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**MALFORMAÇÕES
EXTRACARDÍACAS EM
PACIENTES PORTADORES DE
CARDIOPATIA CONGÊNITA**

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Lista de abreviaturas utilizadas

AVSD: Atrioventricular septal defect

CCs: Cardiopatias congênitas

CHDs: Congenital heart defects

CIA: Comunicação interatrial

CIV: Comunicação interventricular

C(L)T: Corrected (L) transposition

DATASUS: Departamento de Informática do Sistema Único de Saúde

DSAV: Defeito de septo atrioventricular

EA: Ebstein anomaly

EMs: Extracardiac malformations

EP: Estenose pulmonar

H: Heterotaxia

ISCMPA: Irmandade da Santa Casa de Misericórdia de Porto Alegre

LODs: Left obstructive defects

ME: Malformações Extracardiácas

MEMs: Major extracardiac malformations

OMHDs: Other major heart defects

OTDs: Outflow tract defects

PCA: Persistência do canal arterial

PDA: Patent ductus arteriosus

RODs: Right obstructive defects

SDs: Septal defects

SPSS: Statistical Package for Social Sciences

TAPVR: Total anomalous pulmonary venous return

TGA: Transposição das grandes artérias

UFCSPA: Universidade Federal de Ciências da Saúde de Porto Alegre

USD: United States Dollars

UTI: Unidade de terapia intensiva

Resumo da Dissertação

Introdução:

Malformações extracardíacas (MEs) podem estar presentes em pacientes com cardiopatia congênita (CC), levando a um aumento da morbidade e da mortalidade.

Objetivos:

Identificar a frequência e os tipos de MEs observados entre pacientes com CC.

Material e Métodos:

A amostra consistiu de pacientes avaliados na sua primeira hospitalização em uma unidade de tratamento intensivo cardíaca de um hospital pediátrico de referência do Sul do Brasil. Consideraram-se MEs aqueles defeitos que poderiam causar uma limitação física significativa, ou a morte do paciente. O aspecto sindrômico foi definido com base no exame físico realizado por um único geneticista. As CCs foram divididas de acordo com o tipo anatômico e em defeitos cianóticos e complexos.

Resultados:

Dos 343 pacientes, a maioria era do sexo masculino (53,1%), com idades variando de 1 a 5318 dias (mediana de 213 dias). O principal tipo de CC observado foi a comunicação interventricular (CIV) (15,2%). A maioria das CCs foi acianótica (63%) e não complexa (63,6%). Quarenta e cinco pacientes (13,1%) apresentavam MEs. O sistema mais afetado foi o urinário (5,3%), seguido do musculoesquelético (2,9%) e do sistema nervoso central (SNC) (2,9%). A maioria dos pacientes (80%) apresentava MEs detectadas apenas através de exames radiológicos complementares. Cem pacientes (29,2%)

foram classificados como sindrômicos e 56 (16,3%) apresentavam uma alteração cariotípica. Pacientes com CIV apresentaram mais MEs ($P=0,003$), especialmente envolvendo o SNC ($P=0,001$). Verificou-se também uma associação entre aspecto sindrômico e presença de MEs ($P<0,0001$). Esta relação aconteceu com defeitos que afetavam o SNC ($P<0,0001$), face e pescoço ($P=0,001$) e sistema musculoesquelético ($P=0,001$).

Conclusões:

A maioria dos pacientes com MEs apresentou pelo menos um defeito detectado somente através de exames radiológicos complementares. Este achado salienta a importância do rastreio desta população através de exames, como o ultrassom cerebral e abdominal. Portadores de CIV com aspecto sindrômico seriam os mais beneficiados com esta abordagem.

Palavras-chaves: cardiopatia congênita; malformação extracardíaca maior; comunicação interventricular; sistema nervoso central; ultrassom cerebral; ultrassom abdominal.

1. Introdução

1.1. Definição

De acordo com a literatura, existem várias definições para anomalias congênitas. Segundo Guiller e cols. (2007), a anomalia congênita é *“uma condição determinada por fatores causais que atuam desde o nascimento, cuja expressão clínica inclui defeitos em um ou mais órgãos, que podem ser estruturais e funcionais”*. Sendo assim, na maioria das vezes as malformações resultam de alterações no desenvolvimento embrionário que determinam uma estrutura ou insuficiência em obter o desenvolvimento completo no estágio inicial do tecido fetal (Jasen e cols., 2000). Estas anomalias podem estar associadas à presença de outros problemas comportamentais ou de desenvolvimento (Neuhäuser e Vogl, 1980).

As malformações são divididas em dois tipos: maiores e menores. Conforme Kramer e cols. (1987), uma malformação maior é aquela que traz um efeito adverso na função ou aceitação social do indivíduo. Exemplos deste tipo de defeito incluem a fenda lábio palatina, os defeitos de fechamento do tubo neural e as cardiopatias congênitas. Por outro lado, a malformação menor não traz consequência clínica ou medicamentosa para o paciente, como o apêndice pré-auricular, a prega palmar única e a clinodactilia de quintos dedos. O diagnóstico sindrômico é realizado com base na presença destas malformações, levando-se em consideração tanto o número delas como o tipo. Contudo, no geral, esta avaliação é um tanto subjetiva, e pode potencialmente variar conforme o avaliador (Neuhäuser e Vogl, 1980).

Cardiopatía congênita é um termo genérico utilizado para descrever as malformações estruturais ou funcionais do sistema cardiovascular presentes ao nascimento e que causam alterações hemodinâmicas (Ferencz e cols., 1985; Rivera e cols., 2007; Rosa e cols., 2013). Elas podem ser definidas como malformações maiores do coração ou dos grandes vasos que possuem uma significância funcional (Mitchell e cols., 1971). A maior parte desses defeitos surge em decorrência de anormalidades da embriogênese durante o período gestacional que se estende da terceira até a oitava semana, quando ocorre o desenvolvimento das principais estruturas cardiovasculares.

Entretanto, de modo global, as causas genéticas ou ambientais somente são identificadas em cerca de 10% dos casos de cardiopatía congênita, embora a compreensão de prováveis conexões genéticas esteja se ampliando (Jansen e cols., 2000). Os defeitos cardíacos congênitos estão frequentemente associados a anomalias cromossômicas, síndromes reconhecíveis e malformações extracardíacas, tendo isto fortes implicações sobre a terapêutica, o prognóstico e a informação a ser fornecida aos pais (Meberg e cols., 2007; Bensamlali e cols., 2016).

Fatores associados a uma maior incidência de cardiopatías congênitas incluem a ocorrência, durante a gestação, de rubéola materna, desnutrição e diabetes materno. Idade materna superior a 40 anos, e genitor ou irmão com defeito cardíaco congênito e alteração cromossômica (como, por exemplo, a síndrome de Down) são considerados também fatores de risco para esta malformação.

1.2. Classificação

As malformações cardíacas podem ser classificadas em dois grandes grupos, seguindo padrões clássicos. O primeiro, relaciona-se ao efeito da cardiopatia na coloração da pele, e o segundo à anatomia do coração. Do ponto de vista da coloração da pele, as anormalidades cardíacas são divididas em acianóticas e cianóticas (Atik, 2011; Rosa e cols., 2013; Aragão e cols., 2013).

Acianóticas são aquelas malformações nas quais não se verifica alteração da coloração da pele durante a avaliação clínica do paciente, pois a lesão não tem capacidade de obstruir a passagem de sangue venoso para a circulação sistêmica, não alterando assim de forma significativa a oxigenação do sangue. Os tipos mais comuns de defeitos cardíacos acianóticos são a comunicação interatrial (CIA) e a comunicação interventricular (CIV) (Jansen, 2000; Born, 2009; Croti e cols., 2013). As cardiopatias acianóticas são divididas ainda em:

- Obstrução sem desvio ou obstrução do ventrículo direito ou esquerdo (fluxo pulmonar normal): pode ser uma obstrução no preenchimento ventricular ou dificuldade de escoamento ventricular nas grandes artérias. Exemplos: Direita – estenose pulmonar; Esquerda – coarctação da aorta, interrupção do arco aórtico, estenose aórtica e estenose mitral;

- “Shunt” ou desvio esquerda–direita (hiperfluxo pulmonar): pela pressão sanguínea ser maior do lado direito que do esquerdo do coração, uma conexão anormal pode ser formada entre as câmaras cardíacas, fazendo com que o

sangue flua do lado esquerdo para o direito. Exemplos: CIV, CIA, persistência do canal arterial (PCA) e defeito de septo atrioventricular (DSAV).

Por sua vez, cardiopatias cianóticas são aquelas nas quais os pacientes clinicamente apresentam cianose, ou saturação arterial menor que 85%, pois o sangue não oxigenado entra para a circulação sistêmica. A malformação mais frequente deste grupo é a tetralogia de Fallot (Jansen, 2000; Born, 2009; Croti e cols., 2013). As cardiopatias congênitas cianóticas podem ser divididas ainda em:

- Obstrutivas com desvio direita–esquerda (hipofluxo pulmonar): é a obstrução do esvaziamento, ou enchimento do ventrículo direito, como também a existência de uma comunicação que permite que o sangue do ventrículo direito flua para o átrio ou ventrículo esquerdo sem passar pelos pulmões (“shunt” da direita para a esquerda). Exemplos: tetralogia de Fallot, atresia tricúspide, atresia pulmonar com CIV e sem CIV, transposição das grandes artérias (TGA) com estenose pulmonar (EP), anomalia de Ebstein e cardiopatias complexas com EP;

- Mistura (hiperfluxo pulmonar): são doenças complexas, na qual ocorre uma mistura do sangue arterial e do venoso antes de irem para a circulação sistêmica. Exemplos: *truncus arteriosus* comum, atresia mitral e cardiopatias complexas sem EP.

