+), n	33	37	15	10	14	2
Total, n	49	37	22	15	15	11

Data are presented as proportions and mean (95% CI) values
Descriptive statistics
CH - congenital hypothyroidism, CHD - congenital heart disease, CI - confidence interval, DS - Down syndrome, ET - euthyroidism, F/M - female/male ratio, GIS - gastrointestinal system, HB - hyperbilirubinemia, HD- heart disease, I - infection, MMR- motor mental retardation, TF - thyroid function, SH - subclinical hypothyroidism
[a]Number of patients with appropriate thyroid function

Table 3. The characteristics of 101 patients with DS according to thyroid status

Variables	CH	SH	ET	p*
Age, years,	0.2 (0.02-0.5)	1.2 (0.3-2.2)	0.9 (0.4-1.5)	>0.05
F/M ratio	1.0	1.1	1.3	>0.05
TSH, µIU/ml	48.4 (15.9-80.3)	18.5 (3.01-39.9)	3.4 (2.9-3.8)	<0.001
tT4, µg/dl	6.9 (4.3-9.5)	9.9 (8.0-10.2)	10.7 (10.0-11.4)	<0.001
CHD, n	11	28	40	>0.05
Total, n	12	38	51	

Data are presented as proportions and mean/median (95% CI)
*Student's t-test or Mann-Whitney U test
CH - congenital hypothyroidism, CHD - congenital heart disease, DS - Down syndrome, ET - euthyroidism, F/M - female/male ratio, TSH - thyroid stimulating hormone, tT4 - total thyroxine, SH - subclinical hypothyroidism

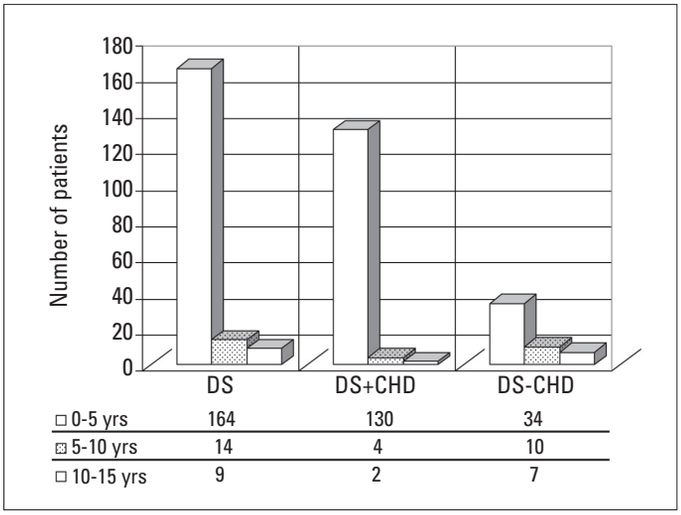

Figure 1. The distribution of age for all patients with DS, DS with CHD, and DS without CHD
CHD - congenital heart disease, DS - Down syndrome

Although there were statistically significant differences in the levels of TSH and tT4 between the congenital and subclinical hypothyroid and the euthyroid groups (p<0.001 for TSH and p<0.001 for tT4), there was not any significant difference in terms of the presence of CHD between level of TSH and tT4.

Congenital heart disease was found in 136 (72.73%) patients with DS by using echocardiography. The other 51 (27.27%) patients did not have any type of CHD.

At the time of admission to the health center, the mean age of the DS children with CHD (female/male ratio 1.11) was 0.74 years (1 day-13.6 years; 0.39-1.09 95% CI of mean) and the mean age of the DS children without CHD (female/male ratio 0.96) was 3.76 years (19 days-14.63 years; 2.5-5.01 95% CI of mean). The age difference at the time of admission was statistically significant for these two groups (p<0.001). The age distribution of DS cases with/without CHD is shown in Figure 1.

Congenital heart defects were detected in 136 out of 187 (72.73%) children with DS. Among these 136 patients, 77 (56.62%) had "isolated" cardiac abnormalities and 59 (43.38%) had "associated" cardiac abnormalities (Table 4).

The most frequent isolated heart defect was secundum type atrial septal defect (ASD) in 34 cases (25%) and there were 41 patients who had ASD in association with other cardiac abnormalities. Within this group, 20 also had ventricular septal defect (VSD) (perimembranous and muscular VSD together in the same patient). The frequency of isolated heart defect and in association with other cardiac abnormalities are shown in Table 4.

