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Original article

Evaluation of dysmorphic children according to echocardiographic findings: A single center experience

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ABSTRACT

Background: Abnormal echocardiographic findings are more common in dysmorphic children. In our study, dysmorphic child development and echocardiographic findings were presented according to prenatal, natal and postnatal periods.

Aim of the study: The aim of this study is to evaluate the frequency and distribution of cardiac anomalies in dysmorphic children. The other aim is to investigate the prenatal, natal and postnatal characteristics of dysmorphic childs according to echocardiography findings.

Design and setting: This study was carried out jointly by the Medical Genetics and Pediatric Cardiology Departments. The files and the genetic reports of the patients were examined and the hospital registry system scanned, retrospectively. The patients were followed up by the medical geneticist from 2012 to 2017. Their systemic physical examination was performed and recorded.

Methods: This is a retrospective study which contains 468 children (244 males and 224 females) who were referred to the department of medical genetics due to dysmorphic features.

Results: Abnormal echocardiography findings were detected in 157 dysmorphic children (33.4%). Atrial septal defect, patent foramen ovale and ventricular septal defect were the most commonly detected echocardiography findings in dysmorphic children. The number of male children in the abnormal echocardiography group was significantly higher than in the normal echocardiography group. The incidences of consanguineous marriage, polyhydramnios, intrauterine growth retardation (IUGR) and preterm delivery in the abnormal echocardiography group were significantly higher than in the normal echocardiography group. Chromosomal aneuploidy rate in the abnormal echocardiography group was significantly higher than in the normal echocardiography group (37.6% vs 1.0%; $p = 0.001$).

Conclusion: According to our study findings, abnormal echocardiography findings were significantly associated with neonatal sex, consanguineous marriage, polyhydramnios, IUGR, preterm delivery and chromosomal aneuploidies in dysmorphic children.

1. Introduction

The ‘dysmorphic’ therm is originated from the Greek words ‘dys’ (disordered, abnormal, painful) and ‘morph’ (shape, form). Dysmorphology is a clinical genetic discipline which examines and interprets patterns of human growth and structural defects. These structural defects include malformation (an intrinsic developmental anomaly, e.g., spina bifida), disruption (an event disrupting intrinsically normal development, e.g., amniotic bands), deformation (an external force altering the shape of development, e.g., face shape due to severe oligohydramnios) and dysplasia (abnormal growth and maturation of cells, e.g., achondroplasia).

Congenital heart disease (CHD) is defined as a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance. This definition excludes the dysfunction of the great arteries, hypertrophic or dilated cardiomyopathies and congenital arrhythmias such as the long QT and the Wolf-Parkinson-White syndromes, even if the disorders are based on abnormalities present at birth [1,2]. Congenital heart malformations are the most frequent (one-third) of all major birth defects.’ The incidence of CHD in the normal population is approximately 0.8% [1,2]. In our literature review, abnormal echocardiographic findings in dysmorphic children have not been

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Table 1
Echocardiography findings in dysmorphic children.

Echocardiography findings	Number (%)
Normal findings	311 (66.4%)
Atrial septal defect	63 (13.5%)
Patent foramen ovale	43 (9.2%)
Ventricular septal defect	32 (6.8%)
Mitral insufficiency	22 (4.7%)
Aortic stenosis	15 (3.2%)
Patent ductus arteriosus	13 (2.8%)
Aortic insufficiency	11 (2.3%)
Tricuspid insufficiency	11 (2.3%)
Other findings	54 (11.5%)

investigated before and this is a unique issue. The echocardiographic findings in dysmorphic children are seen at Table 1.

2. Aim of the study

The aim of this study is to evaluate the frequency and distribution of cardiac anomalies in dysmorphic children. The other aim is to investigate the prenatal, natal and postnatal characteristics of dysmorphic childs according to echocardiography findings.

3. Subject and methods

This is a retrospective study of 468 pediatric patients who were referred to the department of medical genetics due to dysmorphism. The study cohort consisted of 244 boys and 224 girls who are aged between 0 and 18 years.

