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RESEARCH ARTICLE

Frequency of chromosome 22q11.2 deletion among newborns with non-syndromic congenital heart defects from western Mexico

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Abstract

Background: *Congenital heart defects (CHD) are among the most frequent manifestations of 22q11.2 deletion syndrome. Although we found relatively few studies aimed at specifically detecting 22q11.2 deletion in newborns (NB) with CHD, none of them has been performed in Mexico.* **Methods:** *We conducted a prospective hospital-based study from January 2017 to March 2021 in the Genetics and Pediatric Cardiology Services of the Hospital Civil de Guadalajara Dr. Juan I. Menchaca (Guadalajara, Mexico). All consecutive NBs identified with any non-syndromic major CHD confirmed by echocardiography were eligible to participate. A total of 98 NBs were included, 51 males and 47 females. Fluorescence in situ hybridization (FISH) analysis was conducted to search for deletion of chromosome 22q11.2 in interphase nuclei of standard lymphocyte cultures.* **Results:** *We found eight patients (8.2%) with CHD and the 22q11.2 deletion, all of them with conotruncal defects, particularly of the truncus arteriosus (p = 0.013), tetralogy of Fallot (p = 0.024), and pulmonary atresia with ventricular septal defect (p = 0.031) subtypes. With de exception of one infant with hypocalcemia and another with hypocalcemia and thymic aplasia, the diagnosis of 22q11.2 deletion was not clinically suspected in the other patients.* **Conclusions:** *Our results confirm the importance of excluding the presence of the 22q11.2 deletion in every NB with CHDs, particularly of the conotruncal subtype, even in the absence of other manifestations.*

Keywords: *Conotruncal defects. Tetralogy of Fallot. Pulmonary atresia with ventricular septal defect. Bulbous nasal tip.*

Frecuencia de la deleción del cromosoma 22q11.2 en recién nacidos con cardiopatías congénitas no sindrómicas del occidente de México

Resumen

Introducción: *Las cardiopatías congénitas (CC) son una de las manifestaciones más frecuentes del síndrome de deleción 22q11.2. A pesar de que existen relativamente pocos estudios dirigidos a detectar específicamente la deleción 22q11.2 en recién nacidos (RN) con CC, ninguno de ellos ha sido realizado en México.* **Métodos:** *Se realizó un estudio prospectivo de*

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base hospitalaria desde enero de 2017 hasta marzo de 2021 en los Servicios de Genética y Cardiología Pediátrica del Hospital Civil de Guadalajara Dr. Juan I. Menchaca (Guadalajara, México). Todos los RN consecutivos identificados con cualquier tipo de CC mayor no sindrómica confirmada por ecocardiografía fueron elegibles para participar. Se incluyeron 98 recién nacidos, 51 de sexo masculino y 47 de sexo femenino. Mediante el análisis de hibridación fluorescente in situ (FISH, por sus siglas en inglés) se realizó la búsqueda de la deleción del cromosoma 22q11.2 en núcleos en interfase de cultivos de linfocitos estándar. **Resultados:** *Se encontraron ocho pacientes (8.2%) con CC y la deleción 22q11.2, todos ellos con defectos conotruncales, particularmente de los subtipos tronco arterioso (p = 0.013), tetralogía de Fallot (p = 0.024) y atresia pulmonar con comunicación interventricular (p = 0.031). Con excepción de un lactante con hipocalcemia y otro con hipocalcemia y aplasia tímica, el diagnóstico de deleción 22q11.2 no se sospechó clínicamente en los demás pacientes.* **Conclusiones:** *Los resultados de este trabajo confirman la importancia de excluir la presencia de la deleción 22q11.2 en todos los RN con CC, particularmente del subtipo conotruncal, incluso en ausencia de otras manifestaciones.*

Palabras clave: *Defectos conotruncales. Tetralogía de Fallot. Atresia pulmonar con comunicación interventricular. Punta nasal bulbosa.*

Introduction

Congenital heart defects (CHD) are one of the most frequent manifestations of 22q11.2 deletion syndrome (22q11.2DS), particularly in those patients evaluated before 2 years of age in whom CHD can be found in 63%-79% of the cases[1]. In some infants, 22q11.2DS may present as an apparently isolated CHD or combined with other key features, such as typical facial features or developmental and neuropsychiatric disorders that manifest later in life, thus favoring late diagnosis[2].

