Malformations Detected by Abdominal Ultrasound in Children with Congenital Heart Disease

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Abstract

Background: Extracardiac malformations may be present in patients with congenital heart disease (CHD), bringing greater risk of comorbidity and mortality.

Objective: Verify frequency and types of abdominal abnormalities detected in children with and without CHD through abdominal ultrasound (AUS), compare the patients in relation to their dysmorphic/cytogenetic findings and perform an estimative of the cost-effectiveness of the screening through AUS.

Methods: We conducted a cross-sectional study with a control cohort. The cases consisted of patients with CHD admitted for the first time in a pediatric intensive care unit; the controls consisted of children without CHD who underwent AUS at the hospital shortly thereafter a case. All patients with CHD underwent AUS, high-resolution karyotype and fluorescence in situ hybridization (FISH) for microdeletion 22q11.2.

Results: AUS identified clinically significant abnormalities in 12.2% of the cases and 5.2% of controls (p= 0.009), with a power of significance of 76.6%. Most malformations with clinical significance were renal anomalies (10.4% in cases and 4.9% in controls; p= 0.034). In Brazil, the cost of an AUS examination for the Unified Health System is US$ 21. Since clinically significant abnormalities were observed in one in every 8.2 CHD patients, the cost to identify an affected child was calculated as approximately US$ 176.

Conclusion: Patients with CHD present a significant frequency of abdominal abnormalities detected by AUS, an inexpensive and noninvasive diagnostic method with good sensitivity. The cost of screening for these defects is considerably lower than the cost to treat the complications of late diagnoses of abdominal malformations such as renal disease. (Arq Bras Cardiol. 2012; [online].ahead print, PP.0-0)

Keywords: Ultrasonography; Child; Heart Defects, Congenital; DiGeorge Syndrome; Urogenital Abnormalities; Chromosome Aberrations.

Introduction

Congenital heart disease (CHD) is considered the most prevalent congenital abnormality, affecting about 40% of all birth defects¹–⁴. Severe and moderately severe CHD, which require intensive care and complex surgeries and provide greater neurological comorbidity in the postoperative period, represent about 3-6 per 1,000 live births²,⁵–⁶. Extracardiac conditions such as abdominal malformations, associated or not with genetic syndromes, have been observed in 50-70% of cases of CHD and carry a higher risk of comorbidity and mortality, making heart surgery riskier⁷–⁹. Patients affected with these malformations may require further surgical or intensive clinical intervention irrespective of cardiac disease⁷.

The importance and cost-effectiveness of screening children with CHD looking for extracardiac abnormalities by complementary tests such as abdominal ultrasound (AUS) has been recognized but only few studies directly evaluated this approach³,⁴,⁷. The limited information prompted the current investigation aiming to identify the frequency and types of associated abdominal malformations in patients with CHD undergoing AUS in a referral hospital in Southern Brazil. Additionally, we compared the patients for their dysmorphic/cytogenetic findings and estimated the cost-effectiveness of screening children with CHD through abdominal imaging.
Methods

The patient cohorts

In this cross-sectional study with a control cohort, cases were composed by patients with CHD and controls by patients without clinical signs or evidence of this malformation. The case cohort has been described in detail by Rosa et al. and included 164 consecutive patients with CHD hospitalized for the first time in the cardia intensive care unit (ICU) of a pediatric hospital. In all patients, AUS, high resolution GTG-banding karyotype (550 bands) and fluorescence in situ hybridization (FISH) for 22q11 deletion syndrome were successfully performed. Patients were also classified according to the anatomic type of CHD based on the main cardiac defect, in carriers of septal, cyanotic, complex and conotruncal defects. The classification considered the results of echocardiography and catheterization/surgery. AUS was performed as part of the clinical evaluation of these patients.

The control subjects were the first two patients without clinical signs or evidence of cardiac malformation who underwent AUS examination immediately after the subjects with CHD (cases) in the Department of Radiology of the hospital. All of them presented abdominal symptoms or suspicion of an abdominal alteration. The controls were identified through the registration system used for scheduling and completing the reports of the examinations. Patients with incomplete clinical data or abdominal surgery before the AUS were excluded.