Data related with the cohort were obtained from medical records and parent response questionnaires. The prenatal characteristics that were questioned included fetal malpresentation, polyhydramnios, oligohydramnios, intrauterine growth restriction (IUGR), placenta previa, abruptio placenta, premature rupture of membranes and preterm premature rupture of membranes. Delivery time (preterm or term), delivery type (vaginal or cesarean), and indication for cesarean delivery were the natal characteristics that were questioned. Additionally, neonatal sex and anthropometric measurements at birth (weight, length and head circumference) were recorded. As for the postnatal characteristics, the Apgar score and the history for hypoxic ischemic encephalopathy and jaundice were investigated. In addition, detailed pedigree analysis was performed for all patients so that consanguineous marriages, similar cases and genetic diseases in the family could be detected.

Denver Developmental Screening Test-ii (DDST-ii) was applied to evaluate the neurological development of the patients aged over 6 years. In order to assess the motor, social and language skills of the patients aged less than 6 years, the time span for breastfeeding, the time for head and neck control, smiling, rolling prone to supine, sitting without support, creeping, distinguishing individuals, walking, pronouncing simple words, fluent speaking and playing simple games were asked. Moreover, it was questioned whether the patient underwent any surgical operation and the patient had a seizure. If the patient had a history of seizure, it was specified when the first seizure happened, how long it lasted, what the type of seizure was and how many seizures occurred so in total.

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., SPSS IBM, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation (range: minimum-maximum) whereas categorical data were denoted as numbers or percentages where appropriate. Chi-square test was used for the statistical comparisons. Two-tailed p values less than 0.05 were accepted to be statistically significant.

This study was approved by the Ethics Committee of Non-Interventional Clinical Investigations are with the approval number 2016-KAEK2.

4. Results

There were abnormal echocardiography findings in 157 dysmorphic children (33.4%). Atrial septal defect, patent foramen ovale and ventricular septal defect were the most commonly encountered echocardiography findings in dysmorphic children (13.5%, 9.2% and 6.8% respectively). The number of male children was significantly higher in the abnormal echocardiography group than in the normal echocardiography group (66/157, 42.0% vs 178/311, 57.2%; p = 0.002).

There was consanguineous marriage between the parents of 221 dysmorphic children (47.2%). The incidence of consanguineous marriage was significantly higher in the abnormal echocardiography group than in the normal echocardiography group (91/157, 58% vs 130/311, 42%; p = 0.001). The parents of 153 dysmorphic children were first degree relatives (32.7%) whereas the parents of 68 dysmorphic children were second degree relatives (14.5%).

Polyhydramnios was detected during the prenatal period in 15 dysmorphic children (3.2%). Polyhydramnios was significantly more frequent in the abnormal echocardiography group than in the normal echocardiography group (9/157, 5.7% vs 6/311, 1.6%; p = 0.028).

IUGR was diagnosed during the prenatal period in 151 dysmorphic children. The rate of IUGR was significantly higher in the abnormal echocardiography group than in the normal echocardiography group (61/157, 39% vs 90/311, 29%; p = 0.034).

Fifty-five dysmorphic children had preterm delivery (11.8%). The incidence of preterm delivery was significantly higher in the abnormal echocardiography group than in the normal echocardiography group (30/157, 19.1% vs 25/311, 8.0%; p = 0.001).

Cesarean delivery rate was 50.6% in dysmorphic children (237 out of 468). Cesarean delivery rate was higher in children with abnormal echocardiography findings than in children with normal echocardiography but this difference was statistically insignificant (89/157, 56.7% vs 148/311, 47.6%; p = 0.074).

Eighty-eight children with dysmorphology had low Apgar scores (18.8%). The number of children with low Apgar score was higher in the abnormal echocardiography group than in the normal echocardiography group but this difference was statistically insignificant (35/157, 22.3% vs 53/311, 17.0%; p = 0.180).