We found relatively few studies specifically aimed at detecting the 22q11.2 deletion in CHD patients, mainly by fluorescence *in situ* hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), or polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays[3-5]. However, none of these studies had been performed in Mexico.

The studies in older children and adults have shown variable detection of 22q11.2 deletions attributable to factors such as the type of hospital the patients came from, the type of CHD involved, or its severity. Therefore, such frequencies may not necessarily be representative of the neonatal population[1,2]. For this reason, this study aimed to determine the frequency of the 22q11.2 deletion in a consecutive sample of newborns with non-syndromic CHD of any type in a public hospital in western Mexico.

Methods

Subjects

We conducted a prospective hospital-based study from January 2017 to March 2021 in the Genetics and Pediatric Cardiology Services of the Hospital Civil de Guadalajara Dr. Juan I. Menchaca (Guadalajara, Jalisco, Mexico) through the Congenital Anomalies Registry and Research Center (CRIAC, for its Spanish acronym). The hospital-based active surveillance program for congenital defects covers all live births of ≥ 20 weeks of gestation and > 500 g of weight. All consecutive newborns identified with any major CHD confirmed by echocardiography performed by a pediatric cardiologist were eligible to participate. A team of certified clinical geneticists reviewed each patient's information regarding prenatally diagnosed cases, medical records, surgical notes, clinical photographs, imaging studies, and complete dysmorphological examination[6].

Each CHD case was classified into three categories, following the guidelines of the US National Birth Defects Prevention Study[3,7]: (a) isolated CHD, cases with no other major defects; (b) CHD with one extracardiac defect, cases with an additional, unrelated, specific major defect (e.g., gastroschisis, omphalocele, cleft lip, among others); and (c) syndromic, CHD cases with chromosomal abnormalities, monogenic disorders, or three or more major birth defects (e.g., trisomy 13, facio-auricular-vertebral spectrum, VACTERL association).

To determine the frequency of the 22q11 deletion in the population studied, we included only CHD patients with isolated or up to one extracardiac defect, as they presumably have a different etiology than those with specific syndromes. This definition was used because patients with 22q11.2 deletion could have more than 180 clinical features[8]. After informed consent, blood samples were collected for chromosomal and FISH studies.

Cardiac phenotypes were classified according to the International Paediatric and Congenital Cardiac Code[9]. Only ostium secundum and sinus venosus types were

included as atrial septal defects (ASD), excluding patent foramen ovale and patent ductus arteriosus. Each case of CHD was counted separately. For example, in infants with ASD and ventricular septal defect (VSD), both defects were recorded; however, if a VSD was part of a tetralogy of Fallot (TOF) or double outlet right ventricle (DORV), they were not counted separately. Furthermore, each CHD was classified according to its complexity[10]. Patients in whom the 22q11.2 deletion was identified were subsequently re-evaluated for the presence of other 22q11.2DS manifestations. The Research Council and the Ethics Committee of our hospital approved this study.

FISH assays

The FISH assay was used to screen for chromosome 22q11.2 deletion in interphase nuclei of standard lymphocyte cultures using the Cytocell® probe (Cytocell Ltd., Cambridge, UK), which maps the TUPLE1 critical region at 22q11.2 combined with the N85A3 control probe at 22q13.3. In each patient, ~ 200 interphase cells were routinely evaluated.

Statistical analysis

Descriptive statistics were used to identify the type of CHD in the sample and the frequency of 22q11.2 deletion. The χ^2 test was used to compare the frequency of specific CHD between patients with and without 22q11.2 deletion. A p-value < 0.05 was considered significant.

Results

A total of 98 infants with at least one non-syndromic CHD (51 males and 47 females aged between 1 and 30 days) were included. Of these, 75 (76.5%) had no associated defect, and 23 (23.5%) had an additional extracardiac defect (three with cleft lip or palate, three with grade III microtia, two with hypospadias, two with hydrocephaly, and others with microcephaly, encephalocele, cleft palate, scoliosis, hemivertebrae, sacral lipoma, diaphragmatic hernia, omphalocele, intestinal atresia, gastroschisis, anal atresia, multicystic kidney, or cryptorchidism). We found eight patients (8.2%) with CHD carriers of the 22q11.2 deletion detected by the FISH assay. Overall, the number of major CHD observed in the study sample was 164, of which 151 were found in infants with normal FISH and 13 in infants with 22q11.2 deletion.