Table 4. Characteristics of CHD in DS as reported from different study centers

The type of CHD	Centers of the studies															
	A				B		C		D		E		F		G	
	NP	%*	NK	%*	NP	%*	NP	%*	NP	%*	NP	%*	NP	%*	NP	%*
	187	72.7			275	58.2	227	44.1	524	11.1	114	65.8	92	35.9	28	71.4
Isolated	77	56.6	23	29.9	119	74.4	56	56.0	36	62.1	71	94.7	28	85	17	85
ASD	34	25.0	2		39	24.4	8	8.0	7	12.1	1	1.3	4	12	8	40
AV canal	28	20.6	14		9	5.6	19	19.0	2	3.4	33	44.0	17	52	2	10
VSD[a]	8	5.9	3		35	21.9	18	18.0	15	25.9	17	22.7		0	6	30
TF	4	2.9	2		1	0.6	4	4.0	9	15.5	13	17.3	4	12	1	5
PDA	3	2.2	2		33	20.6	7	7.0	3	5.2	7	9.3	3	9.1		0
Associated	59	43.4	19	32.2	41	25.6	44	44.0	22	37.9	4	5.3	5	15	3	15
ASD+VSD	19	14.0	5		5	3.1	7	7.0	4	6.9			4	12	1	5
ASD+PDA	8	5.9	1		17	10.6			4	6.9						
ASD+VSD+PDA	4	2.9	1		1	0.6										
ASD+CoA	1	0.7														
ASD+PS	1	0.7	1		1	0.6			1	1.7						
ASD+VSD+VSDm	1	0.7														
ASD+VSD+PS	4	2.9														
ASD+VSD+CoA	1	0.7	2													
ASD+MI	1	0.7														
ASD+VSD+MI	1	0.7														
AV canal+PDA	8	5.9	6		5	3.1	7	7.0								
AV canal+PS	3	2.2														
AV canal+ASD	1	0.7					5	5.0								
AV canal+TF	1	0.7	1													
AV canal+COA	1	0.7														
AV canal+ASD+PDA	1	0.7														
Tr Type 4	1	0.7	1													
VSD+PDA	1	0.7	1		10	6.3	4	4.0	2	3.4						
VSD+PS	1	0.7							1	1.7			1	3		
MI															2	10
Total	136		42		160		100		58		75		33		20	

Data are presented as proportions, percentages
Descriptive statistics
A: Current study; B: Mexico (1994-1998) (8); C: Atlanta (1989-1995) (4); D: India (1995-2003) (21); E: Pennsylvania (1998-1999); F: İzmir (1992-1996) (19); G: Trabzon (1998) (20)
ASD- atrial septal defect, AV - atrioventricular, CHD - congenital heart disease, CoA- coarctation of aorta, DS - Down syndrome, MI - mitral insufficiency, NP - number of patients, NK - number of catheterizations, PDA - patent ductus arteriosus, PS - pulmonary stenosis, TF - tetralogy of Fallot, VSD - perimembranous ventricular septal defect, VSDm - muscular VSD, VSDa - 7 VSD + 1 VSDm

A hemodynamic study was undertaken in 42 of the 136 (30.88%) children with CHD. The female/male ratio of the patients in this study was 1.33. The mean catheterization age was 2.76 years (0.11-13.96, 1.73-3.80 95% CI of mean). During the follow-up period, 23 out of 77 (29.9%) children with isolated cardiac disease and 19 out of 59 (32.2%) children with associated congenital heart disease underwent cardiac catheterizations. The mean pulmonary artery pressure was 37.98±15.43 mmHg (14-70 mm Hg), the mean peak systolic pressure was 58.82±19.75 mmHg (20-90 mm Hg), and the mean diastolic pressure was 23.15±12.24 mmHg (5-60 mm Hg). The mean age of the 20 patients who had an AV canal defect was 1.12 years at the time of the angiography (0.3-5.5, 0.4-1.9 95% CI of mean). The mean peak systolic pressure was 62.8824±19.81 (24-90) mm Hg, the mean diastolic pressure was 26.59±13.51 (5-60) mm Hg, and the mean pulmonary artery pressure was 42.35±16.69 (15-70) mm Hg for these 20 patients (Table 4).

Follow-up data was available for 145 children with DS, with the duration of the mean follow-up period being 2.88 years (0-15.5, 2.32-3.45 95% CI of mean). Of these patients, 107 had CHD. Patients with CHD were slightly more likely to start follow-up compared to those without heart disease (107/136=78.68% vs 38/51=74.51%). The mean duration of the follow-up period of patients with congenital heart disease was less than that of patients without CHD (2.26 years vs. 4.63 years). The difference between the mean durations of the follow-up periods between these two groups was statistically significant ($p<0.001$).

