22q11.2 deletion syndrome and complex congenital heart defects

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Abstract

Objective: To investigate the frequency of 22q11 deletion syndrome (22q11DS) in patients with complex congenital heart disease. **Methods:** A prospective and consecutive cohort of patients with complex heart defects was evaluated in their first hospitalization at a cardiac intensive care unit of a pediatric hospital. For each patient, an assessment form was completed with demographic information and clinical evaluation. High resolution karyotyping and fluorescence in situ hybridization (FISH) to detect the presence of 22q11 microdeletion, were performed. Heart defects were classified by a cardiologist. **Results:** The sample cohort consisted of 66 patients. Karyotypic anomalies were observed in 5 patients (7.6%); however, none of them had 22q11 deletion. Evaluation by FISH was successfully done in 65 patients, identifying 22q11 microdeletion in two patients (3.1%). Out of the 66 patients with complex defects, 52 were carriers of conotruncal malformations and in 51 patients, analysis for 22q11 microdeletion by FISH was performed. The two patients with 22q11 microdeletion belonged to this group, representing a frequency of 3.9%. They had tetralogy of Fallot. **Conclusion:** 22q11DS is a frequent abnormality among patients with complex and conotruncal heart defects. Variations of the 22q11DS frequency among studies seem to be mainly associated with criteria used for patient selection and specific characteristics of the population analyzed.

Keywords: DiGeorge syndrome; in situ hybridization; fluorescence; heart defects; congenital, chromosomes; human; pair 22.

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Introduction

Congenital cardiac malformations represent a heterogeneous group of diseases with variable hemodynamic consequences and, therefore, with different follow-up and intervention needs. Among these malformations, we highlight the complex heart defects, particularly for its severity. Also within this subgroup are the conotruncal heart defects characterized by changes in the heart outflow tract. These correspond to approximately 50% of congenital cardiopathies seen in newborns[1], representing an important association with genetic disorders, especially 22q11 deletion syndromes (22q11DS, *OMIM* #188400/#192430)[2], also known as velocardiofacial syndrome or DiGeorge syndrome[3,4].

This syndrome is characterized clinically by a high phenotypic variability, without pathognomonic findings, hindering its diagnosis. It is due to a deletion in the region 11 of the long arm of chromosome 22 (i.e., 22q11), being an autosomal dominant disorder affecting families, i.e., an affected individual has a 50% chance of transmitting it to his/her children. As for its diagnosis, high-resolution karyotyping has limitations and is able to identify less than 15% of affected patients. Fluorescence *in situ* hybridization (FISH), which can detect over 90% of the cases, is considered the gold standard[5,6].

Therefore, due to the almost non-existence of related studies among us and the variability of the indices observed in literature, the objective of the present study was to determine the frequency of 22q11DS among patients with complex heart defects.

Methods

This study was performed on a prospective and consecutive cohort of patients in their first hospitalization due to congenital cardiac malformation in the Cardiological Intensive Care Unit (CICU) of Hospital da Criança Santo Antonio (HCSA)/Complexo Hospitalar Hospital Santa Casa de Porto Alegre (CHSCPA) during one year. This cohort was part of the study by Rosa *et al*. For each patient, an assessment form with clinical data, such as gender, age, race, precedence, reason for admission, and cardiological diagnosis was completed. Description of cardiac malformations, as well as their classification into complex and conotruncal defects was performed by a cardiologist participating in the study, always taking into consideration the results of echocardiogram, cardiac catheterization, and description of the cardiac surgery. Patients also underwent high resolution band karyotyping (≥ 550 bands) and fluorescence *in situ* hybridization to detect 22q11 microdeletion using the commercially available DNA probe DiGeorge/*VCFS* Region Probe (*TUPLE* 1), followed by a standard codenaturation protocol.