Protocol

A standard clinical protocol was applied to cases in order to collect data such as sex, age at evaluation, origin, reason for ICU admission, type of CHD, time of hospitalization and clinical outcome (improvement or death during hospitalization). Subsequently, these patients were also evaluated by a clinical geneticist to determine the presence of syndromic features, determined by dysmorphic features and other abnormalities identified in the physical examination, but without prior knowledge of the CHD type and presence of extracardiac abnormalities detected by complementary exams. Based on this clinical exam, patients were grouped into 4 categories: classical syndrome (i.e., a defined syndromic aspect, such as Down syndrome), undefined syndrome (a syndromic aspect, but without a defined diagnosis), CHD associated with dysmorphia (a non-syndromic patient with only some dysmorphism), and isolated CHD. Extracardiac abnormalities detected by complementary exams (in addition to those detected on AUS), when present, were also noted.

Information of the controls was collected at the Department of Radiology and the medical records of the hospital, following a standard protocol. These data consisted of age and sex of patients, their origin, reason for performing AUS, source of the test request (hospital, emergency or outpatient care) and results. The confirmation of the absence of clinical signs or evidence of CHD was made by review of the patients’ medical records.

The AUS in both case and control cohorts was performed by two pediatric radiologists. The abdominal abnormalities detected were classified according to severity (based on the criteria adopted by Czeizel), in clinically significant anomalies and minor alterations. Minor alterations were considered normal variants and clinically irrelevant.

The study was approved by the Research Ethic Committee of the Hospital.

Data processing and statistical analysis

Data were analyzed using SPSS version 12.0 for Windows. Chi-square or Fisher’s exact tests were used to compare proportions; t-student test for independent samples was used to compare means between groups with and without CHD. In case of asymmetry, the Mann-Whitney test was used. The measure of effect used was the odds ratio with confidence interval of 95%. The significance was considered when p < 0.05, for a range of 95%.

An estimative of the cost-benefit of the examination through the AUS as a screening method among patients with CHD was also made, taking into account the cost of the examination within the Unified Health System (SUS), the Brazilian public health system that serves the majority of the sampled patients. This approach was performed in similarity with Gonzalez et al.

Results

General data

Among patients with CHD, 54.2% were male, with ages ranging from 1 day to 150 months (median of 8 months). In the control group, 55.5% were male and age ranged between 15 days and 193 months (median of 71 months). The difference between the ages of the two groups was statistically significant (p < 0.001). Most of the case subjects originated from countryside towns in the state of Rio Grande do Sul (54.3%), whereas the majority of the control subjects came from the state capital Porto Alegre (51.4%), where the hospital is located (Table 1).

By physical examination, patients with CHD were classified as displaying classical syndrome (21.3%), undefined syndrome (12.2%), CHD associated with dysmorphic features (65.9%) and CHD alone (0.6%). In total, 33.5% of the children had syndromic appearance. The main anatomical CHD was ventricular septal defect, observed in 16.5% of the cases (Table 2). Eighty-five patients (51.8%) had septal defect type, 53 (32.3%) cyanotic CHD, 52 (31.7%) complex CHD and 39 (23.8%) conotruncal malformation. The time of diagnosis of CHD occurred mainly perinatal (54.1% of cases), and only 9.4% had diagnosis in the prenatal period. Of those patients with CHD, 42 (25.6%) had other major congenital malformations in addition to cardiac and abdominal abnormalities. The karyotype was abnormal in 24 patients (14.6%) with CHD; trisomy 21 for Down syndrome was the most common anomaly (83.3%). Four patients (2.4%) showed 22q11 microdeletion by FISH (Table 3).

