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Rare genetic cardiovascular diseases: descriptive epidemiological data in a Mexican third-level cardiology hospital outpatient clinic

Enfermedades cardiovasculares genéticas raras: datos epidemiológicos descriptivos en la consulta externa de un hospital mexicano de tercer nivel de cardiología

Blanca Rebeca Ibarra-Ibarra*

Keywords:
rare diseases, genetics, cardiovascular system, prevalence, epidemiology.

Palabras clave:
enfermedades raras, genética, sistema cardiovascular, prevalencia, epidemiología.

ABSTRACT

Introduction: rare cardiovascular diseases are conditions with low prevalence in the general population that affect the cardiovascular system. Most have a genetic etiology with a heritable potential denominated as Rare Genetic Cardiovascular Diseases (RGCVD). Currently, there are scarce epidemiological studies on RGCVD, and the overall prevalence is unknown. **Objective:** descriptive epidemiological analysis of RGCVD, emphasizing the overall prevalence estimation in a cardiovascular hospital. In addition, the cardiovascular phenotype distribution and other related demographic characteristics were analyzed. **Material and methods:** the study consists of a retrospective descriptive epidemiological analysis from January to December 2019 in the outpatient clinic of a cardiovascular third-level hospital in Mexico City. RGCVD patients were identified with an exhaustive review of all clinical records. The overall prevalence of RGCVD was estimated. In addition, the number of diseases, cardiovascular phenotype distribution, and other demographic data of these diseases were analyzed. **Results:** RGCVD comprised 794 of 31,487 patients in the outpatient clinic, corresponding to 104 diseases. The overall prevalence of RGCVD was 2.5% (95%CI, 2.3-2.7) patients. The prevalence of monogenic and chromosomal disorders was 2.1 and 0.4%, respectively. Congenital heart diseases were the most frequent cardiovascular phenotype (42.4%), and the less frequent were cardiac tumor disorders (0.9%). **Conclusions:** the study identified that almost one in 40 patients in the outpatient clinic of a cardiology hospital had an RGCVD. The study also provides useful epidemiological information for further research and planning cardiovascular health services.

RESUMEN

Introducción: *las enfermedades cardiovasculares raras son patologías de baja prevalencia en la población general que afectan al sistema cardiovascular. La mayoría tienen una etiología genética con potencial hereditario denominadas Enfermedades Cardiovasculares Genéticas Raras (ECVGR). En la actualidad, existen escasos estudios epidemiológicos sobre las ECVGR y se desconoce su prevalencia global.* ***Objetivo:*** *análisis epidemiológico descriptivo de las ECVGR, haciendo hincapié en la estimación de la prevalencia global en un hospital cardiovascular. Además, se analizaron la distribución del fenotipo cardiovascular y otras características demográficas relacionadas.* ***Material y métodos:*** *el estudio consiste en un análisis epidemiológico descriptivo retrospectivo de enero a diciembre de 2019 en la consulta externa de un hospital cardiovascular de tercer nivel de la Ciudad de México. Se identificaron pacientes con ECVGR con una revisión exhaustiva de todos los expedientes clínicos. Se estimó la prevalencia global de ECVGR. Además, se analizó el número de enfermedades, la distribución del fenotipo cardiovascular y otros datos demográficos de estas enfermedades.* ***Resultados:*** *las ECVGR comprendieron 794 de 31,487 pacientes de la consulta externa, correspondiendo a 104 enfermedades. La prevalencia global de ECVGR fue de 2.5% (IC95%, 2.3-2.7) de los pacientes. La prevalencia de los trastornos monogénicos y cromosómicos fue de 2.1 y 0.4%, respectivamente. Las cardiopatías congénitas fueron el fenotipo cardiovascular más frecuente (42.4%), y los menos frecuentes fueron los trastornos tumorales cardiacos (0.9%).* ***Conclusiones:*** *el estudio identificó que casi uno de cada 40 pacientes de la consulta externa de un hospital de cardiología tenía una ECVGR. El estudio también proporciona información epidemiológica útil para futuras investigaciones y para la planificación de los servicios de salud cardiovascular.*

* Laboratory of Translational Medicine, UNAM-INC Unit, Cardiogenetics clinic, Department of Outpatient Clinic, Instituto Nacional de Cardiología Ignacio Chávez. Mexico City, Mexico. ORCID: 0000-0002-5979-7507

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Abbreviations:
CI = Confidence Interval.
ICD = International Classification of Diseases.
OMIM = Online Mendelian Inheritance in Man.
RGCVD = Rare Genetic Cardiovascular Diseases.