Entre as duas categorias, a cianótica é aquela que requer maior atenção por causar consequências maiores, como hipertensão pulmonar (os pulmões tornam-se incapazes de oxigenar adequadamente o sangue, o que resulta em dispneia), maior carga de trabalho (o coração aumenta a ação do bombeamento, fazendo maior força e levando à cardiomegalia e à taquicardia),

diminuição do débito cardíaco (o metabolismo celular é inadequado, pois ocorre menos ingestão de nutrientes e de oxigênio) e diminuição da saturação arterial (a presença de hemoglobina não oxigenada nos vasos sanguíneos periféricos causa uma reação sistêmica, onde o organismo produz mais eritrócitos para aumentar a distribuição de oxigênio para as células, sendo que a falta de oxigênio no sangue pode causar alterações cerebrais, como síncope, confusão mental e convulsões) (Jansen, 2000).

De acordo com a classificação anatômica, as anormalidades cardíacas são divididas da seguinte forma (Hoffman e Kaplan, 2002):

1. Comunicação interventricular (CIV), que é a forma mais comum de cardiopatia congênita (Hoffman e Kaplan, 2002). Cerca de 85 a 90% destes defeitos fecham espontaneamente em torno de um ano de idade (Du e cols., 1998). Por isso, a avaliação precoce identifica um número maior de casos do que a realizada mais tardiamente;

2. Persistência do canal arterial (PCA), que é outra lesão comum. Sua incidência varia de acordo com a idade gestacional ao nascimento e a idade no momento do estudo. Prematuros têm uma incidência maior da PCA. Esta alteração se baseia mais em uma anormalidade fisiológica do que estrutural (Anderson e cols., 1978). Sabe-se, no entanto, que o fechamento funcional precede a obliteração do canal arterial. Na maioria dos casos, o canal arterial fecha espontaneamente em torno de quatro a sete dias após o nascimento;

3. Comunicação interatrial (CIA) do tipo *ostium secundum*, quando há um forame oval patente com um pequeno “shunt” da esquerda para a direita do coração;

4. Conexão anômala parcial das veias pulmonares, que é uma malformação rara do coração. Ela se assemelha a uma PCA na produção de sobrecarga de volume do ventrículo direito;

5. Defeito do septo atrioventricular, que é mais comum em indivíduos com trissomia do cromossomo 21 (síndrome de Down) do que naqueles com constituição cromossômica normal;

6. Estenose pulmonar leve, que é muitas vezes confundida com um murmúrio inocente do fluxo pulmonar;

7. Estenose aórtica, que é quando há um gradiente de pressão através da válvula aórtica e uma válvula bicúspide não obstruída;

8. Válvula aórtica bicúspide, que não é normalmente registrada em estudos de incidência com populações pediátricas, visto que as complicações desta alteração são tardias. O indivíduo com esta alteração cardíaca pode desenvolver estenose ou incompetência valvar após os 40 anos de idade;

9. Coarctação da aorta, que é um estreitamento que ocorre na aorta, sendo uma anormalidade facilmente diagnosticada pela combinação de hipertensão de um ou ambos os membros superiores do corpo e pulsos femorais fracos ou ausentes;

10. Insuficiência mitral, consiste no fluxo retrógrado do sangue através da válvula mitral, em direção ao átrio esquerdo, cada vez que o ventrículo esquerdo se contrai (sístole).

1.3. Epidemiologia e morbimortalidade

A prevalência dos defeitos cardíacos congênitos verificada em estudos realizados nos anos 1960 era de 3 a 5 por mil nascidos vivos (Hoffman, 1968). Após, em 1995, esta aumentou para 12 a 14 por mil nascidos vivos (Hoffman, 1995). No Brasil, a prevalência destes defeitos no Estado de Minas Gerais entre os anos 1990 e 2003 foi de 9,58 por mil nascidos vivos (Amorim e cols., 2008). O motivo mais provável para o aumento dessas taxas é que previamente apenas os indivíduos com malformações mais graves eram encaminhados para os centros cardíacos, e muitos cardiologistas eram relutantes em submeter ao cateterismo pacientes com lesões mínimas (Hoffman e Kaplan, 2002).

No período de janeiro de 2013 a maio de 2014 foram registrados no Brasil 1.754.780 hospitalizações pediátricas (Ministério da Saúde - DATASUSa). Destas, 83.076 foram relacionadas a malformações congênitas, deformidades e anomalias cromossômicas em indivíduos com idade entre <1 até 19 anos, representando 4,7% das hospitalizações (Ministério da Saúde - DATASUSb).

As malformações congênitas representam 10% do total de mortes na infância, sendo que metade destes óbitos é causado por malformações cardiovasculares (Pinar, 2004). As malformações congênitas, deformidades e anomalias cromossômicas correspondem a uma das três maiores causas de mortalidade no Brasil em indivíduos com idade entre <1 até 19 anos (2,8%). (Ministério da Saúde - DATASUSc). Dentre as malformações, a do aparelho circulatório atinge 8,1% dos pacientes, sendo que as crianças menores de 1

ano são aquelas com a maior taxa de mortalidade (12,6%) (Ministério da Saúde - DATASUSd). Assim, as cardiopatias congênitas representam o maior contribuinte para a mortalidade infantil relacionado às malformações no nascimento (Reller e cols., 2008).

Devido à rápida deterioração clínica e às altas taxas de morbidade e mortalidade, é fundamental que o diagnóstico das cardiopatias congênitas seja precoce para que se possa prevenir e minimizar as complicações (Pedra e cols., 2005). As malformações cardíacas mais graves, como a tetralogia de Fallot, a TGA e o *truncus arteriosus* correspondem a 20% dos óbitos neonatais (Acharya e cols., 2004). Além disso, antes de completar o primeiro mês de vida, aproximadamente 20 a 30% das crianças com cardiopatia congênita sem tratamento vão a óbito (Gong e cols., 2003; Nina e cols., 2007).

1.4. Diagnóstico e tratamento

Os defeitos cardíacos congênitos podem ser identificados em uma idade cada vez mais precoce devido ao acompanhamento pré-natal e às possibilidades de rastreamento com a utilização de exames diagnósticos (Bregeiron e Witkowski, 2014). Além disso, o interesse sobre as cardiopatias congênitas vem aumentando devido ao grande impacto sobre a saúde, assim como a disponibilidade de exames, como a ecocardiografia, que podem orientar o diagnóstico correto (Hoffman e Kaplan, 2002).

O diagnóstico pode ser realizado utilizando a ecocardiografia, tanto no período pré-natal como perinatal, ou ao longo da vida. Entretanto, a ecocardiografia fetal é indicada apenas para gestantes de alto risco e/ou com

história familiar de malformações. Contudo, algumas cardiopatias congênitas não podem ser diagnosticadas no período pré-natal, como CIVs pequenas e CIAs, PCA e alguns casos de coarctação aórtica (Rivera e cols., 2007; Mone e cols., 2015).

O impacto sobre a saúde pode ser verificado pelo fato de que aproximadamente metade das cardiopatias congênitas é do tipo complexa e necessita de tratamento intervencionista após o nascimento, apresentando mortalidade de 20 a 40% no período neonatal (Allan e cols., 2001).

O tratamento das crianças com estas malformações e múltiplas anormalidades associadas, está relacionada com maior risco de mortalidade. Além disso, fatores como idade (mais jovem) e urgência do procedimento cirúrgico apresentam impacto negativo na evolução do paciente (Wojtalik e cols., 2005).

1.5. Malformações extracardiacas

A equipe de saúde que acompanha pacientes com cardiopatia congênita precisa estar ciente de que malformações extracardiacas (MEs) podem também estar presentes (Holt e Oram, 1960; Van Karnebeek e Hennekam, 1999). A partir dessa informação, pode-se realizar uma avaliação mais detalhada e dirigida dos pacientes com cardiopatia congênita visando a identificação dessas malformações. Com isso, pode-se prevenir futuras complicações, principalmente relacionadas ao desenvolvimento neuropsicomotor, e auxiliar na realização de aconselhamentos para futuras gestações (Karande e cols., 2014).

A ME, quando presente em associação à cardiopatia congênita, pode aumentar o risco de ocorrência de comorbidades e de morte da criança, tornando uma intervenção cirúrgica arriscada (Rosa e cols., 2012; Rosa e cols., 2013). A presença de ME possui um grande impacto na evolução clínica de pacientes com CC, muitas vezes necessitando de avaliação médica por outras especialidades ou uma diferente intervenção cirúrgica, fora a do coração, antes do tratamento da cardiopatia congênita (Egbe e cols., 2014).

A associação entre cardiopatia congênita e ME pode envolver defeitos em diferentes partes do corpo, como os sistemas nervoso central, respiratório, digestório, musculoesquelético e geniturinário (Jaiyesimi e Antia, 1979; Jullian e Farrú, 1986; Rosa e cols., 2013).

