CARDIAC EVALUATION OF CHILDREN WITH CONGENITAL ANOMALIES OF THE KIDNEYS AND URINARY TRACT

Nedima Atić, Hidajeta Begić, Jasminka Ibrahimović, Snežana Zulić, Emina Osmanović

Objective – The purpose of this investigation was to determine the frequencies and types of associated congenital heart disease and other cardiac lesions in children with congenital anomalies of the kidneys and urinary tract (CAKUT). Participants and method – This was a prospective cardiac evaluation of children with diagnosed CAKUT, conducted between January 2013 and December 2015 at the Department of Pediatrics of the University Clinical Hospital, Tuzla. All cases were reviewed for age, gender, consanguinity, occurrence of congenital heart disease (CHD) and CAKUT in family history. Cardiac examination included: physical examination, noninvasive blood pressure measurement, a twelve lead electrocardiogram and echocardiogram. Results – Complete cardiac examination was performed in 144 children with congenital anomalies of the kidneys and urinary tract. Clinically insignificant morphological or hemodynamical changes were noted in 13% or 9.0% children. Congenital heart disease was found in 32 (22.2%), hypertrophic cardiomyopathy in 2 and pulmonary hypertension in 1 of the 144 children. In 4 children congenital heart disease was part of other known genetic syndromes, and all of these cases had severe CHD. In 26 (76.5%) of the total of 32 patients it was already known, and in 6 (23.5%) CHD was discovered during this research. Ventricular septal defect was the most common malformation (13% or 40.6% of patients). Vesicoureteral reflux was the most frequent CAKUT associated with CHD.

Conclusions – The results of this study showed a significant association between CAKUT and CHD. Therefore we suggest performing cardiac assessment of all children with CAKUT.

Introduction

Congenital anomalies of different systems are associated in a wide spectrum of combinations. Congenital anomalies of the kidneys and urinary tract (CAKUT) comprise a broad spectrum of renal and urinary tract malformations that occur in altogether approximately 3-6 per 1000 live born fetuses and cause neonatal death in 1:2000 births (1, 2). These anomalies account for about 40%-50% children with chronic kidney diseases worldwide, and represent a leading cause of end stage renal failure in children (2). CAKUT may occur as isolated malformations or develop in association with additional congenital abnormalities outside the urinary tract, or be a part of the clinical pic-
ture of chromosomal abnormality or genetic syndromes. CACUT has a wide spectrum of clinical presentations, from a completely asymptomatic state to a state incompatible with life. Congenital heart disease (CHD) defines a large set of structural and functional defects that arise during cardiac embryogenesis. The total birth prevalence of CHD in Europe is 8.1 per 1000 liveborns (3, 4), with significant differences (3.9-50 per 1000 liveborns) throughout the world and over time. According to an epidemiological study from 2003, the prevalence of CHD in the Tuzla Canton, Bosnia-Herzegovina, was 6.12 per 1000 liveborns (5). In developed countries it is the main cause of mortality in early childhood and is responsible for one fifth of the total child deaths (6).

Several CHD are known to occur in children with CACUT in syndromic or non-syndromic patterns, and as a result this co-occurrence is the subject of research for a genetic link between CACUT and CHD (7). Clinically this means the increasing risk of morbidity and mortality in these children, in addition to the increasing risk for surgical correction. Previous studies have reported 20%-30% CACUT in children with CHD (8), most of these results were obtained by clinical examination of children with CHD. In recent literature there are only a few studies which have described the frequency in the occurrence of CHD in children with CACUT (9, 10, 11). In our practice all children with hemodynamically significant CHD and those with suspect chromosomal abnormalities or genetic syndromes are subjected to screening for CACUT. Also children with severe forms of CACUT undergo complete a cardiac examination.

We hypothesized that in some children with CACUT, who normally would not be required to undergo cardiac or genetic examination, CHD may remain unrecognized. The purpose of this investigation was to determine the frequencies and types of associated CHD in children with CACUT.

Material and methods

This was a prospective evaluation of cardiac examinations in children with CACUT, conducted between January 2013 and December 2015 (over a period of 2 years) at the Department of Pediatrics of the University Clinical Hospital, Tuzla. Children with diagnosed CACUT, who were admitted to the Department of Nephrology or Outpatients’ department of Nephrology in that period underwent targeted cardiac examinations. The study included all cases of CACUT, those with previously known CHD that was discovered due to cardiac symptoms or as part of genetic examination, as well as those for whom this investigation was the first cardiac examination.