Request for AUS for control patients came from outpatient care in 43.3% of the cases; from the emergency care unit in 29.6% and from hospitalization in 27.1% of patients. The
Table 1 – Demographic characteristics of the sample

| Characteristics          | Cases (n=164) | Controls (n=328) | P       |
|-------------------------|--------------|-----------------|---------|
| Age* (months)           | 8.4 (1.25 – 41.9) | 71.5 (23.8 – 106.8) | < 0.001 |
| Sex                     | (n=164)      | (n=328)         | 0.873   |
| Male                    | 89 (54.3%)   | 182 (55.5%)     |         |
| Female                  | 75 (45.7%)   | 146 (44.5%)     |         |
| Origin                  | (n=164)      | (n=290)         |         |
| Porto Alegre city       | 26 (15.9%)   | 149 (51.4%)* ***|         |
| Cities close to Porto Alegre | 39 (23.8%) | 115 (39.7%)* ***|         |
| Countryside towns of the RS** | 89 (54.3%)* *** | 24 (8.3%) |         |
| Other states in Brazil  | 10 (6.1%)* ***| 2 (0.7%)         |         |

* Median (P25-P75); ** RS: State of Rio Grande do Sul; *** Statistically significant by test of adjusted residuals (p <0.05).

Table 2 – Types of congenital heart disease and results of abdominal ultrasound

| Types of cardiac malformations* | Abnormalities with clinical meaning n (%) | Variant of normality n (%) | Normal n (%) | TOTAL |
|---------------------------------|------------------------------------------|----------------------------|--------------|-------|
| VSD                             | 6 (22.2)                                 | -                          | 21 (77.8)    | 27    |
| AVSD                            | 4 (23.5)                                 | 1 (5.9)                    | 12 (70.6)    | 17    |
| TOF                             | 3 (21.4)                                 | -                          | 11 (78.6)    | 14    |
| CoAo                            | 2 (11.1)                                 | -                          | 16 (88.9)    | 18    |
| PDA                             | 1 (8.1)                                  | 1 (9.1)                    | 1 (9.1)      | 11    |
| TGA                             | 1 (10)                                   | -                          | 9 (90)       | 10    |
| Tricuspid atresia               | 1 (25)                                   | -                          | 3 (75)       | 4     |
| Ebstein anomaly                 | 1 (33.3)                                 | -                          | 2 (66.7)     | 3     |
| Truncus arteriosus              | 1 (33.3)                                 | -                          | 2 (66.7)     | 3     |
| ASD                             | -                                        | 2 (6.7)                    | 28 (93.3)    | 30    |
| HLH                             | -                                        | 1 (16.7)                   | 5 (83.3)     | 6     |
| PA+VSD                          | -                                        | 1 (25)                     | 3 (75)       | 4     |
| PA+IS                           | -                                        | -                          | 3 (100)      | 3     |
| DORV                            | -                                        | -                          | 3 (100)      | 3     |
| Subaortic ring                  | -                                        | -                          | 3 (100)      | 3     |
| TAPVR                           | -                                        | -                          | 2 (100)      | 2     |
| Double Aortic Arch              | -                                        | -                          | 1 (100)      | 1     |
| Aortic stenosis                 | -                                        | -                          | 1 (100)      | 1     |
| DOLV                            | -                                        | -                          | 1 (100)      | 1     |
| Cor triatriatum                 | -                                        | -                          | 1 (100)      | 1     |
| Anomalous coronary artery       | -                                        | -                          | 1 (100)      | 1     |
| Mitral insufficiency            | -                                        | -                          | 1 (100)      | 1     |
| TOTAL                           | 20                                       | 6                          | 138          | 164   |

*VSD: ventricular septal defect; AVSD: atrioventricular septal defect; TOF: tetralogy of Fallot; CoAo: coarctation of the aorta; PDA: patent ductus arteriosus; TGA: transposition of great arteries; ASD: atrial septal defect; HLH: hypoplastic left heart; PA+VSD: pulmonary atresia with ventricular septal defect; PA+IS: pulmonary atresia with intact septum; DORV: double outlet right ventricle; TAPVR: total anomalous pulmonary venous return; DOLV: double outlet of left ventricle.
main reasons for the AUS referral were abdominal pain (36% of orders), suspicion of urinary tract abnormality (16.5%), suspicion of infection (14.7%), suspicion of malignancy (12.5%) and suspicion of gastroesophageal reflux (11.8%). In 56 of the 328 control patients, the reason for the exam could not be identified.