Bosi e cols. (2003), verificaram que 24% das crianças com cardiopatia congênita tinham anomalias extracardíacas associadas. Os sistemas e regiões afetados foram: urogenital (16,9%), musculoesquelético (22,3%), craniofacial (incluindo anomalias oculares e auriculares - 19,3%), gastrointestinais (16,9%), sistema nervoso central (10,6%), respiratório (2,6%) e tegumentar (1,7%).

Em 2005, Güçer e cols. observaram que 45% dos pacientes portadores de cardiopatias congênitas apresentavam ME associadas. Estas foram classificadas em malformações craniofaciais (19,7%), do aparelho geniturinário (15,1%), do sistema musculoesquelético (13,4%), do sistema respiratório (13,1%), do sistema gastrointestinal (11,1%), do sistema nervoso central (10,5%) e do baço (4,6%). Os autores apontam também a presença de MEs em todos os casos de pacientes com CIVs e CIAs. No mesmo ano, Wojtalik e cols. realizaram um estudo retrospectivo observacional no qual identificaram 1856 crianças com cardiopatia congênita, sendo que destas, 84 (4,5%)

apresentavam MEs associadas. Entre os casos que apresentavam MEs associadas, 35,7% envolviam o sistema digestório, 22,4% o urinário e 14,3% o nervoso central (Wojtalik e cols., 2005).

No estudo de Amorin e cols. (2008) foram identificados 87 casos de recém nascidos vivos com cardiopatia congênita sem diagnóstico sindrômico com anomalias em outros órgãos. Os sistemas mais frequentemente acometidos foram o geniturinário (48,3%) e o nervoso central (45,9%), sendo que a maioria apresentava malformações em mais de um sistema ou órgão.

Gonzalez e cols. (2009) investigaram 230 recém nascidos com diagnóstico presumido de cardiopatia congênita (por ecocardiografia fetal). Eles verificaram uma alta prevalência de MEs identificadas através da ultrassonografia craniana (32 a 42%) e abdominal (32 a 69%). Cerca de 50% dos pacientes apresentavam uma ou mais ME. A seguir, em 2010, Lima Leite e cols. descreveram o diagnóstico de MEs através da necropsia em 85,7% dos natimortos estudados com cardiopatia congênita. Dentre elas, destacaram-se as malformações do sistema musculoesquelético (26,7%) e do sistema nervoso central (20%). No ano seguinte, Miller e cols. (2011) relataram que as cardiopatias congênitas estariam mais associadas a defeitos musculoesqueléticos, principalmente associados a alterações que envolvem a diferenciação precoce e a migração das células do mesoderma.

Mais recentemente, em um estudo realizado com 560 crianças diagnosticadas com cardiopatia congênita, Karande e cols. (2014) verificaram que 17,5% delas também apresentavam MEs associadas. Em 2016, Bensamlali e cols. realizaram um estudo com 2036 fetos com cardiopatia

congenita e/ou anormalidade cardíaca e verificaram que 11,7% deles possuíam ME associadas.

Portanto, indivíduos com cardiopatia congênita que apresentam MEs associadas ou não a síndromes genéticas, possuem um risco maior de morbidade e mortalidade (Marino e Digilio, 2000; Clark, 2004; Meberg e cols., 2007). Com isso, é fundamental obter dados sobre como os diferentes tipos de MEs podem influenciar na investigação e nas estratégias terapêuticas destas crianças com cardiopatia congênita (Eskedal e cols., 2004). Isto possui importantes implicações sobre o manejo e o prognóstico destes pacientes.

Desta forma, procuramos através deste estudo identificar a frequência e os tipos de MEs detectadas em crianças com cardiopatia congênita hospitalizadas em uma unidade de tratamento intensivo cardíaca de um hospital de pediátrico de referência do Sul do país.

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2. Objetivos

2.1. Objetivo Geral

Identificar a frequência e os tipos de malformações extracardíacas em crianças diagnosticadas com cardiopatia congênita hospitalizadas em uma unidade de tratamento intensivo pediátrica cardiológica de referência do Sul do país.

2.2. Objetivos Específicos

- Correlacionar os tipos de cardiopatia congênita e o aspecto sindrômico com a presença de malformações extracardíacas;

- Avaliar os tipos de tratamento necessários e realizados envolvendo as malformações extracardíacas identificadas, com o período de realização dos mesmos, bem como o número de intervenções realizadas.

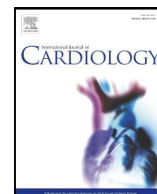
3. Artigo científico redigido em inglês

Major Extracardiac Malformations among Patients with Congenital Heart Defects

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Major Extracardiac Malformations among patients with congenital heart defects



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Congenital heart defects (CHDs) are the most common malformations observed at birth, with an incidence of 4–19:1000 live births [1]. They present a great impact on child morbidity and mortality, causing high costs to health care systems. According to DATASUS, from May 2013 to May 2014, 12,647 patients from 0 to 19 years with CHDs were hospitalized in Brazil, being spent USD 25,735,804.36 in health services [2].

Congenital heart disease may be associated with extracardiac malformations (EMs), increasing morbidity and mortality, and making cardiac surgery a risk. Therefore, it is essential to provide data about the frequency and types of EMs and how they can influence therapeutic strategies for treating children with CHD [1].

Thus, the aim of this study was to identify the frequency and types of major extracardiac malformations (MEMs) among patients with CHDs, as well as possible associations. It was evaluated 343 patients hospitalized for the first time in a cardiac and pediatric intensive care unit of a reference hospital from Southern Brazil, during the period of one year and seven months. Patients were consecutively and prospectively

assessed. Many patients included in our sample were previously described in studies developed by Zen et al. [3] and Rosa et al. [4].

It was considered EMs those that fit the major type at classification suggested by Czeizel [5], i.e., those that could cause the patient's death or a significant physical limitation that require treatment. The syndromic aspect was defined based solely on physical examination by a medical geneticist, taking into account both quantitatives (number of dysmorphisms) and qualitative data (type and pattern of dysmorphic features). The cardiac diagnosis was obtained by echocardiographic studies, being often confirmed by surgery and/or cardiac catheterization. CHDs were divided according to the classification of Botto et al. [6] and in cyanotic and complex defects, following classic patterns.

Data processing was carried out by creating a database in Microsoft Excel 2010 and Statistical Package for Social Sciences (SPSS) version 18.0 for Windows. For analysis, Fisher's exact test and chi-square test were used. P values <0.05 were considered statistically significant. The study was approved by the Ethics Research Committee of the Hospital.

From the 343 patients with CHD who composed our sample, mostly were male (53.1%) and eurodescendant (80.2%), ages ranging from 1 to 5318 days (median of 213 days). Regarding origin, 192 patients (56%) came from interior of the Rio Grande do Sul State. The main reason for hospitalization was to performance of cardiac surgery (67.6%), followed by cardiac evaluation (10.5%) and catheterization (9%). The main group of CHD observed was the septal (28.3%), followed by outflow tract defects (22.2%) (Table 1). Regarding type of CHD, ventricular septal defect (15.2%), atrial septal defect (13.1%) and tetralogy of Fallot (11.7%) were the most frequent defects. Most CHDs were acyanotic (63%) and non-complex (63.6%).

Forty five patients (13.1%) presented MEMs. The most affected systems were the urinary system (5.3%), followed by musculoskeletal (2.9%) and central nervous (2.9%) systems (Tables 1 and 2). The number of MEMs by patient ranged from 0 to 4 (mean of 0.2). The majority of patients (80%) presented MEMs only detected by complementary radiological exams (only 18 patients had defects identified through physical examination).

One hundred patients (29.2%) were classified as syndromic and 56 (16.3%) presented a karyotypical abnormality (Table 2). The main

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Table 1
Extracardiac malformations verified according to congenital heart defects classified by Botto et al. [6].