Table 1 compares the distribution of specific subtypes of CHD according to the presence of 22q11.2 deletion. The most frequent types of CHD in the studied sample were VSD (32.6%), ASD (27.5%), DORV (15.3%), pulmonary valve stenosis (9.2), and TOF (9.2%). All eight infants with 22q11.2 deletion had a CHD classified as a conotruncal defect compared to 37/90 (41.1%) of infants without the deletion (p = 0.001). The particular subtypes of conotruncal defects that showed a significant difference were truncus arteriosus (p = 0.013), TOF (p = 0.024), and pulmonary atresia with VSD (p = 0.031). No other statistically significant differences were found, even considering the number of CHD presented or the severity of the cardiac phenotype.

Except for one infant with hypocalcemia and another with hypocalcemia and thymic aplasia, the diagnosis of 22q11.2DS was not clinically suspected on reevaluation of any of the patients in our cohort. Additional clinical features found retrospectively after the confirmation of 22q11.2 deletion are described in Table 2. In particular, it is noteworthy that upon reevaluation of the facial phenotype, we found a bulbous nasal tip (Figure 1) as the most common morphological feature in our cohort of patients with 22q11.2 deletion.

Discussion

The distribution by subtype of CHD observed in the sample studied was representative and corresponded with the frequency reported in other population-based studies[11], in which VSD, ASD, TOF, and pulmonary stenosis are the predominant defects (Table 1), which allows us to generalize our results.

The frequency of 22q11.2 deletion (8.2%) in 98 newborns with unselected (i.e., either conotruncal or non-conotruncal heart defects) and apparently non-syndromic CHD was slightly higher than that reported in other studies in older children. In those studies, also performed with a FISH assay, the frequency ranged from 1.3% to 5.7%, probably due to differences in the population studied and the selection criteria[3,4]. However, our results agree with the frequency reported in another study (9.6%) in which MLPA identified the 22q11.2 deletion[5].

Consistent with previous studies[2-5], 22q11.2 deletions caused a substantial proportion of cases with TOF, pulmonary atresia or pulmonary stenosis with ventricular septal defects, truncus arteriosus, DORV, and interrupted aortic arch, but not a transposition of the great arteries (Table 1). Notably, the detection rate of

Table 1. Congenital heart defects and 22q11.2 deletion in the studied sample

Subtypes of cardiac defects	Total (n = 98) n (%)	Normal (n = 90) n (%)	22q11.2 deletion (n = 8) n (%)	*p*-value*
Dextrocardia	2 (2)	2 (2.2)	0 (0)	0.843
Conotruncal defects				
Tetralogy of Fallot	9 (9.2)	6 (6.7)	3 (37.5)	0.024
Truncus arteriosus	4 (4.1)	2 (2.2)	2 (25)	0.013
Interrupted aortic arch	6 (6.1)	5 (5.5)	1 (12.5)	0.445
Double outlet right ventricle	15 (15.3)	14 (15.5)	1 (12.5)	0.646
Dextro-transposition of the great arteries	7 (7.1)	7 (7.8)	0 (0)	0.540
Pulmonary stenosis with VSD	4 (4.1)	2 (2.2)	2 (25)	0.031
Atrioventricular canal defect	3 (3.1)	3 (3.3)	0 (0)	0.772
Anomalous pulmonary venous return	7 (5.9)	7 (6.7)	0 (0)	0.778
Left ventricular outflow tract obstruction				
Bicuspid aortic valve	1 (1)	1 (1.1)	0 (0)	0.918
Aortic valve stenosis	1 (1)	1 (1.1)	0 (0)	0.918
Coarctation of the aorta	5 (5.1)	5 (5.5)	0 (0)	0.647
Supravalvular aortic stenosis	1 (1)	1 (1.1)	0 (0)	0.918
Hypoplastic left heart syndrome	3 (3.1)	3 (3.3)	0 (0)	0.772
Mitral valve stenosis	1 (1)	1 (1.1)	0 (0)	0.918
Right ventricular outflow tract obstruction				
Tricuspid valve atresia/stenosis	5 (5.1)	5 (5.5)	0 (0)	0.647
Pulmonary valve atresia	5 (4.1)	4 (4.4)	1 (12.5)	0.353
Pulmonary valve stenosis	10 (9.2)	9 (10.0)	0 (0)	0.647
Hypoplastic right heart syndrome	3 (3.1)	3 (3.3)	0 (0)	0.772
Ebstein malformation of the tricuspid valve	1 (1)	1 (1.1)	0 (0)	0.772
Septal defect (isolated)				
Atrial septal defect	27 (27.5)	25 (27.8)	2 (25)	0.615
Ventricular septal defect	31 (31.6)	30 (33.3)	1 (12.5)	0.285
Single atrium	3 (3.1)	3 (3.3)	0 (0)	0.772
Other specified heart defects				
Single ventricle	6 (5.9)	6 (6.7)	0 (0)	0.591
Pulmonary artery stenosis	3 (3.1)	2 (2.2)	0 (0)	0.644
Summary				
Number of major cardiac defects†	164	151	13	0.231
Cardiac defects per infant				
1	58 (59.2)	54 (60)	4 (50)	0.423
2	29 (29.6)	26 (28.9)	3 (37.5)	0.610
3	7 (7.1)	6 (6.7)	1 (12.5)	0.546
≥ 4	4 (4.1)	4 (4.4)	0 (0)	0.707
Severity of congenital heart defects‡				
Great complexity	53 (54.1)	47 (52.2)	6 (75)	0.194
Moderate complexity	15 (15.3)	14 (15.5)	2 (25)	0.493
Simple	30 (30.6)	29 (32.2)	0 (0)	0.154
Cases with one extracardiac defect	23 (23.4)	22 (24.4)	1 (12.5)	0.231