AUS Results

Abnormalities in the AUS were identified in 15.9% of patients with CHD and in 7.3% of controls, a statistically significant difference (p = 0.005). As opposed to controls, none of the patients with CHD presented abdominal symptoms. Abnormalities with clinical significance were observed in 12.2% of cases and 5.2% of controls (p = 0.009), with power of significance of 76.6%. We verified an even more significance when we compared the CHD patients with controls without suspicion of a urinary tract malformation (p = 0.002). Major malformations with clinical significance consisted especially of renal abnormalities (10.4% in cases and 4.9% in controls) (p = 0.034) (Table 3).

Malformations with clinical significance were identified in 20% of patients with CHD and syndromic appearance and in 8.3% of patients with CHD but no syndromic appearance, a value close of the significance (p = 0.055). However, the frequency of abdominal malformations with clinical significance in the group with CHD and syndromic appearance was significantly higher than in controls (5.2%; p = 0.0006). Moreover, clinically significant abnormalities in the AUS were found in 26.2% of CHD patients with other extracardiac major malformations, which was significantly higher than the 7.4% of CHD patients without these major abnormalities (p = 0.003).

Significant abdominal malformations by the AUS were identified in 10 of 74 (13.5%) children with septal defect, in 7 of 53 (13.2%) with cyanotic CHD, in 5 of 39 (12.8%) with conotruncal CHD and in 7 of 52 (13.5%) with complex CHD. There was no difference between each subgroup of patients with CHD and the remaining patients.

There were five deaths during hospitalization among patients with CHD. Of these, one had abdominal malformations with clinical significance detected by AUS. The median length of ICU stay of CHD patients without abdominal malformations was 3 days (1-73 days), while among those with abnormalities detected by AUS was significantly longer at 6 days (1-95 days; Mann-Whitney test, p = 0.041).

Table 3 – Results of abdominal ultrasound

| RESULTS OF THE ULTRASOUND | CASES | CONTROLS |
|---------------------------|-------|----------|
|                          | Normal KTP* and FISH* | +21* | +18* | XXX* | dup(17p)* | add(18p)* | 22q11DS* | Normal KTP* and FISH* | +21* | +18* | XXX* | dup(17p)* | add(18p)* | 22q11DS* |
| NORMAL                    | 117   | 16 | 1 | 1 | 1 | 1 | 1 | 304 |
| ABNORMAL                  | 19    | 4 | 0 | 0 | 0 | 3 | 24 |
| Variant of normality      | 4     | 1 | - | - | - | - | - | 7 |
| Asymmetric kidneys        | 2     | 1 | - | - | - | - | - | 5 |
| Accessory spleen          | 2     | - | - | - | - | 1 | - | 1 |
| Spleen with single cyst   | -     | - | - | - | - | - | - | 1 |
| Liver cyst                | -     | - | - | - | - | - | - | 1 |
| With clinical significance| 15    | 3 | 0 | 0 | 0 | 2 | 17 |
| Micturation of the renal pelvis | 4 | 2 | - | - | - | - | - | 6 |
| Moderate dilatation of the collecting system | 2 | - | - | - | - | - | 1 | 1 |
| Multicystic kidney        | 2     | 1 | - | - | - | - | - | - |
| Duplication of the renal pelvis | 2 | - | - | - | - | - | - | - |
| Ectopic kidney            | 1     | - | - | - | - | - | - | 3 |
| Unilateral renal agenesis | -     | - | - | - | - | - | - | - |
| Renal hypoplasia          | 1     | - | - | - | - | - | - | - |
| Prominence of the renal pyramids | - | - | - | - | - | - | - | 1 |
| Situs inversus abnominalis| 2     | - | - | - | - | - | - | - |
| Multiloculated gallbladder| 1     | - | - | - | - | - | - | 1 |
| TOTAL                     | 136   | 20 | 1 | 1 | 1 | 1 | 4 | 328 |

*KTP: karyotype by high resolution GTG-banding; FISH: fluorescent in situ hybridization; +21: free trisomy of chromosome 21; +18: free trisomy of chromosome 18; XXX: free trisomy of chromosome X; dup(17p): duplication of the short arm of chromosome 17; add(18p): additional chromosomal material on the short arm of chromosome 18; 22q11DS: 22q11.2 deletion syndrome.
In the Brazilian SUS, the cost of an abdominal ultrasound is about US$ 21. In 20 of 164 patients with CHD, the AUS revealed abnormalities of clinical significance, i.e., one in every 8.2 children. Thus, the cost to identify a patient with a clinically meaningful abdominal abnormality among subjects with CHD was estimated as US$ 176.