Extracardiac malformations (Systems and types)	Group (N)											Total %
	H	C(L)T	OTDs	AVSDs	TAPVR	EA	RODs	LODs	SDs	PDA	OMHDs	
Central Nervous System	1	-	1	1	-	-	-	-	6	1	-	10 (2.9)
Dilated ventricles	1	-	-	-	-	-	-	-	2	1	-	4
Corpus callosum agenesis	-	-	-	-	-	-	-	-	2	-	-	2
Dandy-Walker malformation	-	-	1	-	-	-	-	-	1	-	-	2
Brain hypoplasia	-	-	-	1	-	-	-	-	-	-	-	1
Hydrocephalus	-	-	-	-	-	-	-	-	1	-	-	1
Myelomeningocele	-	-	-	-	-	-	-	-	1	-	-	1
Arnold-Chiari malformation	-	-	-	-	-	-	-	-	1	-	-	1
Face and Neck	-	-	2	1	-	-	-	1	3	-	-	7 (2)
Laryngo/tracheomalacia	-	-	1	-	-	-	-	1	1	-	-	3
Anterior laryngeal web	-	-	-	-	-	-	-	-	1	-	-	1
Eyelid coloboma	-	-	-	-	-	-	-	-	1	-	-	1
Cleft lip	-	-	1	-	-	-	-	-	-	-	-	1
Cleft palate	-	-	-	-	-	-	-	-	1	-	-	1
Choanal atresia	-	-	-	1	-	-	-	-	-	-	-	1
Urinary tract	-	-	5	3	-	1	3	2	3	1	-	18 (5.3)
Pyelocalyceal dilatation	-	-	4	1	-	-	3	-	2	2	-	12
Pyelocalyceal duplication	-	-	-	2	-	-	-	-	-	-	-	2
Multicystic kidney	-	-	-	-	-	1	1	-	-	-	-	2
Renal cyst	-	-	-	-	-	1	-	-	1	-	-	2
Renal agenesis	-	-	1	-	-	-	-	-	-	-	-	1
Hypoplastic kidney	-	-	-	-	-	-	-	1	-	-	-	1
Ectopic kidney	-	-	-	-	-	-	-	-	1	-	-	1
Genital system	-	-	1	-	-	-	-	1	2	-	-	4 (1.2)
Hypospadias	-	-	-	-	-	-	-	1	1	-	-	2
Cryptorchidism	-	-	1	-	-	-	-	-	1	-	-	2
Gastrointestinal tract	-	-	-	-	-	-	1	1	3	1	-	6 (1.8)
Esophageal atresia	-	-	-	-	-	-	-	1	1	-	-	2
Multiseptate gallbladder	-	-	-	-	-	-	-	-	1	-	-	1
Duodenal stenosis	-	-	-	-	-	-	-	-	1	-	-	1
Imperforate anus	-	-	-	-	-	-	1	-	-	-	-	1
Anteriorized anus	-	-	-	-	-	-	-	-	-	1	-	1
Abdomen	2	-	1	1	-	-	-	-	2	-	-	6 (1.8)
Inguinal hernia	-	-	1	1	-	-	-	-	2	-	-	4
Abdominal situs inversus	2	-	-	-	-	-	-	-	-	-	-	2
Thorax	2	-	1	-	-	-	-	2	-	-	-	5 (1.5)
Thoracic situs inversus	2	-	-	-	-	-	-	-	-	-	-	2
Tracheoesophageal fistula	-	-	-	-	-	-	-	1	-	-	-	1
Thymic agenesis	-	-	1	-	-	-	-	-	-	-	-	1
Bronchomalacia	-	-	-	-	-	-	-	1	-	-	-	1
Musculoskeletal system	-	-	1	-	1	-	1	2	3	2	-	10 (2.9)
Vertebral abnormalities	-	-	-	-	-	-	1	1	1	1	-	4
Rib anomalies	-	-	-	-	-	-	-	1	1	1	-	3
Radial agenesis	-	-	-	-	-	-	1	-	1	-	-	2
Congenital hip dislocation	-	-	1	-	-	-	-	-	1	-	-	2
Thumb agenesis	-	-	-	-	-	-	-	-	1	-	-	1
Scoliosis	-	-	-	-	1	-	-	-	-	-	-	1
Club feet	-	-	-	-	-	-	-	-	1	-	-	1
Total (Patients)	8	1	76	40	9	4	34	52	97	13	9	343 (100)

H: Heterotaxia; C(L)T: Corrected (L) transposition; OTDs: Outflow tract defects; AVSDs: Atrioventricular septal defect; TAPVR: Total anomalous pulmonary venous return; EA: Ebstein anomaly; RODs: Right obstructive defects; LODs: Left obstructive defects; SDs: Septal defects; PDA: Patent ductus arteriosus; OMHDs: Other major heart defects.

chromosomal alteration verified was trisomy 21 (87.5%). Syndromic aspect was associated to the presence of atrioventricular septal defect ($P < 0.0001$) and septal defects ($P = 0.048$), in special ventricular septal defects ($P = 0.020$). Abnormal karyotype was related to the presence of atrioventricular septal defect ($P < 0.0001$) and ventricular septal defects ($P = 0.012$).

We did not verify an association between a specific group of CHDs and the presence of MEMs. Despite this, patients with septal defects had more MEMs involving specifically the central nervous system ($P = 0.034$). As for the type of CHD, patients with ventricular septal defect had significantly more MEMs than other types ($P = 0.003$), especially affecting the central nervous system ($P = 0.001$). It was verified an association between syndromic aspect and presence of MEMs ($P < 0.0001$). This relationship happened with defects specifically affecting central nervous system ($P < 0.0001$), face and neck ($P = 0.001$) and musculoskeletal system ($P = 0.001$).

According to the literature, EMs have been described in 7 to 50% of CHD patients [1], and in our study this frequency was 13.7%. These differences may be explained, at least in part, by the profile of the samples, which are very heterogeneous, both in relation to sample sizes as form of EM evaluation.

In our study, the most affected system by MEMs was the urinary tract (6.1%), being the pyelocalyceal dilatation the most common malformation. These findings are in accordance with several studies described in literature [1,7,8]. It is noteworthy in our sample the association verified between central nervous system abnormalities (the second most affected system) and septal defects, more specifically ventricular septal defects. We believe that this finding may be related to the association observed between these CHDs and the syndromic aspect. It is known that EMs are related to genetic syndromes, including chromosomal ones [9]. However, it is noteworthy in our study that the presence of MEMs was only linked to the syndromic aspect and

Table 2

Extracardiac malformations classified according to the presence of syndromic aspect and abnormal karyotype.

Extracardiac Malformation	Syndromic Aspect		Abnormal Karyotype		Total N (%)
	Yes N	No N	Yes N	No N	
Central Nervous System	9	1	3	7	10 (2.9)
Dilated ventricles	3	1	1	3	4
Corpus callosum agenesis	2	-	1	1	2
Dandy-Walker malformation	2	-	-	2	2
Brain hypoplasia	1	-	1	-	1
Hydrocephalus	1	-	-	1	1
Myelomeningocele	1	-	-	1	1
Arnold-Chiari malformation	1	-	-	1	1
Face and Neck	7	-	2	7	7 (2)
Laryngo/tracheomalacia	3	-	1	2	3
Anterior laryngeal web	1	-	-	1	1
Eyelid coloboma	1	-	-	1	1
Cleft lip	1	-	-	1	1
Cleft palate	1	-	-	1	1
Choanal atresia	1	-	1	-	1
Urinary tract	9	9	3	15	18 (5.3)
Pyelocalyceal dilatation	6	5	2	9	11
Pyelocalyceal duplication	1	1	-	2	2
Multicystic kidney	2	-	-	2	2
Renal cyst	2	-	1	1	2
Renal agenesis	-	1	-	1	1
Hypoplastic kidney	-	1	-	1	1
Ectopic kidney	-	1	-	1	1
Genital System	3	1	-	4	4 (1.2)
Hypospadia	2	-	-	2	2
Cryptorchidism	1	1	-	2	2
Gastrointestinal Tract	4	2	1	5	6 (1.8)
Esophageal atresia	1	1	-	2	2
Multiseptate gallbladder	1	-	-	1	1
Duodenal stenosis	1	-	1	-	1
Imperforate anus	-	1	-	1	1
Anteriorized anus	1	-	-	1	1
Abdome	3	3	-	6	6 (1.8)
Inguinal hernia	2	2	-	4	4
Abdominal situs inversus	1	1	-	2	2
Thorax	3	2	1	4	5 (1.5)
Thoracic situs inversus	1	1	-	2	2
Tracheoesophageal fistula	1	-	-	1	1
Thymic agenesis	-	1	-	1	1
Bronchiomalacia	1	-	1	-	1
Musculoskeletal system	8	2	1	9	10 (2.9)
Vertebral abnormalities	3	1	-	4	4
Rib anomalies	3	-	-	3	3
Radial agenesis	2	-	1	1	2
Congenital hip dislocation	2	-	1	1	2
Thumb agenesis	1	-	1	-	1
Scoliosis	-	1	-	1	1
Club feet	1	-	-	1	1
Total	100	243	56	287	343 (100)

not to the presence of a chromosomal abnormality, indicating that many non-chromosomal syndromes frequently occur with presence of these defects. From all patients with trisomy 21, the main chromosomal alteration verified in our sample (87.5%), only 12.2% had a MEM. This result also highlights the importance of the physical examination performed by a clinical geneticist or other trained health professional in dysmorphology.

Most patients with a MEM from our sample (80%) presented at least one defect only detected through complementary radiological exams. This finding also stands out the importance of the screening through brain and abdominal ultrasound of this population, an approach suggested by some authors [4,10]. Based on our findings, patients with septal defects, especially ventricular septal defects presenting a syndromic aspect, may be the most benefited with this approach.

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none.

Conflict Of interest

The authors report no conflicts of interest.

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4. Considerações finais

O presente estudo faz parte de dois projetos maiores intitulados **“Incidência e caracterização clínica de pacientes com cardiopatia congênita que internam na Unidade de Tratamento Intensivo Cardiológica do Hospital da Criança Santo Antônio e detecção da síndrome de deleção 22q11.2 através de exame de cariótipo sincronizado e de técnica de hibridização in situ fluorescente (FISH)”** e **“Identificação de fatores de risco gestacionais e familiares para cardiopatia congênita em pacientes admitidos na unidade de tratamento intensivo (UTI) de um hospital pediátrico de Porto Alegre”**, aprovados pelos Comitês de Ética em Pesquisa (CEP) da Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) e da Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA).

Nosso estudo traz informações relevantes que permitem a compreensão do perfil dos pacientes com cardiopatia congênita hospitalizados em uma UTI pediátrica de um centro de referência. A existência das malformações extracardíacas associadas muitas vezes dificulta ou retarda as intervenções relacionadas à própria cardiopatia congênita. Além disso, pode ser necessário tratar primeiro a malformação extracardíaca, para depois corrigir a cardiopatia congênita. Os profissionais da área da saúde, ao conhecer melhor as cardiopatias congênitas e suas possíveis associações, podem atuar intervindo de forma preventiva e terapêutica, melhorando a qualidade de vida e a sobrevida destes pacientes.