Discussion

The profile of the karyotype analysis in our group of patients with DS was similar to that of other studies, with Trisomy +21 being the most frequently observed karyotype (3, 8).

Many studies have suggested that the clinical examination of the cardiovascular system by a doctor other than a cardiologist may not be sufficient in order to detect the presence of heart disease. It has been reported that the use of an ECG in tandem with a clinical evaluation increases both the sensitivity and specificity of the diagnosis, giving a positive diagnosis rate comparable to that of clinical assessments made by cardiologists (11). The use of a neonatal ECG has been found to detect the presence of complete atrioventricular (AV) canal in neonates with DS. On the other hand, it overlooked other heart defects such as small patent ductus arteriosus (PDA) and small ASD. When echocardiography is not easily available due to geographic or economic constraints, careful clinical assessment with the interpretation of an ECG is accepted as an adequate and appropriate screening method for children with DS. It is well known that echocardiography offers an excellent non-invasive tool to diagnose cardiac malformations in infants with DS, especially during the newborn period (11-15). The American Academy of Pediatrics and the Down Syndrome Medical Interest Group recommends routine neonatal echocardiography, including for patients who do not have a heart murmur (16-18). Therefore, one of our two inclusion criteria for evaluation was the presence of complete echocardiographic evaluation in the medical records of the patients that were reviewed.

The frequency and type of heart defects among DS patients in published studies differ according to study design and population characteristics. For example, frequencies of CHD in DS ranging from 16% to 65% have been reported. Additionally, Ünal et al. (19) (35.9%) and Ayancı et al. (20) (71.4%) have reported different frequencies of CHD in DS from different regions of Turkey. The incidence of DS with CHD in our study was high (72.73%) compared to other studies (4, 7, 8, 14, 19, 20). This high incidence is mostly attributable to two facts. First, this study was performed in a referral center for pediatric cardiology and genetics. Second, all DS patients in this study were subjected to echocardiographic and electrocardiogram evaluation (3, 4, 8, 13, 20, 21).

Studies in adults with SH have revealed that thyroid hormone deficiency may cause abnormalities in both myocardial structure and function (9, 11, 15). It has, however, been shown that these abnormalities can be reversed by L-Thyroxine therapy. On the other hand, Toscano et al. (9) showed that there weren't any abnormalities in myocardial structure or function in DS children with SH. They suggested that thyroid function and health status should be monitored carefully, and L-Thyroxine treatment should only be started when clinical signs and symptoms of hormone deficiency have clearly been shown. The TRH stimulation test has been used to evaluate SH in children with DS since 1995. Thyroid function tests were carried out on 101 (54.0%) of the patients in our study group. The risk of having congenital heart disease did not significantly differ among these groups.

The presence of CHD is a potential risk factor for the occurrence of pulmonary vascular disease between the ages of 6 months to 1 year. DS patients with AV canal have a higher pulmonary vascular resistance in the first year of life and progression to fixed pulmonary vascular obstructive disease is more rapid than in children with normal chromosomes (22). Studies show that CHD in DS children can be surgically corrected with a low death rate in infancy, thus leading to the elimination of problems associated with congestive heart failure and pulmonary hypertension (23-25). Our study group included 20 DS patients with AV canal, all of whom showed pulmonary hypertension based on hemodynamic studies. They were about 1 year old at the time of catheterization and needed medical and/or surgical treatment.

This study was a retrospective evaluation of the records of DS patients at the time of diagnosis. A review of the data showed that 72.73% of the children with DS had CHD. Based on the fact that we recommend that all patients with DS should be evaluated with careful physical and echocardiographic examination on admission.

Study limitations

One of the limitations of our study, we can not carry out thyroid function tests and echocardiographic evaluations simultaneously since our study is retrospective. Therefore, we are unable to conclude whether or not subclinical hypothyroidism contributed to the impairment of cardiac function. Another limitation is that we have a limited data about our patients' post operative status because most of our patients operated at other congenital cardiovascular surgery centers.

Conclusion

Careful clinical and hemodynamic evaluation should be both carried out to timely diagnose any life threatening deteriorations in cardiac conditions of patients complicated with congenital heart defects. These data will provide some help for designing follow-up plans for patients with DS who may have concurrent cardiac or thyroid diseases.

Conflict of interest: None declared.