INTRODUCTION

Rare diseases affect between 3.5 and 5.9% of the world's population, impacting around 350 million people at any time in life. Rare diseases are a heterogeneous group of disorders with a genetic etiology in almost 72%.[1-3] There is no global consensus about the definition of a rare disease, but in general terms, a rare disease is defined as a disease that affects < 50/100,000 people.[4]

Rare genetic cardiovascular diseases affect the cardiovascular system with or without extracardiac manifestations, with an individually low prevalence, mainly caused by rare and ultra-rare genetic variants with heritable potential.[2,5,6]

There are currently scarce epidemiological studies on rare genetic cardiovascular diseases that delineate their distribution and situation in different world regions, clinical settings, and healthcare systems.[7] Moreover, most studies are biased toward estimating the prevalence of some diseases, providing a fractioned and limited perspective of rare genetic cardiovascular diseases' global panorama.[3,8] These are routinely seen in cardiovascular clinical practice. However, the overall rare genetic and nongenetic cardiovascular prevalence in cardiology is hitherto unknown.

It is crucial to estimate the total number of people affected with rare genetic cardiovascular diseases to provide helpful information for improving medical care in the future. Furthermore, this information could establish some bases to encourage translational research that promotes the creation of health policies consistent with the needs of patients suffering from these diseases. Therefore, the objective herein was to conduct a descriptive epidemiological analysis of the rare genetic cardiovascular diseases in the outpatient clinic of a third-level cardiology hospital, emphasizing the estimation of their overall prevalence. Additionally, cardiovascular phenotype distribution, the outpatient prevalence per disease, type of genetic disease, type of rare disease, and other related demographic characteristics were analyzed to evaluate the situation of rare genetic cardiovascular diseases in a cardiovascular clinical setting.

MATERIAL AND METHODS

Study design and setting

The design was a retrospective, descriptive epidemiological study of the full range of patients with rare genetic cardiovascular diseases in a third-level cardiovascular hospital outpatient clinic in Mexico City (*Instituto Nacional de Cardiología Ignacio Chávez*) from January to December 2019. The hospital is a recognized national reference for the attention of pediatric and adult cardiovascular diseases.

Definitions, study population, and data collection

The operational definition of a rare genetic cardiovascular disease was a rare disease cataloged in the online rare diseases database Orphanet[2] with a genetic etiology (monogenic or chromosomal disorders) affecting the cardiovascular system with or without extra cardiovascular clinical features. The diagnoses of patients with rare genetic cardiovascular diseases were identified through an exhaustive review of all the diagnoses settled in the electronic clinical records of the 31,487 patients who visited the outpatient clinic. A medical geneticist conducted the review. The study included confirmed clinical diagnoses of patients with rare genetic cardiovascular diseases. The medical geneticist assessed each diagnosis to determine if it met the specific criteria of each rare genetic cardiovascular disease, regardless of whether a confirmatory genetic test was conducted. Diagnoses of common cardiovascular diseases or rare diseases without cardiovascular involvement were excluded from the study. In addition, the clinical data for each patient with a rare genetic cardiovascular disease, including the diagnosis (disease name), cardiovascular phenotype, age, and sex, were collected for further analysis. Each rare genetic cardiovascular disease name was matched with its related preferred disease term

and ORPHAcode, obtained from Orphanet.[2] In diseases without a specific ORPHAcode, the ORPHAcode of a group of disorders was assigned according to the phenotype.

Type of genetic disorder

Identified rare genetic cardiovascular diseases were classified according to the type of genetic disorder in two categories: chromosomal disorders and monogenic disorders. Chromosomal disorders include numerical and structural chromosomal abnormalities and genomic rearrangements. Monogenic include Mendelian inheritance patterns and non-Mendelian patterns. The information regarding the etiology was obtained from Orphanet[2] and OMIM (Online Mendelian Inheritance in Man).[9]

Type of rare disease

In order to analyze the situation of the rare genetic cardiovascular diseases identified in the outpatient clinic, each rare cardiovascular disease was categorized into three types of rare diseases according to the disease prevalence reported in Orphanet.[2] The prevalence reported for each disease could be related to the prevalence in the general population or birth prevalence. Therefore, the type of rare diseases was categorized as follows: rare (prevalence between < 1/2,000 - > 1/50,000),[4] ultrarare (prevalence between ≤ 1/50,000 - < 1/1'000,000),[10] and unknown prevalence.