O material coletado neste projeto continuará sendo utilizado para a avaliação de possíveis associações das malformações extracardíacas maiores com outras variáveis, como dismorfias menores e prognóstico, bem como de tipos de tratamento necessários e realizados envolvendo estas malformações, com o período de realização dos mesmos e o número de intervenções realizadas. Isto resultará assim no desenvolvimento de novos estudos, incluindo dissertações e teses.

Concomitante ao desenvolvimento deste projeto, também foram produzidos outros artigos científicos vinculados ao Grupo de Genética Humana da UFCSPA (ver em Anexos).

5. Anexos

5.1. Pareceres dos Comitês de Ética da UFCSPA e SCMPA



Irmandade da Santa Casa de Misericórdia de Porto Alegre

Rua Prof. Annes Dias, 285 - Telefone: (51) 3214.8080 - Fax: (51) 3214.8585
 CEP 90020-090 - Porto Alegre - Rio Grande do Sul - CNPJ: 92815000-0001-68
 Site: www.santacasa.org.br - E-mail: marketing@ santacasa.tche.br



Compromisso com a excelência

Dr. Giorgio A. Paskulin
 Pesquisador Responsável
 Projeto 1014/05

Carta nº 004/06 CEP/ISCMPA

Porto Alegre, 10 de março 2006.

O Comitê de Ética em Pesquisas da Irmandade da Santa Casa de Misericórdia de Porto Alegre, em resposta à solicitação do pesquisador responsável, referente ao projeto de pesquisa intitulado: *"Prevalência e caracterização clínica dos pacientes portadores de microdeleção 22q11 detectados através da técnica de hibridização in situ fluorescente (FISH) que internam por suspeita de cardiopatia congênita numa Unidade de Tratamento Intensivo de um hospital pediátrico"*, que está sendo conduzido em nossa Instituição sob a responsabilidade do Dr. Giorgio A. Paskulin, emiti a seguinte informação:

"A Conep após o envio do presente projeto para avaliação, informa que o referido estudo não necessita da aprovação da mesma, sendo de responsabilidade do CEP a aprovação final. O presente Comitê após esta análise, não encontra óbices ao desenvolvimento do estudo em nossa Instituição".

Sendo o que tínhamos para o momento, manifestamos nossos protestos de apreço e consideração.

Atenciosamente,

Dr. Cláudio Telöken
 Coordenador do CEP/ISCMPA

Comitê de Ética em Pesquisa - CEP/ISCMPA Fone/Fax (51) 3214-8571 - e-mail: cep@santacasa.tche.br
 Reconhecido: Comissão Nacional de Ética em Pesquisa - CONEP / Ministério da Saúde
 IRB - Institutional Review Board pelo U.S. Department of Health and Human Services (DHHS)
 Office for Human Research Protections (ORPH) sob número - IRB00002509.
 FWA - Federalwide Assurance sob número - FWA00002949.



MINISTÉRIO DA EDUCAÇÃO
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CEP 90050-170 – PORTO ALEGRE – RS - cep@fffcempa.tche.br

Of. 192/06-CEP

Porto Alegre, 13 de abril de 2006.

Ilmo. Sr.

Prof. Giorgio Adriano Paskulin

Nesta Faculdade

Senhor Professor

Informamos que seu projeto “Prevalência e Caracterização Clínica dos Pacientes que Internam na Unidade de Tratamento Intensivo Cardiológica do Hospital da Criança Santo Antônio e Detecção da Síndrome de Deleção 22q11 Através de Exame de Cariótipo Sincronizado e de Técnica de Hibridização in situ Fluorescente (FISH).”, Processo nº 048/05, foi avaliado pelo Comitê de Ética em Pesquisa, na reunião de 13 de abril de 2006, sendo o projeto aprovado, conforme parecer consubstanciado nº 153-06, em anexo.

Outrossim informamos que de acordo com o Art. 4º, letra c, do Regulamento do CEP, V. Sa. deverá nos encaminhar relatórios semestrais do desenvolvimento do projeto.

Atenciosamente,



Prof. José Geraldo Vernet Taborda
Coordenador do CEP/FFFCMPA

5.2. Outros artigos publicados não relacionados à dissertação

RESEARCH LETTER

Trisomy 18 and holoprosencephaly

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Gabriela S. da Silva⁴ | Jamile D. Correia² | Ernani B. da Rosa² |
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TO THE EDITOR:

Trisomy 18 or Edwards syndrome is considered the second most common autosomal trisomy at birth, with an estimated prevalence of 1:3,600–1:8,500 live births (Embleton, Wyllie, Wright, Burn, & Hunter, 1996; Rasmussen, Wong, Yang, May, & Friedman, 2003; Root & Carey, 1994). Its clinical manifestations are broad and involve multiple systems (Cereda & Carey, 2012; Rosa et al., 2011; Rosa, Rosa, Zen, Graziadio, & Paskulin, 2013). As for central nervous system abnormalities, several anomalies have been described among patients with trisomy 18 and include cerebellar hypoplasia, corpus callosum agenesis, hydrocephalus, Arnold-Chiari malformation, microgyria, arachnoid cysts, and brain periventricular heterotopia (Cereda & Carey, 2012; Rosa et al., 2013; Viora et al., 2007). Neural tube defects, such as anencephaly and myelomeningocele, have also been described as part of the clinical spectrum of the syndrome (Rosa et al., 2013). However, the association between trisomy 18 and holoprosencephaly, despite having been previously described, appears to be unusual (Berry, Gosden, Snijders, & Nicolaides, 1990; Chen et al., 2012; Ong, Tonks, Woodward, Wyldes, & Kilby, 2007; Springett et al., 2015; Viora et al., 2007; Wong et al., 1999).

Analyzing the sample of patients evaluate in the Fetal Medicine Service of the Hospital Materno Infantil Presidente Vargas, a reference service in Rio Grande do Sul, Brazil, in the period from January 2005 to July 2016, we identified 14 fetuses diagnosed with trisomy 18. From them, only one (7.1%) presented the finding of holoprosencephaly. The patient was the first child of a young couple. The mother started the evaluation at 22 weeks of gestation due to the ultrasound finding

of fetal holoprosencephaly with associated facial features (including hypotelorism, hypoplastic nose, and midline labial cleft). Clenched fist with overlapping fingers and rocker bottom feet were also noted later (Figure 1). Holoprosencephaly was confirmed through magnetic resonance imaging (Figure 2). Fetal echocardiography revealed the presence of a large ventricular septal defect. The child, a girl, died 40 hr after birth.

The association between holoprosencephaly and trisomy 18 is not common (Solomon, Rosenbaum, Meck, & Muencke, 2010). It is estimated that holoprosencephaly occurs in 4–8% of patients with trisomy 18 (Demir, Dogan, Peker, Bulan, & Tuncer, 2013), a frequency very similar to that observed in our study (7.1%). Furthermore, from all patients with holoprosencephaly that have chromosomal abnormalities, trisomy 18 is found in only 1 to 2% of cases (Solomon et al., 2010). In our literature review, we found few papers describing this association. Several of them consist of case reports (Berry et al., 1990; Chen et al., 2012; Demir et al., 2013; Ong et al., 2007; Viora et al., 2007; Wong et al., 1999). It is noteworthy that the description of holoprosencephaly in case series of patients with trisomy 18 is considered very rare. Actually, we identified only one that made reference to this finding. In the large series of patients described by Springett et al. (2015), which evaluated 468 live born babies with trisomy 18, 21% had description of a nervous system anomaly; however, only 2 (0.4%) presented arhinencephaly/holoprosencephaly.

Holoprosencephaly is the most common structural defect of the developing forebrain in humans (Solomon et al., 2010; Winter, Kennedy, & Woodward, 2015) and it is often accompanied by facial defects of varying severity (Ong et al., 2007). Its etiology is heterogeneous and

