

CONGENITAL HEART DISEASE IN CHILDREN WITH DOWN SYNDROME WHO ARE MONITORED AT PAEDIATRIC CARDIOLOGY CENTERS IN BOSNIA AND HERZEGOVINA

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Received: December 12, 2010
Accepted: February 3, 2011

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Objective - The research was undertaken with the aim of establishing the range and frequency of congenital heart disease (CHD) in children with Down syndrome (DS), who are monitored at paediatric cardiology centres in Bosnia and Herzegovina, its association with other anomalies, the time of diagnosis of DS and CHD, and to analyse their surgical care.

Patients and methods - By a cross-sectional study, data was collected on children aged from 0 to 18 years with DS and CHD who were monitored at paediatric cardiology centres of primary, secondary and tertiary health care (Banja Luka, Bihać, Bijeljina, Mostar, Sarajevo, Tuzla and Zenica) in Bosnia and Herzegovina.

Results - Data for 100 children (51 boys and 49 girls) of an average age of 6.1 (from 0 to 17.1) were collected and analysed. The most frequently diagnosed CHD was atrioventricular septal defect, which was found in 36% of children followed by ventricular septal defect in 33%. In 79% children the CHD was isolated and 21% had multiple heart anomalies. Associated anomalies of other systems were found in 26% of children. In only one case was an intrauterine suspicion of DS established. A statistically significant reduction in the age of post-natal diagnosis of DS and CNHD was registered. In 73% patients cardio-surgical treatment was indicated, 43% underwent surgery, 19% are waiting for surgery and in 11% pulmonary hypertension developed.

Conclusion - The range of CHD found in children with DS in Bosnia and Herzegovina does not differ from most similar research. The results obtained show that in the period in question there was insufficient prenatal diagnostics of DS and CHD. Postnatal diagnostics, although also insufficient at the beginning of the period in question, significantly improved over time, which resulted in a reduction of the age at which the diagnosis of DS and CHD was established. Moreover there was a clear reduction in the time difference between the diagnosis of DS and the diagnosis of CHD. However, the possibilities of early cardio-surgical treatment are still limited. The results should serve

in drawing up a plan of prospective monitoring of these patients in Bosnia and Herzegovina in order to define better their specific health needs.

Ključne riječi: Down syndrom ■ Congenital heart disease ■ Children ■ Bosnia and Herzegovina

Introduction

Down syndrome (DS) or Trisomia 21, with an incidence of 1 in 700-800 live births, is the most clinically relevant chromosomal abnormality in human populations. With its characteristic phenotypic properties, DS is known for massive malformations of various organ systems, as well as an increased tendency to higher risk of certain diseases. The incidence of congenital heart defects (CHD) in the general population is around 0.8%, but in children with Down syndrome it is as high as from 40 to 50% (1). Since it causes the development of clinical symptoms of congestive heart failure, pulmonary hypertension, frequent pneumonia, and delays in growth, CHD significantly affects morbidity and mortality in this population. The range and frequency of certain types of CHD in children with DS also vary in relation to the general population (2). Knowing these facts can help in the early postnatal and intrauterine diagnosis of DS, which is the basis for early therapy and thus the prevention of complications. Although atrioventricular septal defect has been mentioned as the most common CHD (43%) (1), the range and frequency of CHD in these children differ in different parts of the world (3, 4).

These differences may be caused by geographical factors. Care and survival of children with DS associated with CHD greatly depend on the degree of development of health care in general, but especially pediatric cardiology and cardiac surgery in a particular environment. This study was undertaken with the aim of establishing the frequency and range of CHDs, their association with other anomalies, and the time of diagnosis of DS and CHD in

children with DS monitored in the pediatric cardiology centers in Bosnia and Herzegovina, and to analyze their surgical care.

Patients and methods

Data were collected by the authors of the study using a pre-designed questionnaire in the period from January 1, 2010 to March 31, 2010. In addition to basic information (the initials of subjects, date of birth, date of establishing the clinical and genetic diagnosis of DS and diagnosis of CHD) data were requested on the presence of anomalies and diseases of other systems and information on treatment undertaken. The ages of the patients and the age of clinical diagnosis of DS and diagnosis of CHD were calculated as a decimal using the decimal age calendar (5).

Diagnosis of CHD in all analyzed subjects was set by ultrasonography. Children with the diagnosis of patent foramen ovale, ventricular septal defect or ductus arteriosus, which later spontaneously closed, are not included in the study.