Cardiovascular phenotype distribution

To analyze the distribution of the cardiovascular phenotype of the identified patients with rare genetic cardiovascular diseases, the cardiovascular phenotype of each patient was classified into one of the six groups (arrhythmic and conduction disorders, cardiac tumor disorders, cardiomyopathies, congenital heart diseases, vascular disorders, and other cardiovascular disorders) and its corresponding morphological subgroup.

Statistical analysis

The overall prevalence of rare genetic cardiovascular diseases, the prevalence per disease, and the prevalence of monogenic and chromosomal disorders were estimated using the total number of patients who attended the outpatient clinic in 2019 as a denominator. The 95% confidence interval (CI) was estimated for overall, monogenic, and chromosomal disorders prevalences. The prevalence per disease was calculated per 10,000 patients. Continuous variables were expressed as median (25^{th} - 75^{th} percentile). Categorical variables were expressed as absolute and relative frequencies, as appropriate. The differences in continuous variables among groups of cardiovascular phenotypes were calculated with the Kruskal-Wallis H test and, in categorical variables, with the χ^2 test. Data and statistical analyses were performed in Stata Statistical Software: Release 16 (StataCorp LLC. 2019).

RESULTS

Of the total population of patients who attended the outpatient clinic in 2019 (n = 31,487), 794 patients had a diagnosis of a rare genetic cardiovascular disease. The overall period prevalence of rare genetic cardiovascular diseases was 2.5% (95%CI, 2.3-2.7) of the patients in the outpatient clinic of the analyzed third-level cardiovascular hospital. The patients with rare genetic cardiovascular diseases corresponded to 104 disease names *(Table 1)*. The frequency of patients and the prevalence in the outpatient clinic per 10,000 patients for each rare genetic cardiovascular disease are shown in *Table 1*. Of the patients with rare genetic cardiovascular diseases, 51% were women, and the median age was 23 (13-38). Thirty-nine percent of patients correspond to pediatrics ages (0-18 years).

Eighty-seven out of 104 diseases observed corresponded to monogenic disorders, and 17 were chromosomal disorders *(Table 1)*. Therefore, the number of patients affected with monogenic disorders was 668/794 (84.1%), and patients with chromosomal disorders accounted for 126/794 (15.9%). The prevalence of monogenic and chromosomal disorders of the rare genetic cardiovascular diseases in the outpatient clinic was 2.1% (95%CI, 2.0-2.3) and 0.4% (95%CI, 0.3-0.5), respectively.

According to the reported prevalence for each disease in Orphanet,[2] 33 diseases

Table 1: Rare genetic cardiovascular diseases identified in the outpatient clinic of a cardiology hospital in 2019.