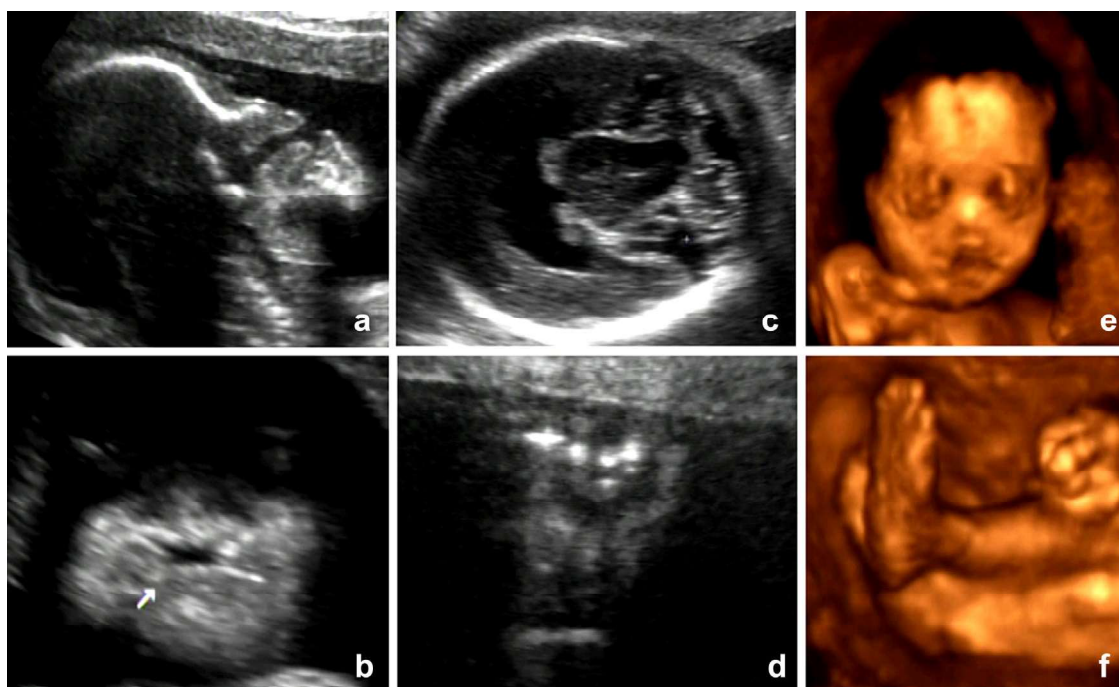


FIGURE 1 Two and three-dimensional ultrasounds showing the craniofacial features (including hypotelorism, hypoplastic nose, and a midline labial cleft) and holoprosencephaly identified in the fetus (a–c and e). Clenched fist and rocker bottom feet can also be seen in “d” and “f,” respectively. [Color figure can be viewed at wileyonlinelibrary.com]

involves both genetic and environmental causes; however, it is estimated that chromosomal abnormalities are responsible for 24–46% of cases (Berry et al., 1990; Ong et al., 2007; Solomon et al., 2010; Winter et al., 2015). Among them, trisomy 13 is the most common, accounting for up to 75% of cases (Solomon et al., 2010). It is noteworthy that trisomy 18 has also been rarely described among patients with holoprosencephaly. In the sample of 38 fetuses with holoprosencephaly described by Berry et al. (1990), there is the description of one case (2.6%) with trisomy 18. Ong et al. (2007) evaluating 113 reported cases of holoprosencephaly among births and terminations found that one of them (0.9%) had trisomy 18. In the case series of Lim et al. (2008) with 13 patients with holoprosencephaly, there was description of only one case of trisomy 18 (7.7%). From the three fetuses with first-trimester ultrasound diagnosis of holoprosencephaly described by Wong et al. (1999), one presented trisomy 18.

However, stand out that in the study developed by Goetzinger, Stamilio, Dicke, Macones, & Odibo, 2008, evaluating a large sample of 62,111 women referred for ultrasound and genetic evaluation, 32 fetuses were diagnosed with holoprosencephaly and none of them had trisomy 18.

It is also noteworthy that holoprosencephaly is associated with monosomy 18p. Around 10–15% percent of these patients have severe brain/facial malformations evocative of holoprosencephaly spectrum disorders (Turleau, 2008). Nowadays, it is known that there is a gene located at 18p11.31 region, called *TGIF* (Transforming Growth Factor-Beta-Induced Factor) [OMIM *602630], whose mutations (related to haploinsufficiency of this gene) are one of the known genetic causes of holoprosencephaly (Gripp et al., 2000; Turleau, 2008). However, unlike some of the major and better-understood holoprosencephaly-related genes mutations (i.e., *SHH*, *ZIC2*, and *SIX3*), *TGIF* mutations appear to be far less penetrant

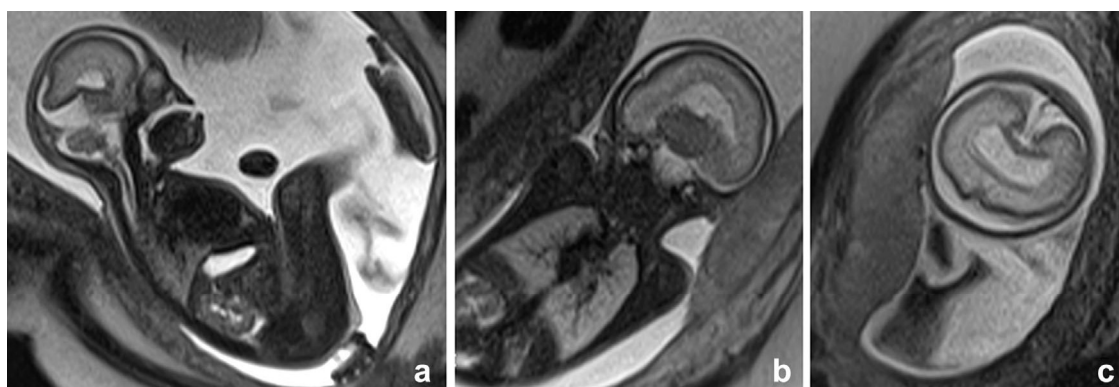


FIGURE 2 Aspect of the holoprosencephaly at magnetic resonance (a–c)

(Keaton et al., 2010). Moreover, until now there are no evidences about the possible effect of a gain function or a triplication of *TGIF*.

Thus, our findings agree with previous observations that holoprosencephaly is infrequently associated with trisomy 18. Maybe, these cases could be more common in prenatal series, as noted in some studies describing trisomy 18 among fetuses with holoprosencephaly. Trisomy 18 should always be remembered in cases of holoprosencephaly, especially without features of trisomy 13, as polydactyly, micro/anophthalmia, cleft lip/palate, and aplasia cutis. More reports will be important to understand what mechanisms and genes located at chromosome 18 could be related to the development of holoprosencephaly in individuals with trisomy 18, as well as to verify the real frequency of holoprosencephaly among individuals with this chromosomal abnormality.

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Trisomy 18 and Eye Anomalies

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TO THE EDITOR:

Trisomy 18 or Edwards syndrome is a well-known chromosomal condition that occurs in around one per 3,600–8,500 live births [Carter et al., 1985; Goldstein and Nielsen, 1988; Root and Carey, 1994; Embleton et al., 1996; Rasmussen et al., 2003]. Despite the high infant mortality usually associated seen in these patients [Lin et al., 2006; Niedrist et al., 2006; Rosa et al., 2011], recent studies are documenting an improvement in their survival [Shanske, 2006; Hsiao et al., 2009; Meyer et al., 2016; Nelson et al., 2016]. Reports of long-term survivors also have been published [Shanske, 2006; Hsiao et al., 2009], which reinforces the need for evaluation and treatment of associated abnormalities even to improve the quality of life of these patients.

Trisomy 18 is clinically characterized by a broad spectrum of abnormalities. More than 100 different clinical features were already described, and these include eye anomalies [Rosa et al., 2011; Cereda and Carey, 2012; Rosa et al., 2013]. However, it is noteworthy, that eye anomalies have been scarcely reported and poorly mentioned in literature [Calderone et al., 1983; Springett et al., 2015].

Reviewing the clinical features of our sample of patients with trisomy 18 that belong to the same study by Rosa et al. [2011] that evaluated a consecutive sample attending in a Clinical Genetics Service from South Brazil, we verified that from 31 patients, 4 (13%) had description of eye anomalies. These consisted of corneal opacities ($n = 2$), microphthalmia ($n = 1$), and cataract ($n = 2$). One of the patients with corneal opacities presented with corneal leukoma associated with cataract, and received the diagnosis of Peters anomaly. All four patients had full trisomy 18, and one of them also had triple X (48,XXX,+18). Two were female and two male. Their ages at moment of the evaluation ranged from 7 to 18 days (mean of 11.5 days). None of them presented with additional features (as, for e.g., history of congenital infections) that could justify the presence of these eye anomalies.

How to Cite this Article:

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A large number of different ocular findings have been described in trisomy 18. These usually consist of external eyes abnormalities, as short and slanting palpebral fissures, inner epicanthic folds, ptosis, sparse or abnormally long eyelashes, abnormally thick lids, and blepharophimosis [Evans et al., 1990; Rosa et al., 2013]. In our literature review, we found only one study describing the frequency of eye anomalies in trisomy 18. Springett et al. [2015] reported a frequency of 5% among 468 live births with trisomy 18. Although, this frequency seems to be lower than in our series, there was not a significant difference from the frequency verified in our study, when we applied the Fisher exact test ($P = 0.061355$).

Calderone et al. [1983] conducted a comprehensive review about the ophthalmologic histopathology associated with trisomy 18. The authors at that time stand out about the misconception that eye anomalies are not common in trisomy 18. These impressions seems to be related to the small number of studies that addresses this issue and the nature of the case assessment, usually limited to

Conflicts of interest: None.

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external eye abnormalities apparent at clinical evaluation [Calderone et al., 1983]. Thus, many ophthalmologic findings could be underdiagnosed and the relatively low number of cases described could reflect incomplete examination and reporting.

Calderone et al. [1983] pointed that the most commonly affected ocular structures in trisomy 18 appear to be the cornea, anterior uveal tract, lens, and retina. Retinal folds would be the single most common histopathological finding [Calderone et al., 1983]. In our sample, none of the patients underwent ophthalmologic histopathology. However, we verified the presence of some few reported findings. Microphthalmia, corneal opacities and cataractous changes, features verified in our study, were occasionally reported, especially in older studies, published in 1960's and 1970's and in some journals not indexed to PubMed [Calderone et al., 1983; Jaruratanasirikul and Jinorose, 1994; Mataftsi et al., 2011; Acar et al., 2014].