The age of patients at the time of diagnosis of DS and CHD was analyzed over a 17-year period, that is the period from diagnosis in the oldest patients to the earliest diagnosis in the youngest. On this basis, all subjects were divided into three groups in relation to their actual age. The first group consisted of 28 subjects born before 2000 (older than 10 years, hereinafter referred to as the first group), another 25 patients were born between 2000 and 2005 (patients in 5-10 years of age; hereinafter the second group) and the third group consisted of 47 patients born from 2005 to 2010 (patients younger than 5 years, hereinafter referred to as the third group).

Statistical analysis

The results obtained are presented as absolute and relative numbers. Using Shapi-

ro-Wilk's test, we examined the normality of data distribution. Those results which followed a normal distribution are expressed as the arithmetic mean \pm SD, and those with abnormal distribution as the median and range. To test the statistical significance of the differences between the ages of patients at the time of diagnosis of DS and the diagnosis of CHD, with respect to the time of birth, we used Kruskal-Wallis's test of multiple testing due to the abnormal distribution of data. Statistical hypotheses were tested at a significance level of $\alpha = 0.05$, i.e. the difference between samples was considered significant if $p < 0.05$. Data were analyzed using the statistical software Arcus QuickStat (6).

Results

Demographic data are presented in Table 1. Of the 100 patients with DS and CHD from seven medical centers in Bosnia and Herzegovina, 51 patients were male and 49 female. The average age of patients at the time of completing the questionnaire was 6.1 years (ranging from 0.1 to 17).

The range of CHD and their association with heart defects and anomalies of other systems are shown in Table 2.

The most common CHDs diagnosed were atrioventricular septal defects, ventricular septal defects and secundum atrial septal defect. Other heart anomalies and anomalies of other systems were most often associated with these three major hemodynamic abnormalities. 21 subjects had complex CHD, while in 79 patients CHD was isolated. The most frequent complex associated CHD were found in the group of children with ventricular septal defect.

The leading associated CHD was ostium secundum interatrial septal defect, which was present in 11 patients, followed by arteriosus ductus in seven and pulmonary stenosis in three patients. Abnormalities of the musculoskeletal system were found in six patients, congenital hypothyroidism in six, anomalies of the urogenital system in five, followed by anomalies of the gastrointestinal system in four patients, and abnormalities of the central nervous system in three, and ocular abnormalities in two patients.

In only one patient was the diagnosis of suspected Down syndrome intrauterine, while in the other patients suspicion of DS, and clinical diagnosis of DS was set at birth. Cytogenetic diagnosis of DS was made after birth in 73 patients. In 13 patients the clini-

Table 1 Demographic data

Pediatric cardiology centers in which the subjects controlled	Subjects			
	n	Age at time of examination (years, median, range)	Sex	
			Female	Male
Banja Luka	16	4,6 (0,1-14)	6	10
Bihac	28	5,4 (0,1-17)	16	12
Bijeljina	3	6,6 (3,1-12,7)	-	3
Mostar	17	8,1 (0,4-16)	8	9
Sarajevo	9	3,8 (0,9-15)	6	3
Tuzla	20	5,3 (0,1-17)	10	10
Zenica	7	1,2 (0,1-13,5)	3	4
Total	100	6,1 (0,1-17)	49	51

Table 2 Congenital heart disease and their association with other diagnosed congenital anomalies

Congenital heart disease	n	Associated congenital anomalies	
		Anomalies of the heart (n)	Anomalies of other systems (n)
Atrioventricular septal defect	36	3	13
Ventricular septal defect	33	13	7
Atrial septal defect ostium secundum	17	3	3
Atrial septal defect ostium primum	5	2	-
Tetralogy of Fallot	4	-	2
Pulmonary stenosis	2	-	-
Patent ductus arteriosus	2	-	1
Aortic stenosis	1	-	-
Total	100	21	26

cal diagnosis of DS was made after the first month of life. In 37 patients CHD was diagnosed after the first month of life.