*X^2 with Yates's correction
†Since each CHD was counted separately, the total in each group may be > 98, > 90, or > 8, respectively.
‡Classified according to Stout et al.[10]
VSD: ventricular septal defect.

22q11.2 deletion among patients with CHD did not vary significantly when including patients with or without extracardiac malformations (5.7% vs. 1.3%, respectively)[12,13]. This indicates that CHD cases with extracardiac anomalies should not be excluded from 22q11.2 microdeletion studies because other features characteristic of 22q11.2DS may not be evident in neonates or very young infants[3,4,12].

Moreover, our findings do not differ substantially from those reported in a previous large study of 62 older children from Mexico with 22q11.2DS, in whom CHD was found in 97%, with a predominance of conotruncal

Table 2. Clinical findings in infants with congenital heart defects and 22q11.2 deletion

Findings	Patient								Total (n = 8)
	1	2	3	4	5	6	7	8	
Age at first examination (days)	1d	1d	1d	1d	1d	1d	1d	1d	
Gender									
Male	+	-	-	-	-	-	-	-	1/8
Female	-	+	+	+	+	+	+	+	7/8
Congenital heart defects									
Conotruncal cardiac defects	+	+	+	+	+	+	+	+	8/8
Tetralogy of Fallot	-	+	+	-	-	-	+	-	3/8
Pulmonary stenosis with VSD	-	-	-	+	-	-	-	+	2/8
Truncus arteriosus	-	-	-	-	+	+	-	-	2/8
Double outlet right ventricle TOF type	+	-	-	-	-	-	-	-	1/8
Atrial septal defects	-	-	+	-	+	-	-	-	2/8
Ventricular septal defects	-	-	-	-	-	+	-	-	1/8
Interrupted aortic arch	-	-	-	-	-	-	-	+	1/8
Pulmonary valve atresia	-	-	-	-	+	-	-	-	1/8
Typical facial features									
Hooded eyelids	-	-	-	-	-	-	-	-	0/8
Upslanting palpebral fissures	+	-	-	-	-	-	+	+	3/8
Malar flatness	-	-	+	+	-	-	-	-	2/8
Tubular nose	-	-	-	-	-	-	-	-	0/8
Bulbous nasal tip	+	+	+	+	+	-	+	+	7/8
Microtia (grade I)	-	+	-	+	-	-	+	-	3/8
Cleft lip and palate	-	-	-	-	-	+	-	-	1/8
Hypocalcemia*	+	-	-	-	+	-	-	-	2/11
Thymic aplasia*	-	-	-	+	+	-	-	-	2/11
Others									
Seizures*	-	-	-	-	+	-	-	-	1/8
Hypothyroidism*	-	-	-	+	-	-	-	-	1/8

*Identified during the first week of life.
d: days; TOF: tetralogy of Fallot; VSD: ventricular septal defects.

defects (77%) followed by other lesions (20%)[13]. The fact that we did not find cases with defects such as isolated aneurysmal cervical aortic arch may be explained because our sample of newborns was studied for the CHD complaint and does not necessarily represent a cohort of infants with 22q11.2DS.