All cases were reviewed for age, gender, consanguinity, and occurrence of CHD and CACUT in their family history. Data on the occurrence of associated anomalies in other systems (non-cardiac and non-renal), chromosomal anomalies and genetic syndromes were extracted from the available medical documentation.

Cardiac examination included physical examination, noninvasive blood pressure measurement, a twelve lead electrocardiogram and echocardiogram. Data from the cardiac auscultation performed were described as normal, normal with innocent murmur, and abnormal (12). Arterial hypertension was considered when systolic blood pressure and/or diastolic blood pressure were ≥95 percentile for gender, age and height (13). Interpretation of data obtained by electrocardiogram (EKG) was described as normal (which included physiological changes in children) or abnormal (14). The echocardiogram was performed with M-mode; 2D-mode, pulsed, continuous and color-Doppler...
provided US system (Vivit 3, Sinc Master 550b), using a 4.4-8 MHz transducer. Examination was done by the transthoracic approach, with the patient in the supine and left decubitus position. Cardiac anatomy was routinely assessed by a sequential segmental analysis, that included subcostal, both apical, both parasternal and suprasternal views (15). The results of the echocardiography were described as normal, or with insignificant morphological or hemodynamic changes, and finally as CHD. All cases of CHD were coded in the International Classification of Diseases (ICD) version 10 (Q20-26) (16). Cases of patent ductus arteriosus and patent foramen ovale in premature infants as the only finding, as well as bicuspid aortic valve were not included as CHD.

**Statistical analysis**

Descriptive statistics were reported as percentages with a 95% confidence interval, when indicated in cases of categorical variables. Median and range were used for age, given the wide variability in our series.

**Results**

We identified 151 patients diagnosed with CAKUT during the study period. Seven, or 4.6%, of them refused to participate. Complete investigations were performed in 144 children with CAKUT, 94 males and 50 females. One patient had chromosomal abnormalities, trisomy X (47XXX), four had genetic syndromes, and 12 had other (non-cardiac and non-renal) anomalies. The general clinical details of 144 children with CAKUT included in investigation are shown in Table 1.

The most frequent CAKUT was vesicoureteral reflux (30 children) representing 20.8% of the total CAKUT. The next most frequent anomaly was hydronephrosis, present in 29 children or 20.1% of all cases. All types of CAKUT and their association with CHD are listed in Table 2.

Fifty-one or 35.4% patients had already undergone cardiac examinations when they were enrolled in the study, while for the other 93% or 64.6% this was the first cardiac examination. Cardiac auscultation was normal in 78, an innocent murmur was audible in 28 and a pathological murmur or pathological change of sounds was found in 38 children with CAKUT. Arterial hypertension was noted in 4 children. Electrocardiography was normal in 119; pathological ECG was found in 25 children, 23 of those with CHD, and 2 children with a structurally normal heart. Clinically insignificant morphological or

| Table 1 General details of 144 children with CAKUT included in the investigation |
|-----------------------------------|-----------------|
| Clinical details                  |                 |
| Age (median and range)            | 4.63 (0.02-16.5) |
| Male to female ratio              | 1.5:1           |
| Bilateral renal or urinary tract lesions (n; %) | 26 (18.0) |
| Chromosomal abnormalities (n; %)  | 1 (0.7)         |
| Genetic syndromes (n; %)          | 4 (2.8)         |
| Other (non-cardiac and non-renal) anomalies (n; %) | 12 (8.3) |
| Family history of renal anomalies (n; %) | 8 (5.5) |
| Consanguinity (n; %)              | -               |
| Control cardiac examination (n; %) | 51 (35.4)      |
| First cardiac examination (n; %)  | 93 (64.6)       |