Name of rare genetic cardiovascular disease	ORPHAcode[2]	n	Prevalence per 10,000 patients in the outpatient clinic	Type of rare disease*	Type of genetic disease
Marfan syndrome	558	178	56.5	Rare	Monogenic
Romano ward syndrome (long QT syndrome type 1, 2, and 3)	101,016	79	25.1	Rare	Monogenic
Noonan syndrome	648	72	22.9	Rare	Monogenic
22q11.2 deletion syndrome	567	43	13.7	Rare	Chromosomal
Williams syndrome	904	42	13.3	Rare	Chromosomal
Loeys-Dietz syndrome	60,030	38	12.1	Unknown	Monogenic
Left ventricular noncompaction	54,260	29	9.2	Unknown	Monogenic
Turner syndrome	881	24	7.6	Rare	Chromosomal
Brugada syndrome (types 1, 2, and 3)	130	21	6.7	Rare	Monogenic
Familial isolated dilated cardiomyopathy	217,656	20	6.4	Rare	Monogenic
Holt-Oram syndrome	392	18	5.7	Ultrarare	Monogenic
Familial isolated arrhythmogenic right ventricular dysplasia	154	16	5.1	Unknown	Monogenic
Supravalvular aortic stenosis	3,193	14	4.4	Rare	Monogenic
Classical Ehlers-Danlos syndrome	287	11	3.5	Rare	Monogenic
Familial thoracic aortic aneurysm and aortic dissection	91,387	11	3.5	Ultrarare	Monogenic
Heterotaxia (visceral heterotaxy)	450	9	2.9	Rare	Monogenic
Neurofibromatosis type 1	636	9	2.9	Rare	Monogenic
Andersen-Tawil syndrome	37,553	8	2.5	Unknown	Monogenic
Tuberous sclerosis complex	805	8	2.5	Rare	Monogenic
Congenital contractural arachnodactyly	115	6	1.9	Unknown	Monogenic
Jervell and Lange-Nielsen syndrome	768	6	1.9	Ultrarare	Monogenic
Vascular Ehlers-Danlos syndrome	286	6	1.9	Ultrarare	Monogenic
Hypermobile Ehlers-Danlos syndrome	285	5	1.6	Rare	Monogenic
Klippel-Feil syndrome	2,345	5	1.6	Ultrarare	Monogenic
CHARGE syndrome	138	4	1.3	Rare	Monogenic
Lown-Ganong-Levine syndrome	844	4	1.3	Ultrarare	Monogenic
Wolf-Hirschhorn syndrome	280	4	1.3	Rare	Chromosomal
Cardiofaciocutaneous syndrome	1,340	3	1	Unknown	Monogenic
Coffin-Lowry syndrome	192	3	1	Ultrarare	Monogenic
Cornelia de Lange syndrome	199	3	1	Ultrarare	Monogenic
Friedreich ataxia	95	3	1	Ultrarare	Monogenic
Hereditary hemorrhagic telangiectasia	774	3	1	Rare	Monogenic
Klippel-Trenaunay syndrome	90,308	3	1	Ultrarare	Monogenic
Sotos syndrome	821	3	1	Rare	Monogenic
Alagille syndrome	52	2	0.6	Ultrarare	Monogenic
Apert syndrome	87	2	0.6	Ultrarare	Monogenic
Crouzon syndrome	207	2	0.6	Ultrarare	Monogenic
Duchenne muscular dystrophy	98,896	2	0.6	Rare	Monogenic
Emery-Dreifuss dystrophy	261	2	0.6	Ultrarare	Monogenic
Frontonasal dysplasia	250	2	0.6	Unknown	Monogenic

Continue to Table 1: Rare genetic cardiovascular diseases identified in the outpatient clinic of a cardiology hospital in 2019.

Name of rare genetic cardiovascular disease	ORPHAcode[2]	n	Prevalence per 10,000 patients in the outpatient clinic	Type of rare disease*	Type of genetic disease
Hereditary ATTR amyloidosis	271,861	2	0.6	Unknown	Monogenic
Johanson-Blizzard syndrome	2,315	2	0.6	Ultrarare	Monogenic
Kearns-Sayre syndrome	480	2	0.6	Ultrarare	Monogenic
MASS syndrome	156,532	2	0.6	Unknown	Monogenic
Noonan syndrome with multiple lentigines (LEOPARD)	500	2	0.6	Unknown	Monogenic
Smith-Magenis syndrome	819	2	0.6	Rare	Monogenic
Spondylocostal dysostosis	1,797	2	0.6	Unknown	Monogenic
47,XYY syndrome	8	1	0.3	Rare	Chromosomal
Aarskog-Scott syndrome	915	1	0.3	Rare	Monogenic
Achondroplasia	15	1	0.3	Rare	Monogenic
Acute intermittent porphyria	79,276	1	0.3	Ultrarare	Monogenic
Arterial tortuosity syndrome	3,342	1	0.3	Ultrarare	Monogenic
Autosomal dominant interatrial communication	1,478	1	0.3	Unknown	Monogenic
Autosomal recessive multiple pterygium syndrome	2,990	1	0.3	Ultrarare	Monogenic
Axenfeld-Rieger syndrome	782	1	0.3	Ultrarare	Monogenic
Becker muscular dystrophy	98,895	1	0.3	Ultrarare	Monogenic
Blackfan-Diamond anemia	124	1	0.3	Ultrarare	Monogenic
Carney complex	1,359	1	0.3	Unknown	Monogenic
Catecholaminergic polymorphic ventricular tachycardia	3,286	1	0.3	Rare	Monogenic
Complex chromosomal rearrangement; t(1;3)	263,708	1	0.3	Unknown	Chromosomal
Complex chromosomal rearrangement; t(14;22)	263,708	1	0.3	Unknown	Chromosomal
Complex chromosomal rearrangement; t(7;12)	263,708	1	0.3	Unknown	Chromosomal
Complex chromosomal rearrangement; t(8;18)	263,708	1	0.3	Unknown	Chromosomal
Congenital heart block	60,041	1	0.3	Unknown	Monogenic
Costello syndrome	3,071	1	0.3	Ultrarare	Monogenic
Distal trisomy 18q	1,716	1	0.3	Unknown	Chromosomal
Distal trisomy 6p	1,745	1	0.3	Ultrarare	Chromosomal
Ellis Van Creveld syndrome	289	1	0.3	Unknown	Monogenic
Fabry disease	324	1	0.3	Rare	Monogenic
Familial atrial fibrillation	334	1	0.3	Unknown	Monogenic
Familial dilated cardiomyopathy with conduction defect due to LMNA mutation	300,751	1	0.3	Unknown	Monogenic
Fragile X syndrome	908	1	0.3	Rare	Monogenic
Incontinentia pigmenti	464	1	0.3	Ultrarare	Monogenic
Kabuki syndrome	2,322	1	0.3	Rare	Monogenic
Kallmann syndrome-heart disease syndrome	2,326	1	0.3	Ultrarare	Monogenic
Kyphoscoliotic Ehlers-Danlos syndrome	536,545	1	0.3	Unknown	Monogenic
Larsen syndrome	503	1	0.3	Ultrarare	Monogenic
McCune Albright syndrome	562	1	0.3	Ultrarare	Monogenic
Meckel syndrome	564	1	0.3	Rare	Monogenic
Mosaic trisomy 8	96,061	1	0.3	Unknown	Chromosomal