Discussion

Studies performed before the 80s, evaluating the presence of extracardiac abnormalities in patients with CHD, had important limitations. They were carried out at times when cardiac and extracardiac evaluations using ultrasound were not yet routinely available14-17. In a literature review, only two publications in English language were found with similar goal to our study, that was to evaluate presence of abdominal malformations in patients with CHD through AUS7,8. In contrast, our study is unique in that all CHD patients underwent AUS, high resolution karyotype and FISH for detection of microdeletion 22q11.2, and all were examined by a clinical geneticist9,10.

The case and control subjects differ regarding age, as expected based on their clinical conditions. The cases with CHD, precisely because of this comorbidity, tended to have more severe disease than those who do not exhibit this anomaly and, therefore, were assessed earlier. The Pediatric ICU, where these patients were treated, is a regional referral center for cardiac diseases, thus patients with CHD have originated mostly from the countryside towns of the state of Rio Grande do Sul. The control subjects, however, were represented mainly by residents in the hospital city (Porto Alegre) or metropolitan area.

In our study, there was an association between CHD and abnormalities with clinical significance identified through AUS (12.2% in cardiac patients and 5.2% in controls, p = 0.009). This result presented an even more significance because all patients who composed our control group had abdominal symptoms or suspicion of an abdominal alteration, i.e., they are not truly asymptomatic. Besides when we compared the CHD patients with controls without suspicion of a urinary tract abnormality, the result presented an even more pronounced significance. The lower frequency of abdominal abnormalities observed in our study among CHD patients, compared to Gonzalez et al.19, could be due to the fact that our patients with CHDs were not restricted to newborns and also that all subjects underwent AUS, regardless of clinical suspicion. In the study of Murugasu et al.19, the patients were submitted only to the ultrasound study of the urinary tract, and 11.9% clinically significant abnormalities were found. Most of the other studies that described extracardiac malformations in patients with CHD did not indicate which methods were used to detect abdominal abnormalities, and were performed retrospectively through review of patient records17,18,21-25,27-30.

Renal anomalies were the most common abdominal malformations of our study, detected in 10.4% of cases. The urinary tract malformations were also prevalent in the study of Bosi et al.22. Stephensen et al.22, Amorim et al.28 and Gonzalez et al.9. Genitourinary tract abnormalities were found from 7.4 to 15.1% of patients with CHD in different series18,20,24,26 and in 15.2% of live births and in 25.3% of stillbirths in the study of Amorim et al.28. Kramer et al.19, using postangiography urography, found 8.9% of upper urinary tract abnormalities in 302 patients with CHD. Interestingly, no patient with CHD in our study had clinical symptoms of abdominal disease at the diagnosis through AUS, which coincides with the results of Murugasu et al.19 and Kramer et al.19, who found symptoms in a single patient. Thus, it is important to investigate renal malformations before cardiac surgery, even in asymptomatic patients29. However, we cannot exclude the possibility that symptomatic patients with more severe abdominal abnormalities have not survived long enough to be evaluated into a referral hospital.

The significantly higher frequency of clinically relevant abdominal malformations detected by AUS in cardiac patients with syndromic appearance in relation to the control subjects, is also a relevant finding in our study. It demonstrates the importance of physical examination, by an expert such as a clinical geneticist, on the suspicion of occurrence of malformations in other organs or systems. In our literature review, we did not find reports classifying patients into syndromic or not by dysmorphological physical examination7,8,10,18,30. Kramer et al.19 pointed that the recognition of minor malformations may serve as indicator of general problems in morphogenesis and may constitute valuable clue in the diagnosis of specific patterns of malformations. Additionally, we found a statistically significant association between malformations detected by AUS and patients with congenital abnormalities other than cardiac and abdominal (26.2%, p = 0.003). Similarly, Murugasu et al.19 found abdominal malformations in 39.1% of CHD patients with additional malformations who underwent ultrasound of the urinary tract and in 4.7% of cardiac patients without other obvious abnormalities.