The time of diagnosis of DS and CHD for the studied groups is shown in Figure 1. The mean (median) age at which clinical diagnosis of DS was set in the first group of children was statistically significantly higher compared to the second group of children, ($K-W\chi^2 = 15.072$, $df = 2$, $P = 0.049$), as well as in relation to the children in the third group ($K-W\chi^2 = 23.669$, $df = 2$, $p = 0.005$), while there was no statistically significant difference between the second and third groups ($K-W\chi^2 = 8.596$, $df = 2$, $p = 0.2101$) in the age of diagnosis of DS. The mean (median) age of diagnosis of CHD in the first group of children was significantly higher compared to children from the third group ($K-W\chi^2 = 26.170$, $df = 2$, $p < 0.0001$), but compared to the second group there was no statistically significant difference ($K-W\chi^2 = 10.8$, $df = 2$, $p = 0.1493$). However, the mean age at which the diagnosis of CHD was set in children in the second was statistically higher than in the third group ($K-W\chi^2 = 15.370$, $df = 2$, $p = 0.0236$). In addition to the downward trend

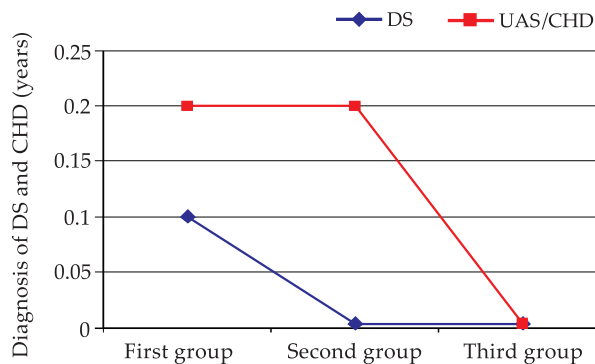


Figure 1 The age of patients at the time of diagnosis of Down syndrome and congenital heart disease in relation to examined groups

in age at diagnosis, a reduction was found in the time difference from diagnosis of DS to diagnosis of CHD.

Analysis of the planned surgical treatment of patients with Down syndrome in relation to the type of CHD is shown in Table 3.

Information on the medical treatment necessary and outcome of the planned treatment of the 100 patients analyzed is known for 88 of them. Surgery was necessary in 73 or 83% of children with CHD. The 11 children in whom surgery was not possible

Table 3 Analysis of surgical treatment of children with Down syndrome in relation to the type congenital heart disease

Congenital heart disease	Hirurški tretman/Surgical treatment (n)				
	Children	Unnecessary	Operated	Waiting for surgery	Impossible
Atrioventricular septal defect	34/36	-	17	10	7
Ventricular septal defect	25/33	2	15	4	4
Atrial septal defect ostium secundum	33/17	10	2	3	-
Atrial septal defect ostium primum	5/5	-	3	2	-
Tetralogy of Fallot	7/4	-	4	-	-
Pulmonary stenosis	2/2	2	-	-	-
Patent ductus arteriosus	2/2	-	2	-	-
Aortic stenosis	1/1	1	-	-	-
Ukupno/Total	88/100	15	43	19	11

were found to have pulmonary hypertension with atrioventricular septal defect in 7 of them, and ventricular septal defect in 4. In the course of data collection, 7 children with atrioventricular septal defect died whilst waiting for surgery.

Discussion

In our study, the most frequent CHD in children with DS was atrioventricular septal defect, which was found in more than one third of patients, followed by perimembranous ventricular septal defect and atrial septal defect. These three CHD account for more than 90% of all cases, while muscular ventricular septal defect and transposition of major arteries were not found. These results are consistent with the results of most other studies (2, 7, 8, 9, 10, 11). However, according to results from Vida et al. (12), the most common abnormality in children with DS in Guatemala was persistent ductus arteriosus, and atrioventricular septal defect was found in only 9.5% of cases and was only fourth in terms of frequency. Similar results were

recorded in some other countries in Central and South America (Mexico, Peru, Colombia) (12). The cause of the high incidence of persistent ductus arteriosus in these parts of the world is unknown, but as one of the unproven hypotheses the authors cite the low values of the partial pressure of oxygen in high altitude conditions (12). The high incidence of ventricular septal defect in children with DS in the Chinese population (13) is considered to be genetic predisposition, which is hypothetically associated with the presence of three different alleles on chromosome 21, as a specific combination responsible for this genetic predisposition (14).