The SPSS (version 12.0) and PEPI (version 4.0) softwares were used for data processing and analysis. Fischer's exact test was used to compare the frequencies observed in our study and in literature. Values of $p < 0.05$ were considered significant. This study was approved by the Research Ethics Committee of UFCSPA and CHSCPA.

Results

Out of 207 patients with congenital cardiopathies hospitalized for the first time in the CICU, and whose guardians consented to their participation in the study, 66 (31.9%) had complex malformations. Forty-three were males (62.5%) and 23 females (34.8%), and the majority were Caucasians (77.3%). Their ages ranged from 1 day to 10 years (51% were younger than 1 month). Most patients were from the country side of Rio Grande do Sul State (59.1%), and cardiac surgery was the main reason for CICU admission (74.2%). Heart defects presented by the patients are listed in Table 1. Tetralogy of Fallot (30.3%) was the most important of these defects. As for karyotyping, changes were observed in five patients (7.6%): four with free chromosome 21 trisomy, and one with free chromosome 18 trisomy. No case of 22q11 deletion was identified by this examination. Analysis using FISH technique was successfully performed in 65 patients, identifying 22q11 microdeletion in two cases (3.1%) (two patients with tetralogy of Fallot). Out of 66 patients with complex cardiac defects, 52 patients had conotruncal defects, and 51 of them underwent investigation for 22q11 microdeletion. The two patients with 22q11 microdeletion were in this group, representing a frequency of 3.9% (2/51) (Table 2).

Discussion

In our literature review, we found only one study evaluating the frequency of 22q11DS among patients with complex heart defects. Mehraein *et al*.[7], evaluating a cohort of 40 patients, observed a deletion index of 22.5%. This was significantly higher than in our study (3.1%). We believe that this might be related to selection criteria in the first study, which evaluated a cohort originated from departments of clinical genetics and pediatric cardiology in Germany.

It is known that 22q11DS has an important relationship with conotruncal defects[3], and, in our cohort, 52 out of 66 (78.8%) patients with complex congenital cardiopathy had this defect. They represented all individuals with conotruncal defect in the initial cohort of 207 patients. The frequency of 22q11DS in our study (3.9%) was similar to other indices, which are between 4% and 15%[4,8-15], but different from others who reported indices between 17% and 49%[1,16-20] (Table 2). These differences seem to be particularly related to the age of patients, their precedence, and frequency of specific heart defects, such as interruption of the aortic arch, which, among the conotruncal malformations, is associated even more with 22q11DS.

Table 1 – Congenital heart defects observed, classified according to the results of karyotypic analysis and FISH technique

		Normal Karyotype			Abnormal karyotype and normal FISH	
Congenital heart defects	Total N	Normal FISH	del22q11.2	Without FISH	+21	+18
TOF *	20	14	2		3	1
TGV *	12	11		1		
LV hypoplasia	8	8				
PA + NS *	5	5				
PA + IVC *	5	5				
RVDO *	4	4				
TA	4	4				
AT *	3	3				
LVDO *	2	2				
TAPVR	2	2				
AVSD (+ TOF) *	1				1	
Total	66	58	2	1	4	1
% +	100	88	3	1,5	6	1,5

PA, pulmonary atresia; TA, tricuspid atresia; IVC, interventricular communication; AVSD, atrioventricular septal defect; LVDO, left ventricular double outlet; RVDO, right ventricular double outlet; TAPVR, total anomalous pulmonary venous return; NS, normal septum; TA, truncus arteriosus; TGV, transposition of the great vessels; TOF, tetralogy of Fallot; LV, left ventricle; +21, free trisomy of chromosome 21; +18, free trisomy of chromosome 18; *Conotruncal defects in the cohort; + Calculated in 66 patients.