Microphthalmia is characterized by a small structurally normal eye [Verma and Fitzpatrick, 2007]. Its overall prevalence is 1–2.5 per 10,000 births [Verma and Fitzpatrick, 2007; Stoll et al., 2012]. Microphthalmia is usually associated to other ocular and systemic findings [Nishina et al., 2012]. Around 25% of the patients with microphthalmia present a chromosomal abnormality, as trisomy 13 (Patau syndrome) and Wolf–Hirschhorn syndrome [Verma and Fitzpatrick, 2007; Stoll et al., 2012]. Microphthalmia was described in patients with trisomy 18 by Jaruratanasirikul and Jinorose [1994] and Acar et al. [2014]. García-Castro and Reyes de [1975] also reported a patient with microphthalmia presenting an associated nictitating membrane. Moreover, Calderone et al. [1983] did mention in their review of older reports of patients with trisomy 18 presenting microphthalmia. It is noteworthy, that the patient of Jaruratanasirikul and Jinorose [1994], similarly to ours, also presented a chromosomal constitution with triple X (48, XXX,+18). Springett et al. [2015] described a frequency of 2.1% for microphthalmia/anophthalmia among 468 live births with trisomy 18. The aim of the microphthalmia treatment is maximising existing vision and stimulating orbital growth. The retinal development, among other eye characteristics, is closely related to the potential for visual development in microphthalmic patients [Verma and Fitzpatrick, 2007].

Neonatal corneal opacity, a finding verified in two patients of our sample (6.5%), is a term used to describe the loss of corneal transparency that occurs at birth or even 4 weeks after birth [Nischal, 2012]. It is a severe condition and often causes blindness at birth [Mataftsi et al., 2011; Nischal, 2012]. The term “neonatal corneal opacity” covers a broad spectrum of diseases primary or secondary to other pathologies. Congenital corneal opacities have an estimated prevalence of six cases per 100,000 newborns [Ciralsky and Colby, 2007; Mataftsi et al., 2011; Nischal, 2012]. They are the result of a failure in the separation of embryonic tissue for forming the cornea of other underlying tissues [Mataftsi et al., 2011]. The causes of corneal opacities are varied, and include environmental and genetic factors [Ciralsky and Colby, 2007; Mataftsi et al., 2011], as certain chromosomal abnormalities, such as mosaic trisomy 8 and 22q11 deletion syndrome [Mataftsi et al., 2011]. There have been reports of association between trisomy 18 and congenital corneal opacity. However, the cases reported to date do not allow drawing

conclusions about the nature of the relationship between both conditions [Calderone et al., 1983; Mataftsi et al., 2011]. Early diagnosis is important to early intervene [Ciralsky and Colby, 2007]. Early corneal transplantation has been advocated to prevent complications such as amblyopia, wherein the penetrating keratoplasty technique has shown promising [Ciralsky and Colby, 2007].

Peters anomaly is a major cause of congenital corneal opacity [Kurilec and Zaidman, 2014; Hope et al., 2015; Ni et al., 2015]. It is a rare form of anterior segment dysgenesis in that the corneal haze may or may not be accompanied by iridocorneal adhesions and associated defects in the subsequent cornea layers [Weh et al., 2014; Hope et al., 2015]. Another feature is the absence of Descemet's membrane and endothelium in the opacity area [Kurilec and Zaidman, 2014; Hope et al., 2015; Ni et al., 2015]. These anomalies cause visual loss through obstruction of vision axis [Weh et al., 2014]. Peters anomaly can be isolated or associated with systemic defects [Kurilec and Zaidman, 2014; Weh et al., 2014], including chromosomal abnormalities as 22q11 deletion syndrome [Kurilec and Zaidman, 2014] and cri-du-chat syndrome [Hope et al., 2015]. In our literature review, we did not find descriptions of patients with trisomy 18 and Peters anomaly, as observed in our sample. There are several surgical options for the treatment of Peters anomaly, including the peripheral optical iridectomy and penetrating keratoplasty [Ni et al., 2015].

Infantile cataracts represent an important cause of treatable blindness in infants worldwide (12–15% of visually impaired children) [Krishnamurthy and Vanderveen, 2008], showing an estimated prevalence between one and 13 cases per 10,000 births [SanGiovanni et al., 2002]. Most of them are congenital. Cataracts have been associated with some chromosomal abnormalities, as trisomy 21 and trisomy 13. The treatment requires appropriate timing of surgery, amblyopia treatment, refractive correction, and vigilance for the occurrence of post-operative complications [Krishnamurthy and Vanderveen, 2008].

These findings corroborate the idea that eye anomalies are findings not uncommon in trisomy 18, and that they belong to the clinical spectrum of the syndrome. It is noteworthy, that many of these ophthalmologic findings verified in trisomy 18, as microphthalmia, are very common in trisomy 13 (Patau syndrome), other relatively common chromosomal condition considered an important differential diagnosis with trisomy 18 [Petry et al., 2013; Rosa et al., 2013]. This observation was also highlighted by Calderone et al. [1983] in their review.

Thus, eye anomalies seem to be an underdiagnosed finding among patients with trisomy 18, probably due to incomplete examination and reporting. We also think that the severity and poor prognosis frequently associated to trisomy 18 may have some influence over these low frequencies, making difficult to assess the patients and consequently decreasing the chances of evaluation and description. Our study reinforces the importance of the eye abnormalities within the clinical spectrum of trisomy 18 and highlights the need for ophthalmologic evaluation of these patients, especially for those presenting long term survival. Large and prospective studies will be important to better evaluate the

frequency, types, and possible consequences of eye anomalies in patients with trisomy 18.

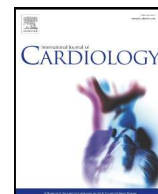
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Short communication

Birth weight, length and head circumference: Progression and impact over the outcome of patients with congenital heart disease

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ABSTRACT

Background: There are few studies assessing the birth measures of patients with congenital heart disease (CHD). Our aim to evaluate their progression and impact over the outcome.

Methods: The cases consisted of patients with CHD during their first hospitalization in a reference cardiac and pediatric intensive care unit (ICU) from Southern Brazil. Controls were composed of patients with no clinical evidence of CHD hospitalized soon after cases. The cases underwent high-resolution karyotype and fluorescence in situ hybridization (FISH) for 22q11 microdeletion. We analyzed birth weight, length and head circumference of patients of both groups. For CHD patients, we evaluated their progression and impact until hospitalization at ICU.

Results: Our sample was composed of 198 cases and controls. We observe a difference in birth weight of CHD patients only in relation to general population. There was a significant increase in children with CHD and weight below the lower limit from birth until the hospitalization at ICU, and this occurred more in those without complex CHD. Syndromic patients and with an extracardiac malformation also presented a greater difficulty to maintain not only the weight but also the length/height until the hospitalization. Individuals with weight below the lower limit at hospitalization who died had a tendency to present longer stay at ICU.

Conclusions: Some CHD patients, especially without complex defects, and with syndromic aspect and a major extracardiac malformation, present a higher difficult to maintain their weight and growth, and, therefore, may be at risk and should be more closely monitored.

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1. Introduction

Congenital heart disease (CHD) is considered the most prevalent malformation, affecting 6–8:1000 live births [1]. Despite the better of survival and quality of life of children with CHDs, these defects still represent a public health problem worldwide [2]. They often require surgery and hospitalization in intensive care units (ICUs) [3], and there is a paucity of these units and centers of expertise in our country [4].

It is noteworthy that there are few studies assessing the birth characteristics and their mean along the life of CHD patients [5,6]. Thus,

our aim was to verify the progression and impact of the birth weight, length and head circumference over the outcome of CHD patients.

2. Methods

Cases and controls were consecutively and prospectively allocated during 1 year (August 2005 to July 2006). The cases consisted of patients with CHD during their first hospitalization at cardiac ICU of the Hospital da Criança Santo Antônio (HCSA), a referral pediatric cardiac center in Southern Brazil. The controls were composed of patients with no clinical evidence of CHD who were hospitalized for the first time at same ICU, soon after cases.

The cases underwent high-resolution GTG-Banding karyotype and fluorescence in situ hybridization (FISH) for 22q11 microdeletion, using the DNA probe TUPLE1 (Vysis, Abbott Molecular Inc.). The variables analyzed were sex, gestational age, delivery type, and weight, length and head circumference at birth and at physical exam in the ICU hospitalization. Variables only analyzed in cases were reason for hospitalization, type of cardiac malformation, presence of complex CHD, syndromic aspect, results of karyotype

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and FISH analyses, association with major extracardiac malformations, time of hospitalization and survival during hospitalization at ICU.

For assess the weight, length and head circumference, Margotto [7] curves were used at birth and growth charts present in Jones [8] at physical exam. The measures were adjusted according to the length [9]. Syndromic aspect was determined based on physical exam, especially considering the number and types of dysmorphisms. The classification elaborated by Botto et al. [10] was used for CHD division. CHD were also classified as complex or not.

Data processing was done by creating a database in Statistical Package for Social Sciences (SPSS) version 18.0 for Windows and by PEPI (version 4.0; Artemisia Press, Salt Lake City, UT, USA). For categorical data, chi-square with Yates correction and Fisher's exact tests were used. To evaluate survival, Kaplan-Meier and log-rank tests were used. For control of confounding factors, multivariate Cox proportional hazards model was applied. To compare frequencies derived from paired samples, the McNemar test was used. $P < 0.05$ values were considered as statistically significant. This study was approved by the Ethics Committee of University and Hospital.