The CHD spectrum that we find in children with Down syndrome is different than the general population (10). The most frequent CHD diagnosed in children with Down syndrome are atrioventricular septal defect, ventricular septal defect, atrial septal defect, ductus arteriosus persistent and tetralogy of Fallot (1, 10). At the same time, other anomalies, such as obstruction of the systemic circulation, coarctation of the aorta, and valvular aortic stenosis, are very rare (10). No

report has been published of the presence of transposition of the major arteries in children with DS. Numerous genetic studies have focused on genetically decoding the association between DS and CHD (15, 16).

The high tendency for certain abnormalities to occur with, at the same time, the absence of other types of CHD in children with DS was confirmed by the results of our study. The two most commonly diagnosed CHD in our study were anomalies with a severe left-right shunt, requiring early diagnosis and early onset of drug therapy, and at the same time they are an indication for early surgical treatment.

In only one patient was intrauterine diagnosis set of suspected Down syndrome, while in the others, suspicion of DS, and clinical and cytogenetic diagnosis was set after birth. It is significant to note that 13 patients were diagnosed with DS and 37 patients with CHD after the first month of life. Given that the phenotype characteristics of children with DS and the well-known fact of the high association between DS and the CHD, this postnatal diagnosis of DS and CHD in these patients was late. These results can be explained by the fact that most of them were born before 2000, a period when there was intense migration of the population and poorly organized health care. However, in this period, as well as the downward trend in age at diagnosis, there was also a decrease in the time difference from diagnosis of DS to diagnosis of CHD, suggesting that the care of children with DS, from the point of view of attention paid to CHD in Bosnia and Herzegovina, has been constantly rising. This positive trend is in line with measures to develop health care for children, resulting in an improvement of care for children with DS and the development of modern pediatric cardiology.

A significant contribution to the early postnatal diagnosis of CHD in children with

DS has come from the establishment of postnatal screening for CHD. Improvement of inadequate prenatal diagnosis in our country is expected after the introduction organized prenatal diagnosis of fetal echocardiography and networking. Data on implementation of planned treatment of CHD in our patients are known for 88 patients. Surgery was required in 73 patients, 43 underwent surgery, 19 were awaiting surgery, and in 11 patients surgery was not possible. In seven patients in whom surgery was not possible pulmonary hypertension was found, and seven children with atrioventricular septal defect died while waiting for surgery. CHD are the most common cause of death in children with DS in the first months of life. Therefore, early recognition and definition of the CHD, early hormonal treatment of congestive heart failure and early intervention allow survival and improve the quality of life of these children. Thanks to improvement in pediatric cardiology and cardiac surgery for congenital heart anomalies, in the developed world today about 85% of children with DS and CHD reach their first birthday, and 50% of them lived longer than 50 years (1).

Timely surgical correction of CHD, which for most children means an operation in the first 6 months of life, as well as enabling survival, significantly reduces the incidence of serious complications (2). The most common complication that develops in these children is pulmonary hypertension, which was recorded in 11% of our patients. This information, and the number of children who died during the three-month collection of data, point to the still limited ability of early cardio-surgical treatment of children with DS and CHD.

Limitation of study

During the study we found several significant flaws that could affect these results. First, the survey does not include children with DS and

CHD that died in this period. Another factor that may affect the results obtained is the lack of data on antenatal diagnoses of DS and termination of pregnancy, as well as the lack of verifiable data on DS and CHD in spontaneous abortions. Finally, the study covers 7 leading pediatric cardiology outpatient clinics in major cities in Bosnia and Herzegovina, so it does not include data on children who, for whatever reason, did not undergo regular check-ups or who, for organizational reasons, were referred to the cardiology clinics in their own community.

Conclusion

Despite the significant limitations of the study and the difficulties in interpreting the significance of data obtained from this study, it is the first study involving children with Down syndrome and CHD from all areas of Bosnia and Herzegovina. The range of CHD

in children with DS in Bosnia and Herzegovina is no different than found in most similar studies. The observed 17 year period is evidence of the lack of prenatal diagnosis of DS and CHD. Postnatal diagnosis, although also insufficient at the beginning of the reference period was later significantly enhanced, resulting in a reduction of the age at the time of diagnosis of DS and CHD. In addition, there is a clear reduction in the time difference from the diagnosis of DS to the diagnosis of CHD. However, there are still limited opportunities for early cardio-surgical treatment. This study should be the basis for developing a plan for an organized prospective study of these patients in Bosnia and Herzegovina in the future, in order to define their specific health needs.

Conflict of Interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organisation.

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