Continue to Table 1: Rare genetic cardiovascular diseases identified in the outpatient clinic of a cardiology hospital in 2019.

Name of rare genetic cardiovascular disease	ORPHAcode[2]	n	Prevalence per 10,000 patients in the outpatient clinic	Type of rare disease*	Type of genetic disease
Mucopolysaccharidosis type 2 (Hunter)	580	1	0.3	Ultrarare	Monogenic
Mucopolysaccharidosis type 6 (Maroteaux-Lamy)	583	1	0.3	Ultrarare	Monogenic
Muenke syndrome	53,271	1	0.3	Rare	Monogenic
Multiminicore myopathy	598	1	0.3	Unknown	Monogenic
Oculopharyngeal muscular dystrophy	270	1	0.3	Ultrarare	Monogenic
Opitz GBBB syndrome	2,745	1	0.3	Ultrarare	Monogenic
Partial duplication of the long arm of chromosome 13; t(13;14)	262,932	1	0.3	Unknown	Chromosomal
Partial duplication of the long arm of chromosome 13; t(13;15)	262,932	1	0.3	Unknown	Chromosomal
Partial duplication of the short arm of chromosome 11	262,785	1	0.3	Unknown	Chromosomal
Pfeiffer syndrome	710	1	0.3	Unknown	Monogenic
Pseudopseudohypoparathyroidism	79,445	1	0.3	Unknown	Monogenic
Robinow syndrome	97,360	1	0.3	Unknown	Monogenic
Rubinstein-Taybi syndrome	783	1	0.3	Ultrarare	Monogenic
Seckel syndrome	808	1	0.3	Ultrarare	Monogenic
Short QT syndrome	51,083	1	0.3	Unknown	Monogenic
Shprintzen-Goldberg syndrome	2,462	1	0.3	Ultrarare	Monogenic
Steinert myotonic dystrophy	273	1	0.3	Rare	Monogenic
Stickler syndrome	828	1	0.3	Rare	Monogenic
TARP syndrome	2,886	1	0.3	Ultrarare	Monogenic
Tel Hashomer camptodactyly syndrome	3,292	1	0.3	Ultrarare	Monogenic
Tetrasomy 12p (Pallister-Killian syndrome)	884	1	0.3	Rare	Chromosomal
Trisomy X	3,375	1	0.3	Rare	Chromosomal
TTR-related cardiac amyloidosis	85,451	1	0.3	Unknown	Monogenic
Van den Ende-Gupta syndrome	2,460	1	0.3	Ultrarare	Monogenic

CHARGE = coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital abnormalities, and ear abnormalities. ATTR = transthyretin-related amyloidosis. MASS = mitral valve, aorta, skeletal, and skin. LMNA = lamin. GBBB = first letter from the last names of the families that was first diagnosed. TARP = talipes equinovarus, atrial septal defect, robin sequence, and persistence of left superior vena cava. TTR = transthyretin.