3. Results

The sample consisted of 396 patients, 198 cases and 198 controls. For cases, 52% of them were male, ages ranging from 1 to 4934 days (median 220 days). The main reason for hospitalization was cardiac surgery (74.7%). Septal defects (32.3%) and outflow tract defects (18.7%) were the main types of CHDs. Sixty-five patients (32.8%) presented a complex heart defect, 30.8% a syndromic aspect, 16.2% a chromosomal abnormality and 18.7% a major extracardiac malformation. The median time of hospitalization at ICU was 3 days (ranged from 1 to 95 days) and death occurred in 15 cases (7.6%).

As for controls ($N = 198$), most of them were male (55.1%) and their ages ranged from 5 to 6422 days (median 1455 days). The main reasons for hospitalization included respiratory dysfunction (21.1%) and tumor resection postoperative (13.7%). Non-cardiac malformations were described in 29 patients (15.3%).

Birth characteristics observed in cases and controls can be seen in Table 1. No statistically significant differences were observed between the weight, length and head circumference from both groups (Table 1). The cases at birth presented a median weight of 3037.5 g (2688.8;3407.5), length of 48 cm (46;49.5) and head circumference of 34 cm (32;35). On the other hand, the controls at birth had a median weight of 3200 g (2705;3500), length of 49 cm (46;51) and head circumference of 34 cm (32.9;35). We did not verify difference between the medians from both groups.

Table 1
Comparison of the birth findings verified between patients with (cases) and without congenital heart disease (controls).

Variables	Case	Control	P
Gestational age (N)	198	198	0.345
<37 weeks (%)	12.6	17.7	
37–42 weeks (%)	86.9	81.8	
>42 weeks (%)	0.5	0.5	
Sex (N)	198	198	0.614
Male (%)	52	55.1	
Female (%)	48	44.9	
Type of delivery (N)	198	198	0.227
Vaginal (%)	49.5	56.1	
Cesarean section (%)	50.5	43.9	
Weight percentile (N)	196	189	0.070
<P10 (%)	2.6	6.9	
P10–90 (%)	89.2	82	
>P90 (%)	8.2	11.1	
Low weight at birth (<2500 g) (N)	196	189	0.789
Yes (%)	18.3	16.9	
No (%)	81.6	83.1	
Length percentile (N)	189	174	0.497
<P10 (%)	13.8	12.1	
P10–90 (%)	77.7	75.8	
>P90 (%)	8.5	12.1	
Head circumference percentile (N)	167	94	0.690
<P10 (%)	2.4	4.3	
P10–90 (%)	88.6	86.1	
>P90 (%)	9	9.6	

N = number of patients.

As for CHD groups, only patients with patent ductus arteriosus (PDA) ($N = 9$) showed weight ($P = 0.011$), length ($P = 0.009$) and head circumference values ($P = 0.002$) below the lower limit at birth. However, this happened due to prematurity ($OR = 4.729$, $CI95\% = 1.23–18.14$, $P = 0.024$). Patients with syndromic aspect and carriers of chromosomal abnormality had more birth weight below the lower limit ($P = 0.029$ and $P = 0.035$, respectively). Carriers of chromosomal abnormality showed a mean weight ($P = 0.033$) and length at birth ($P = 0.004$) smaller than those without the same.

McNemar difference test revealed an increase of nearly 5-fold in children with CHD and weight below the lower limit when we compared the measures between birth and hospitalization (2.6% versus 12.2%, $P < 0.001$), and this increase more occurred in patients without complex CHD (3.1% versus 15.3%, $P = 0.001$). Syndromic patients presented a greater difficulty in maintaining an adequate weight ($P = 0.021$), as well length/height ($P = 0.002$), similarly to those with a major extracardiac malformation ($P = 0.009$) (Table 2).

Table 2

Comparison of the weight, height/length and head circumference of the patients with congenital heart defect at moment of birth and at physical exam.

Findings	n	At birth				P
		↓ lower limit	↓ lower limit	Normal	Normal	
		At physical exam/hospitalization				
		↓ lower limit	Normal	↓ lower limit	Normal	
		%	%	%	%	
Weight						
Complex heart defect	196					0.269
Yes	65	–	1.5	6.2	92.3	
No	131	0.7	2.3	14.5	82.5	
Syndromic aspect	196					0.021
Yes	59	1.7	5	17	76.3	
No	137	–	0.7	9.5	89.8	
Chromosomal anomaly*	196					0.168
Yes	31	3.2	3.2	13	80.6	
No	165	–	1.8	11.5	86.7	
Major extracardiac malformation	196					0.103
Yes	36	–	2.8	22.2	75	
No	160	0.6	1.8	9.4	88.2	
Length/height						
Complex heart defect	188					0.233
Yes	63	14.3	6.3	17.5	61.9	
No	125	6.4	4	24	65.5	
Syndromic aspect	188					0.002
Yes	55	9	7.3	38.2	45.5	
No	133	9	3.8	15	72.2	
Chromosomal anomaly ^a	189					0.093
Yes	4	50	–	–	50	
No	185	8.1	4.8	21.6	65.4	
Major extracardiac malformation	188					0.009
Yes	33	12.2	3	42.4	42.4	
No	155	8.4	5.2	17.4	69	
Head Circumference						0.697
Complex heart defect	167					
Yes	59	–	3.4	1.7	94.9	
No	108	–	1.8	3.7	94.5	
Syndromic aspect	167					0.106
Yes	50	–	2	8	90	
No	117	–	2.5	0.9	96.6	
Chromosomal anomaly ^a	171					–
Yes	8	–	–	50	50	
No	163	–	2.5	3	94.5	
Major extracardiac malformation	167					–
Yes	30	–	–	3.3	96.7	
No	137	–	2.9	2.9	94.2	

^a Considered if there was an anomaly in karyotype or FISH for 22q11microdeletion.

The median time of hospitalization from the patients who died was significantly higher (IQR 5–21 and 2–8, 25, respectively) ($P < 0.001$). Among them, the duration of hospitalization had a tendency to be higher among those with a weight below the lower limit at the time of hospitalization ($P = 0.076$). In Cox regression analysis, considering the death outcome and the covariates syndromic aspect, presence of chromosomal abnormalities and weight below the lower limit at birth, no difference in cumulative risk for death was found.

4. Discussion

Children with CHD have been described with lower body weight when compared to healthy children of the same age group [11,12], and this finding has been associated to a higher risk of mortality [13]. In our study, we did not observe a difference in birth weight between patients with and without CHD. We believe that this lack of difference may be related to the characteristics of our control group, where many patients presented important comorbidities. However, it is noteworthy that when we compare our data with general population (DATASUS database - <http://datasus.saude.gov.br/>), we observed a very significant difference in the frequency of low birth weight (<2500 g) (18.3% versus 9.5%) ($P < 0.0001$). When evaluating the types of CHD, we found that patients with PDA presented smaller weight, length and head circumference values at birth. However, this was influenced by gestational age.

Chromosomal abnormalities have been described in 3 to 18% of patients with CHD [14], and in our sample this rate was 16.2%. It is known that carriers of chromosomal abnormalities often are syndromic, present other extracardiac malformations and have low birth weight [15]. This was in accordance with our results, where patients with chromosomal abnormality ($P = 0.035$) and syndromic aspect ($P = 0.029$) presented a lower birth weight.

The degree of growth lack at preoperative period has been associated with some morbidities, as longer hospital stays and increased mortality [5,12,16]. In our sample, we verified a significant increase (of nearly 5-fold) in children with CHD and weight below the lower limit when we compared the measures between birth and physical exam. Some authors suggest that this decrease could happen secondary to hemodynamic instability [11]. It is noteworthy that this decrease in the growth especially occurred in our sample among patients without complex CHD. Our findings suggest that these patients may be being neglected and should be better monitored. This difficulty to maintain the weight was also verified among patients with syndromic aspect ($P = 0.021$). Perhaps, this finding had been influenced by the presence of some associated extracardiac features, as swallowing disorders.

As for the length at birth, we did not find differences when comparing patients with and without CHDs ($P = 0.117$). However, we observed that patients with complex heart defect ($P = 0.233$) and chromosomal abnormalities ($P = 0.093$) had lower birth lengths. Moreover, syndromic patients and individuals with major extracardiac malformations had a greater difficulty in maintaining adequate measures ($P = 0.002$ and $P = 0.009$, respectively), what may be related to a chronic malnutrition status secondary, perhaps, to some features as feeding difficulties.

We did not observe a difference in relation to head circumference at birth between patients with and without CHD. No differences were also noted when we compared the types of CHDs, the presence or not of complex defects ($P = 0.697$) and the syndromic aspect ($P = 0.106$) (Table 2). In literature, some CHDs, such as tetralogy of Fallot, have been associated with microcephaly which strengthens the evidence for possible central nervous system damage due to intrauterine hypoxia [17].

The patients who died had a median time of hospitalization significantly higher. Moreover, it was observed that among them the median length of hospitalization had a tendency to be higher among those with a weight below the lower limit at time of hospitalization. These findings alert to the need for a better care for factors that may influence the weight and growth of CHD patients, such as syndromic aspect and presence of a major extracardiac malformation. Patients without complex defects may also be at risk. All this is important since they may have an influence over the outcomes after cardiac surgery and life span.

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Conflict of interests

None.

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