Table 2 – Comparison of 22q11DS frequency among patients with conotruncal heart defects observed in our study and the literature

Studies	Age	N	Conotruncal cardiopathy*		22q11DS (%)	p
			+	Others		
Iserin *et al.*[1]	NB	104	95 (44)	9 (6)	50 (48)	0.0000
Derbent *et al.*[20]	1 m - 9 y	30	ND (5)	ND (4)	9 (30)	0.0016
Goldmuntz *et al.*[16]	ND	17	17 (5)	-	5 (29)	0.0088
Goldmuntz *et al.*[18]	ND	251	179 (42)	72 (3)	45 (18)	0.0100
Webber *et al.*[17]	1d - 4m	46	41 (6)	5 (2)	8 (17)	0.0434
Worthington *et al.*[19]	ND	90	81 (13)	9 (2)	15 (17)	0.0306
Khositseth *et al.*[14]	ND	61	49 (8)	12 (1)	9 (15)	0.0639
Devriendt *et al.*[8]	ND	140	ND	ND	18 (13)	0.1071
Lewin *et al.*[9]	ND	73	53 (7)	20	7 (10)	0.3054
Anaclerio *et al.*[12]	1 d - 5 y	329	ND (27)	-	27 (8)	0.3999
Takahashi *et al.*[10]	1 m - 16 y	64	35 (4)	29 (1)	5 (8)	0.4604
Ziolkowska *et al.*[4]	0 - 20 y	214	160 (ND)	54 (ND)	15 (7)	0.5401
Beauchesne *et al.*[3]	18 y - 70 y	103	103 (6)	-	6 (6)	1.0000
Lammer *et al.*[15]	ND	485	296 (30)	189	30 (6)	0.5320
Voigt *et al.*[11]	4 d - 58 y	100	42 (4)	58	4 (4)	1.0000
Present study	1 d - 10 y	51	28(2)	23	2 (4)	-

N, number of patients; NB, newborn; d, days; m, months; y, years; ND, not described; *Numbers in parenthesis correspond to patients with 22q11DS and respective conotruncal defect; +, Conotruncal defects more commonly associated with 22q11DS: AAI (aortic arch interruption); TA (truncus arteriosus); TOF (tetralogy of Fallot); IVC/PA (interventricular communication with pulmonary atresia).

Iserin *et al.*[1] described a higher index of 22q11DS (48%) when evaluating newborns seen in a pediatric cardiology service in France, who presented with conotruncal defects more commonly associated with this syndrome (Table 2). It is known that these are severe defects and, depending on the age of evaluation and place of birth, individuals might not be alive to be evaluated, as suggested by Rosa *et al.*[3]. This situation is even worse in places where prenatal diagnosis of congenital cardiopathies is inadequate and there is not an appropriate infrastructure for adequate care and treatment of those patients, as in our case[3]. On the other hand, Voigt *et al.*[11], who found a frequency of SD22q11 quite similar to our work (4%), evaluated a group of patients who underwent cardiac catheterization in a cardi-

ology center in Germany. Note that these patients were characterized by more advanced age, ranging from 4 days to 58 years (mean 6.1 years), a high frequency of transposition of great vessels (a defect with little association with 22q11DS), and absence of aortic arch interruption, similar to what was observed in our cohort (Table 2).

Most of these studies do not describe patients with different chromosomal abnormalities other than 22q11DS. In our study, patients with Down's syndrome and Edwards' syndrome were identified. In this case, we do not know whether it is related to type of patient selection or even the population characteristics, since in many cases, those studies were performed in countries where, unlike Brazil, gestational interruption in cases of fetus with chromosomal anomalies is allowed. Thus, these aspects could interfere with the frequencies observed among individuals in the postnatal period. On the other hand, in other studies, such as Worthington *et al.*[19], patients with chromosomal abnormalities, or even those with an identifiable non-22q11DS syndrome, were excluded (Table 2).

Conclusion

In conclusion, 22q11DS is a common abnormality among patients with complex congenital heart and conotruncal defects. Variations between studies seem to be associated mainly with the selection process and characteristics of the population. Identification of these patients is essential for their adequate management and genetic counseling.

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