The type of CHD in our case cohort showed no association with presence of clinically relevant abdominal alterations. In contrast, Gonzalez et al.19 found that the group with septal defects had a chance 3.7 times higher than the other CHD patients of presenting an abnormal AUS. However, only patients with suspicion of an abdominal abnormality underwent AUS and children with ventricular septal defect were the least likely to have undergone such examination19. Güçer et al.26 found an association of gastrointestinal and genitourinary abnormalities with conotruncal CHDs. Nonetheless, these authors conducted a retrospective study in autopsies, in which the detected gastrointestinal and genitourinary abnormalities were not limited to the abdomen but have included at least the esophagus and genital area26. Other important difference between our study and Güçer et al.26 is that multiple and more severe anomalies are expected to be more frequent in autopsies than in live births.

There was no association between chromosomal abnormalities identified by karyotyping and clinically relevant abdominal abnormalities detected through the AUS, i.e., many patients with normal karyotype also present these defects, which suggests that chromosomal anomalies are not predictors for presence of abdominal malformations. The frequency of chromosomal abnormalities reported in subsets of patients from other studies ranged from 2.6 to 12.5% (usually around 9%)7,8,18,21,22,26,29,30. Our study detected the highest rate (14.6%) and was the only one to perform karyotype analysis in all patients and to specifically assess this approach.

The frequency of 22q11.2 microdeletion observed in our cohort was 2.4%, contrasting with 0.7% in other studies.
However, this was the only study to perform FISH analysis for microdeletion 22q11.2 in all patients. Two of the four patients with the 22q11.2 microdeletion syndrome had clinically significant abnormality by AUS, representing 10% of the CHD patients with such characteristic. It is known that renal malformations are common findings in 22q11.2 microdeletion syndrome.\cite{34,35}

In our sample, there was 1 death (5%) during hospitalization among the patients with CHD and clinically significant abnormality in AUS, while 4 deaths (2.8%) occurred in the sample of CHD with normal AUS. In the study by Meberg et al.,\cite{27} mortality was significantly higher in patients with CHDs with associated disorders (29%), compared to those with CHD alone (6%, \( p < 0.0001 \)). In addition, more patients with extracardiac malformations underwent therapeutic procedures (45%) than those with CHD alone (27%, \( p < 0.0001 \)).

In our cohort, patients with CHD and malformation detected by AUS showed double of hospitalization time compared with children with CHD alone. It is known that polyvalved patients require more intensive care, suffer more complications and more surgeries, presenting also a worse prognosis.\cite{7,24}

Gonzalez et al.\cite{27} found that 36.6% of the patients with CHD had at least one significant defect identified by AUS. Taking into account that only children with suspected abnormalities were investigated, and that the AUS had a cost of US$ 866, the estimated cost to diagnose a child with an abdominal malformation with clinical significance was approximately US$ 2,363.\cite{27} However, in Brazil, the cost to find an abnormality with clinical significance in the abdomen by AUS was estimated at approximately US$ 176, if the examination is performed by the SUS. This system offer health assistance to all population, approximately US$ 176, if the examination is performed by the SUS. This system offer health assistance to all population, regardless of the country where this non-invasive screening with AUS is performed, it is still cheaper than treating comorbidities arising from complications of late diagnoses of abdominal malformations. Moreover, the cost for abdominal US is much lower than the costs to treat comorbidities arising from abdominal malformations, such as end stage renal disease in childhood.

**Conclusions**

This study demonstrated that patients with CHD have increased frequency of abdominal abnormalities identifiable by abdominal US, regardless of presenting other extracardiac malformations or syndromes. This finding suggest that it is valid to screen by US all children with CHD, even those who do not have abdominal symptoms, because the procedure is not invasive and has a good sensitivity when compared to other methods.\cite{28,30} This screening becomes even more important among syndromic patients and carriers of extracardiac malformations. Moreover, the cost for abdominal US is much lower than the costs to treat comorbidities arising from complications of late diagnoses of abdominal malformations, such as end stage renal disease in childhood.

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**Study Association**

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