No studies in Mexico have investigated the appearance of newborns with 22q11.2DS. However, two studies analyzed facial features in Mexican patients[13,14]. Although they included only a few newborns, both studies concluded that typical facial characteristics such as a long face, short and up-slating palpebral fissures, hooded eyelids, bulbous tubular nose, and downward labial commissures are distinctive in Mexican patients with 22q11.2DS. Both studies recognize that these facial features are difficult to observe in newborns.

Based on these findings, our study confirms the importance of investigating the presence of a 22q11.2 deletion in all infants with CHD, particularly of conotruncal type, even in the absence of other vital manifestations also easily detectable during the neonatal period, such as hypocalcemia or thymic aplasia (Table 2). This could help to reduce the late diagnosis of 22q11.2DS since, for example, in countries such as Canada or the United States is performed until an average age of 4.7 years and after visiting at least seven different medical specialties[15]. Although the information on the age at diagnosis in Mexico is unknown, only a minority of 22q11.2DS patients are diagnosed during the neonatal period.

We also emphasize that the presence of a bulbous nasal tip (Figure 1) on the initial examination of a

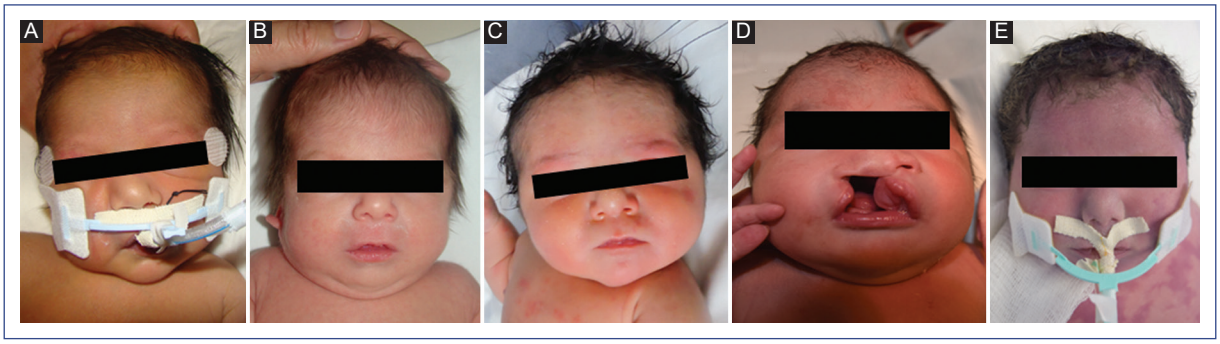

Figure 1. Facial features of newborns with congenital heart defects and 22q11.2 deletion. Except for the patient in panel (D), a regular appearance is observed in the others but with an evident bulbous nasal tip. The lobe is forward-facing and uplifted on the patient in panel (C). Notably, the cleft lip and palate in the patient in panel (D) are not suggestive of the facial gestalt of 22q11.2 deletion syndrome.

newborn with a conotruncal defect may help support the suspicion of 22q11.2DS (Table 2) because the other minor anomalies of typical 22q11.2DS facial dysmorphia are usually apparent or recognizable in older children or adults[2,13].

A limitation of this study is the relatively small number of patients studied. Therefore, our estimates of 22q11.2 deletion frequency and the phenotypic frequencies observed in infants with 22q11.2 deletion may have been underestimated. The 22q11.2DS is usually diagnosed by FISH using commercial probes, including TUPLE1 (flanked by LCR A-B of 22q11.2 deletion). Another limitation of the study is that this probe has a detection yield of 85% for classic 2.55 Mb deletion spanning LCR A-D but only 5% and 2% of the atypical deletions spanning LCR A-B and A-C, respectively[4,13,14,16]. Therefore, it is possible that our interphase FISH studies missed some cases with deletions without the involvement of the A-B region.

In conclusion, in our sample of infants with unselected and apparently non-syndromic CHD, almost one in ten had the 22q11.2 deletion, increasing this proportion to approximately one in five among those with conotruncal defects. This confirms the relevance of the contribution of FISH studies in diagnosing patients with 22q11.2DS at increasingly younger ages.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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