References

1. Siffel C, Czeizel AE. Using the Hungarian Birth Defects Registry for surveillance, research and intervention. Cent Eur J Public Health 1997; 5: 79-81.
2. Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. Am J Med Genet 1998; 77: 431-8.
3. Kava PM, Tullu MS, Muranjan MN, Girisha KM. Down syndrome: clinical profile from India. Arc Med Res 2004; 35:31-5.
4. Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ, et al. Population-based study of congenital heart defects in Down syndrome. Am J Med Genet 1998; 80: 213-7.
5. Wells GL, Barker SE, Finley SC, Colvin EV, Finley WH. Congenital heart disease in infants with Down's syndrome. South Med J 1994; 87:724-7.
6. Hayes A, Batshaw ML. Down syndrome. Pediatr Clin North Am 1993; 40:523-35.
7. McElhinney DB, Straka M, Goldmuntz E, Zackai EH. Correlation between abnormal cardiac physical examination and echocardiographic findings in neonates with Down syndrome. Am J Med Genet 2002; 113:238-41.
8. De Rubens Figueroa J, Del Pozzo Magaña B, Pablos Hach JL, Calderón Jiménez C, Castrejón Urbina R. Heart malformations in children with Down syndrome. Rev Esp Cardiol 2003; 56:894-9.
9. Toscano E, Pacileo G, Limongelli G, Verrengia M, Di Mita O, Di Maio S, et al. Subclinical hypothyroidism and Down's syndrome; studies on myocardial structure and function. Arc Dis Child 2003;88:1005-8.
10. American Society of Echocardiography. Recommendations for continuous quality improvement in echocardiography. J Am Soc Echocardiogr 1995; 8: S1-28.
11. Shashi V, Berry MN, Covitz W. A combination of physical examination and ECG detects the majority of hemodynamically significant heart defects in neonates with Down syndrome. Am J Med Genet 2002; 108: 205-8.
12. Tubman TR, Shields MD, Craig BG, Mulholland HC, Nevin NC. Congenital heart disease in Down's syndrome: two-year prospective early screening study. BMJ 1991; 302: 1425-7.
13. Bhatia S, Verma IC, Shrivastava S. Congenital heart disease in Down syndrome: an echocardiographic study. Indian Pediatr 1992; 29: 1113-6.
14. Rosenberg HC, Jung JH, Soltan HC, Li MD, Sheridan G. Cardiac screening of children with Down's syndrome. Can J Cardiol 1994; 10: 675-7.
15. Narchi H. Neonatal ECG screening for congenital heart disease in Down syndrome. Ann Trop Paediatr 1999; 19: 51-4.
16. American Academy of Pediatrics Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics 2001; 107: 442-9.
17. Cohen WI. Health care guidelines for individuals with Down syndrome (Down syndrome preventive medical checklist). Down Syndrome Quart 1996; 1: 1-10.
18. Feingold M. Cardiac studies on Down syndrome infants. Am J Med Genet A 2003; 120A: 444.
19. Ünal N, Ercal DM, Meşe T, Hüdaoğlu S, Yunus S, Aydın A, et al. Doksan iki Down sendromlu olgunun doğumsal kalp hastalıgı sıklığı yönünden değerlendirilmesi. DEÜ Tıp Fakultesi Dergisi 1998; 12: 31-6.
20. Aynacı FM, Orhan F, Celep F, Karagüzel A. Frequency of cardiovascular and gastrointestinal malformations, leukemia and hypothyroidism in children with Down syndrome in Trabzon, Turkey. Türk J Pediatr 1998; 40: 103-9.
21. Venugopalan P, Agarwal AK. Spectrum of congenital heart defects associated with Down syndrome in high consanguineous Omani population. Indian Pediatr 2003; 40: 398-403.
22. Clapp S, Perry BL, Farooki ZQ, Jackson WL, Karpawich PP, Hakimi M, et al. Down's syndrome, complete atrioventricular canal, and pulmonary vascular obstructive disease. J Thorac Cardiovasc Surg 1990; 100: 115-21.
23. Hals J, Hagemo PS, Thaulow E, Sorland SJ. Pulmonary vascular resistance in complete atrioventricular septal defect. A comparison between children with and without Down's syndrome. Acta Paediatr 1993; 82:595-8.
24. Newfeld EA, Sher M, Paul MH, Nikaidoh H. Pulmonary vascular disease in complete atrioventricular canal defect. Am J Cardiol 1977; 39:721-6.
25. Malec E, Mroczek T, Pajak J, Januszewska K, Zdebska E. Results of surgical treatment of congenital heart defects in children with Down's syndrome. Pediatr Cardiol 1999; 20:351-4.