CAKUT=Congenital anomalies of the kidneys and urinary tract.
had mitral valve prolapse without mitral regurgitation and 6 others had valve regurgitation. Haemodynamic changes were noted in 13 children. Three had a bicuspid aortic valve, 4 had mitral valve prolapse without mitral regurgitation and 6 others had valve regurgita-

| CAKUT                                                                 | Patients (n; %) | CHD (n; %) |
|-----------------------------------------------------------------------|-----------------|------------|
| Vesicoureteral reflux                                                 | 30 (20.8)       | 9 (30.0)   |
| Hydronephrosis                                                        | 29 (20.1)       | 7 (24.1)   |
| Ureteropelvic junction obstruction                                    | 29 (20.1)       | 5 (17.2)   |
| Renal agenesis/hypoplasia                                            | 18/6 (12.5/4.1) | 5/0 (27.7/0) |
| Hypospasia                                                            | 6 (4.1)         | 2 (33.3)   |
| Urethral/reinal pelvis duplication                                    | 5 (3.5)         | -          |
| Multicystic dysplastic kidney                                         | 5 (3.5)         | 1 (20)     |
| Ectopic kidney                                                        | 4 (2.8)         | 1 (25)     |
| Megaueter                                                             | 2 (1.4)         | -          |
| Ren arcuatus                                                          | 2 (1.4)         | -          |
| Bladder extrophy                                                      | 1 (0.7)         | -          |
| Posterior urethral valves                                             | 1 (0.7)         | -          |
| Associated CACUT                                                      | 6 (4.1)         | 2 (33.3)   |
| Total                                                                 | 144 (100)       | 32 (22.2)  |

CAKUT = Congenital anomalies of the kidneys and urinary tract; CHD = Congenital heart disease.

| CAKUT                                                                 | Patients (n) | NCE | CNC | VSD | ASD | PDA | PS | AS | TF | CoA | CCHD | CMP/PH |
|-----------------------------------------------------------------------|--------------|-----|-----|-----|-----|-----|----|----|----|-----|------|--------|
| VUR                                                                   | 30           | 20  | 1   | 2   | 3   | -   | -  | 1  | 1  | 2   | -    | -      |
| Hydronephrosis                                                        | 29           | 20  | 1   | 2   | 2   | -   | -  | 1  | 1  | -   | 1/0   |        |
| Ureteropelvic junction obstruction                                    | 29           | 21  | 3   | 3   | -   | 1   | 1  | -  | -  | -   | -    | -      |
| Renal agenesis/hypoplasia                                            | 18/6         | 12/6| 1/0 | 1/0 | 0/1 | 1/0 | 1  | 1  | -  | -   | -    | -      |
| Hypospasia                                                            | 6            | 2   | 2   | 1   | -   | -   | -  | 1  | -  | -   | -    | -      |
| Ureteral/reinal pelvis duplication                                    | 5            | 4   | 1   | 1   | -   | -   | 1  | -  | -  | -   | -    | -      |
| Multicystic dysplastic kidney                                         | 5            | 3   | 1   | 1   | -   | -   | -  | -  | -  | -   | -    | 1/0    |
| Ectopic kidney                                                        | 4            | 4   | -   | -   | -   | -   | -  | -  | -  | -   | -    | -      |
| Megaueter                                                             | 2            | 1   | -   | -   | -   | -   | -  | -  | -  | -   | -    | 0/1    |
| Ren arcuatus                                                          | 2            | 1   | 1   | -   | -   | -   | -  | -  | -  | -   | -    | -      |
| Bladder extrophy                                                      | 1            | -   | -   | -   | -   | -   | -  | -  | -  | -   | -    | -      |
| Posterior urethral valves                                             | 1            | 1   | -   | -   | -   | -   | -  | -  | -  | -   | -    | -      |
| Associated CACUT                                                      | 6            | 2   | 2   | 1   | -   | -   | -  | -  | -  | -   | 1    | -      |
| Total                                                                 | 144          | 96  | 13  | 13  | 4   | 2   | 3  | 2  | 3  | 2   | 3    | 2/1    |
tion (mitral, aortic) in morphologically and structurally intact valves. CHD was found in 32 (22.2%), hypertrophic cardiomyopathy in 2 and pulmonary hypertension in 1 of the 144 children with CAKUT. In 4 children CHD was part of known genetic syndromes, and all of these cases were major CHDs. Cardiac surgery was indicated in 15 or 46.9% of all the 32 children with associated CHD. Twenty-six or 76.5% patients of the total 32 CHDs were already aware of their association, and in 6 (23.5%) CHD was discovered during the current research. Ventricular septal defect was the most common malformation (in 13 or 40.6%), followed by atrial septal defect secundum type (5 or 15.6%). The most frequent association of CAKUT with CHD was found in children with vesicoureteral reflux. Table 3 shows the distribution of the results of cardiac examinations in children with different types of CAKUT.