Seizures occurred during the postnatal period in 23 children with dysmorphology (4.9%). The number of children who had seizures were higher in the abnormal echocardiography group than in the normal echocardiography group but this difference was statistically insignificant (12/157, 7.6% vs 11/311, 3.5%; p = 0.054).

There were chromosomal aneuploidies in 62 dysmorphic children (13.2%). Chromosomal aneuploidies included Down syndrome in 42 children, Edwards syndrome in 12 children and Patau syndrome in 8 children. Moreover, there were chromosomal abnormalities in eight children with DiGeorge syndrome and six children with Williams syndrome. All children with both dysmorphism and chromosomal abnormalities had abnormal echocardiography findings. Chromosomal aneuploidy rate was significantly higher in the abnormal echocardiography group than in the normal echocardiography group (59/157, 37.6% vs 3/311, 1.0%; p = 0.001).

5. Discussion

Congenital heart disease is defined as a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance. This definition excludes the dysfunction of the great arteries, hypertrophic or dilated cardiomy-

opathies and congenital arrhythmias such as the long QT and the Wolf-Parkinson-White syndromes, even if the disorders are based on abnormalities present at birth [1,2].

The present study aims to evaluate the prenatal, natal and postnatal characteristics of the dysmorphic children according to echocardiography findings. Approximately 33.5% of the children with dysmorphology had abnormal echocardiography findings. Atrial septal defect, patent foramen ovale and ventricular septal defect were the most commonly encountered echocardiography findings in dysmorphic children (13.5%, 9.2% and 6.8% respectively). Similarly, a clinical study found that congenital heart diseases were significantly more frequent in dysmorphic patients than in healthy population (33.5% vs 1.6%). When compared to healthy children, the dysmorphic children had significantly higher incidences of atrial septal defect (0.2% vs 13.5%), patent foramen ovale (2.7% vs 9.2%) and ventricular septal defect (0.5% vs 6.8%) [1].

Consanguinity can lead to an increase in the incidence of congenital heart diseases due to the pooling of recessive genes. A study conducted within the Rural Arab Population in Northern Israel reported that the congenital heart diseases were more frequent in children born to consanguineous marriages [3]. Another study conducted in developing countries also detected a significant relationship between consanguinity and congenital heart diseases [4]. A South India study claimed that consanguinity was significantly more frequent in the families with congenital heart diseases when compared to normal families (40.3% vs 15.5%) [5]. Moreover, a large *meta*-analysis concluded that the incidences of cardiac septal defects were significantly increased in the setting of consanguinity [6]. On the other hand, Roodpeyma et al. could not find any relationship between consanguinity and congenital heart diseases [7]. In the present study, the incidence of consanguinity was significantly higher in the abnormal echocardiography group than in the normal echocardiography group (58% vs 42%, p = 0.001).

Polyhydramnios is defined as an amniotic fluid index (AFI) > 25 cm or gestational-age-specific AFI > 97.5 percentile. As for the present study, polyhydramnios was significantly more frequent in the abnormal echocardiography group than in the normal echocardiography group (5.7% vs 1.6%, p = 0.028). This finding could be attributed to the existence of 20 children with Ras/mitogen-activated protein kinase (MAPK) pathway (RASopathies) in the study cohort. There were 8 children with Noonan syndrome, 6 children with cardiofaciocutaneous syndrome, 4 children with Costello syndrome and two children with Leopard syndrome and all of these patients except one had abnormal echocardiography findings. The RASopathies are a family of disorders resulting from dysregulation of the RAS/MAPK signaling pathway. These disorders are Noonan syndrome, Noonan syndrome with loose anagen hair, Costello syndrome, cardiofaciocutaneous syndrome, Leopard syndrome, neurofibromatosis type 1, Legius syndrome and neurofibromatosis-Noonan syndrome [8,9].