* According to the diseases prevalences in Orphanet;2 rare (< 1/2,000 - > 1/50,000), ultrarare (≤ 1/50,000 - < 1/1'000,000), and unknown prevalence.

correspond to the definition of rare diseases with a prevalence between < 1/2,000 and > 1/50,000, 38 correspond to ultrarare diseases (≤ 1/50,000 - < 1/1,000,000), and 33 had an unknown prevalence in the general population or at birth *(Table 1)*. Ultrarare diseases and rare genetic cardiovascular diseases with an unknown prevalence comprise a diverse spectrum, including skeletal dysplasias, cardiac neoplasm syndromes, unbalanced reciprocal translocation syndromes, muscular dystrophies, inborn errors of metabolism, and other syndromes, as shown in *Table 1*.

The cardiovascular phenotype presented in each rare genetic cardiovascular disease patient was classified to determine its distribution. The frequency per cardiovascular phenotype groups and subgroups is shown in *Table 2*. The most frequent cardiovascular phenotype was congenital heart diseases (42.4%;

Table 2: Cardiovascular phenotype distribution of the 794 patients with rare genetic cardiovascular in the outpatient clinic.

Cardiovascular phenotype	n (%)
Arrhythmic and conduction disorders	
Primary electrical diseases	117 (90.0)
Preexcitation syndrome	5 (3.9)
Atrioventricular block	3 (2.3)
Other cardiac arrhythmias*	3 (2.3)
Atrial fibrillation and flutter	2 (1.5)
Cardiac tumor disorders	
Cardiac rhabdomyoma	6 (85.7)
Cardiac myxoma	1 (14.3)
Cardiomyopathies	
Left ventricular noncompaction	29 (32.6)
Dilated cardiomyopathy	27 (30.3)
Arrhythmogenic right ventricular cardiomyopathy	16 (18.0)
Hypertrophic cardiomyopathy	15 (16.9)
Restrictive cardiomyopathy	2 (2.2)
Congenital heart diseases	
R-sided and L-sided obstructive lesions‡	161 (47.8)
Septal defects§	67 (19.9)
Conotruncal heart defects¶	45 (13.3)
Valvular heart diseases‖	38 (11.3)
Other congenital heart diseases**	16 (4.7)
Heterotaxy	10 (3.0)
Vascular disorders	
Thoracic aortic aneurysm and dissection	211 (97.7)
Arteriovenous malformation	3 (1.4)
Varicose veins	2 (0.9)
Other cardiovascular disorders	
Primary pulmonary hypertension	6 (40.0)
Cardiac dysautonomia	5 (33.3)
Ischemic heart disease	2 (13.3)
Pericardial effusion	1 (6.7)
Ventricular dysfunction	1 (6.7)

* Sinus node disease, supraventricular tachycardia, and ventricular premature depolarization.
‡ Right-sided obstructive lesions (pulmonary stenosis, stenosis of the pulmonary arteries, and pulmonary atresia with intact ventricular septum) and left-sided obstructive lesions (aortic stenosis, bicuspid aortic valve, coarctation of the aorta, supravalvular aortic stenosis, hypoplastic left heart syndrome, mitral stenosis, and mitral double outlet).
§ Atrial septal defects, ventricular septal defects and atrio ventricular septal defects (with or without minor abnormalities).
¶ Tetralogy of Fallot, pulmonary atresia with ventricular septal defects, double outlet of the left ventricle, pentalogy of Fallot, pulmonary valve agenesis, truncus arteriosus, transposition of great arteries, and interrupted aortic arch.
‖ Mitral prolapse valve, pulmonary, and tricuspid, aortic and mitral insufficiency.
** Total and partial anomalous pulmonary venous return, Epstein's anomaly, vascular ring, patent arterial duct, persistent left superior vena cava, and anomalous pulmonary venous drainage.