Discussion

This is the first prospective, observational study in our region, aim at detecting and defining the spectrum of associations of CHD and other cardiac changes in children with CAKUT. According to numerous epidemiological reports, CAKUT has been found to occur at the rate of one child in every 600 births (1, 2, 17). The term “CAKUT” covers malformations of the kidney (renal agenesis, hypoplasia, dysplasia, double kidneys), anomalies of the ureter (obstructive, as seen in proximal ureteral stenosis, or refluxive). Anomalies of the bladder and urethra are also assigned to this group (18, 19). CAKUTs are presented as a group of diseases with different degrees of severity and many of them require a multidisciplinary approach, accurate diagnosis and good treatment. The current study included 144 children (0.2-16.5 years) with CAKUT, living in the Tuzla Canton area which has a population of 92,047 children aged 1-14 years (20). Regarding this data, it may be considered that this study included more than half of all the cases of CAKUT. Apart from its size, the sample contains a wide spectrum of malformations grouped in CAKUT. The three most frequent malformations were: vesicoureteral reflux, hydronephrosis and ureteropelvic junctional obstruction, and they constitute more than 60% of the sample. Primary vesicoureteral reflux is the most common CAKUT in childhood, which is diagnosed mostly after an episode of urinary tract infection (21). Routine screening of patients with urinary infection can the explain the high proportion of vesicoureteral reflux. Another CAKUT, bladder extrophy, which we noted in only one case, is a very rare anomaly, occurring with a 2:1 male-female ratio (22). Bilateral lesions were found presented in 22.2% cases. We observed a very small percentage of known chromosomopathies, genetic syndromes and associated non-renal and non-cardiac anomalies in our sample, in comparison with data in the literature (10, 23). This may be explained in the most part by the fact that some were lost because they were in critically ill infants, but also by the absence of systematic genetic search in our practice. Positive family history of CAKUT was found in only 5.5% of all cases, while the frequency of renal abnormalities in close relatives reported in the literature is higher (23, 25).

The percentage of trivial cardiac lesions without clinical significance in our series accounted for 9.0% of patients, and is parallel with the general child population. Arterial hypertension, found in three children, was part of the clinical picture of chronic kidney disease, and in one case there was renovascular hypertension. We found a total of 32 (22.2%) children with CHD, which is compatible with other similar studies in the relevant literature (9,10). In our investigation, CHD was the leading associated congenital
malformation. According to the results of some other authors, although they reported a similar percentage, CHD occurrence was in third place (26). About two thirds of the cases of CHD, 65.6%, were found with the three most frequent CAKUTs (vesicoureteral reflux, hydronephrosis and ureteropelvic junctional obstruction). The most common cardiac malformation was ventricular septal defect, which is similar to other investigations (9, 11, 27). These data and data on the structure and frequency of other CHDs, atrial septal defect, pattern ductus arteriosus, tetralogy Fallot are in line with epidemiological population based studies (1, 4, 5). All syndromic cases and 5 children with other associated non-renal anomalies had CHD, which suggested a genetic cause of this connection. We hypothesized that some of them are still unrecognized. In their retrospective study, Miller et al. (26) observed a higher frequency of specific combinations, such as hydronephrosis with cardiac malrotation, right ventricle obstruction intra-atrial and intraventricular communication. Our data did not prove any significant connection between specific CAKUT and CHD. Among the children with associated CHD, nearly half had major heart defects which required cardiac surgery. The majority of CHD (26 of the total of 32) had been detected earlier, because they had had cardiac symptoms, or during routine genetic testing. Although a small number of associated CHD were detected during this targeted search, this was very important for their future follow-up.

During the investigation we observed numerous limitations, which led to the fact that the results we obtained are not completely representative. The relatively small CAKUT population, missing data on autopsies and perinatal mortality, the lack of a uniform register of congenital malformations, and incomplete results of genetic testing are some of them.

Conclusions

The general characteristics of our sample indicated that the need for clinical access for all congenital pathologies required improving most segments of children health care. This means that the basis of the diagnostic evaluation of all congenital abnormalities is multidisciplinary work which includes the accepted diagnostic algorithms, possibilities of genetic testing and official registration. Based on the results of CAKUT and CHD association, we suggest performing cardiological assessment of all children with CAKUT. For investigation of specific associations, we will need to continue this targeted search and registration.

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