It has been hypothesized that congenital heart diseases cause IUGR or both IUGR and congenital heart diseases arise from a common etiology such as maternal disease [10]. Indeed, Rizzo et al. found a dose-response effect of fetal ventricular ejection force and subsequent birth weight, suggesting that impaired cardiac function may lead to a reduction in fetal weight [11]. A literature review by Reller et al. found that the frequency of congenital heart diseases was significantly higher in individuals with low birth weight than in the normal population [12]. Another study pointed out that low birth weight increased the risk of congenital heart diseases and atrial septal defect and tetralogy of Fallot were the most commonly identified congenital heart defects in newborns with low birth weight [13]. However, a recently published clinical study showed that IUGR in children with congenital heart diseases could be attributed to chromosomal abnormalities and extracardiac malformations rather than the congenital cardiac anomaly itself [14]. This study indicated that IUGR was significantly more frequent in the abnormal echocardiography group than in the normal echocardiography group (39% vs 29%, p = 0.034).

In this study, cesarean delivery rate was higher in children with abnormal echocardiography findings than in children with normal echocardiography but this difference was statistically insignificant (56.7% vs 47.6%, p = 0.074). This finding could be the result of significantly increased cesarean delivery rates in Turkey because Turkey is the second country with the highest cesarean delivery rate (47.5%) following Iran in Asia [15].

The Apgar score assesses breathing, heart rate, muscle tone, reflexes and skin color of the newborn. The first minute score determines how well the baby has tolerated the delivery process and the fifth minute score shows how well the newborn is doing outside the uterus. A decrease in cardiac functions affects all components of Apgar score because heart is a vital organ which has an impact on all functions of the body [16–18]. On the contrary, this study was unable to detect a statistically significant difference between the abnormal and normal echocardiography groups in aspect of the number of dysmorphology patients with low Apgar score (22.3% vs 17.0%, p = 0.180). This finding could be due to the relatively small study cohort and the variations in demographic and clinical characteristics of the reviewed patients.

Unfortunately, the literature does not consist of any studies that investigate the relationship between seizures and congenital heart diseases. Naef et al. demonstrated that the children with congenital heart diseases undergoing cardiopulmonary surgery had favorable outcomes but remained at risk for long-term neurodevelopmental impairments, particularly those with a genetic disorder and a complicated postoperative course [19]. The seizure risk was higher in the abnormal echocardiography group than in the normal echocardiography group but this difference was statistically insignificant (7.6% vs 3.5%, p = 0.054).

Chromosomal aneuploidy is a major cause of congenital heart diseases. That is, congenital heart disease occurs in approximately 40% to 50% of trisomy 21 patients, 20% to 50% of Turner syndrome patients, and in almost all cases of both trisomy 13 and trisomy 18 patients. Although almost any cardiac malformation can occur with aneuploidy syndromes, atrioventricular septal defect is typically observed in trisomy 21 and coarctation of aorta is typically encountered in Turner syndrome. Nevertheless, other lesions such as transposition of the great arteries are strikingly underrepresented. These findings imply that cardiac malformations do not happen as a result of a global change in genomic content, but rather as a result of an alteration in specific genes [20,21]. Complying with literature, the abnormal echocardiography group had significantly higher chromosomal aneuploidy rate than the normal echocardiography group in this study (37.6% vs 1.0%, p = 0.001).

The power of the present study is limited by its relatively small cohort, the absence of a healthy control group and the lack of longitudinal data. The findings of the present study showed that abnormal echocardiography findings were significantly associated with neonatal sex, consanguineous marriage, polyhydramnios, IUGR, preterm delivery and chromosomal aneuploidies in dysmorphic children. Further research is warranted to understand the clinical significance of abnormal echocardiography findings in pediatric patients with dysmorphism.

6. Conclusion

It is important to evaluate patients in detail with prenatal, natal and postnatal periods. Abnormal echocardiographic findings were more common in dysmorphic patients than in normal population. We found that abnormal echocardiography findings were significantly associated with neonatal sex, consanguineous marriage,

polyhydramnios, IUGR, preterm delivery and chromosomal aneuploidies in dysmorphic patients. In our literature review, abnormal echocardiographic findings in dysmorphic patients have not been investigated before, and this is a unique issue.

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