n = 337/794), followed by vascular disorders (27.2%; n = 216/794), arrhythmic and conduction disorders (16.4%; n = 130/794), cardiomyopathies (11.2%; n = 89/794), and the less frequent phenotypes were other cardiovascular disorders (1.9%; n = 15/794) and cardiac tumor disorders (0.9%; n = 7/794). There was a statistically significant difference among the cardiovascular phenotype groups in age (χ^5 = 106; p= 0.0001) *(Figure 1)* and sex (χ^5 = 17.9; p = 0.003) *(Figure 2)*. The youngest and oldest cardiovascular phenotype groups were cardiac tumor disorders (4 [1-13] years) and cardiomyopathies (37 [24-50] years), respectively *(Figure 1)*. In addition, cardiac tumor disorders had a higher proportion of females (85.7%) *(Figure 2)*. Sixty-two percent of all patients (n = 489/794) with rare genetic cardiovascular diseases corresponded to three cardiovascular phenotype subgroups. The cardiovascular phenotype subgroup related to thoracic aortic aneurysm and dissection had the largest number of patients, corresponding to 26.6% of all patients (n = 211/794), followed by obstructive congenital heart disease lesions (20.3%; n = 161/794) and primary electrical diseases (14.7%; n = 117/794) *(Table 2)*. These three subgroups of cardiovascular phenotypes correspond principally to Marfan syndrome, Loeys-Dietz syndrome, Noonan syndrome, Williams syndrome, Romano-Ward syndrome, Brugada syndrome, and others.

DISCUSSION

Scarce studies have addressed the number and prevalence of rare cardiovascular diseases because of their low prevalence and difficulty in recognition.[1,7,8] However, knowing the prevalence of rare genetic cardiovascular diseases is of utmost importance since there is an increase in prevention and follow-up algorithms,[11,12] new treatments, and gene therapies that may benefit patients.[13] Rare genetic cardiovascular diseases are frequently encountered in clinical practice, but the overall prevalence of rare genetic cardiovascular conditions in a clinical setting was previously unknown in Mexico and worldwide. In the present research, the overall period prevalence of rare genetic cardiovascular diseases was

2.5%; in other words, almost 1 in 40 patients has a rare genetic cardiovascular disease in a cardiovascular outpatient clinic. Although the prevalence may appear low relative to other cardiovascular diseases, it is not insignificant, especially considering that a significant proportion of rare genetic cardiovascular diseases harm the quality of life, reduce life expectancy, and have economic implications that could cause higher medical care costs.[14-16]

In the present study, the prevalence of monogenic rare genetic cardiovascular diseases was 2.1%. In this regard, a recent study estimated the prevalence of monogenic cardiovascular diseases in patients referred to cardiac catheterization with an unbiased whole-exome sequencing approach. The prevalence of patients with pathogenic and likely-pathogenic variants with a clinical phenotype was 1.7%.[17] Nevertheless, the estimated prevalence includes both common genetic diseases and rare genetic cardiovascular diseases without reporting the overall estimated prevalence for those rare diseases. The higher prevalence of monogenic disorders observed in the present study could be related to a broader spectrum of conditions in the cardiovascular outpatient clinic and the inclusion of pediatric ages.

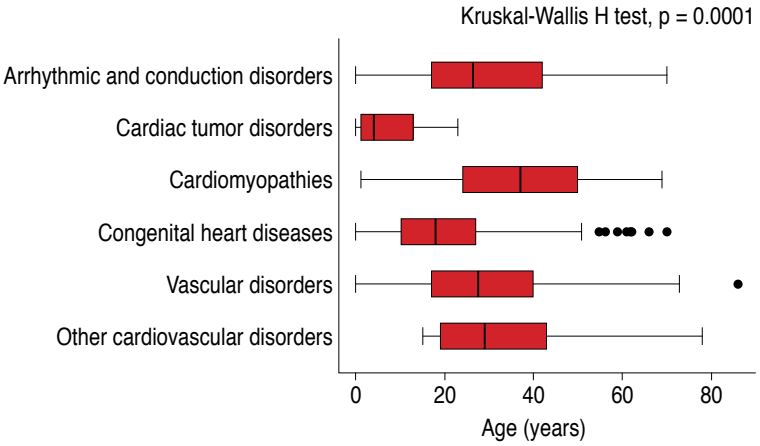

Figure 1: Distribution of age of patients with rare genetic cardiovascular diseases among cardiovascular phenotype groups.

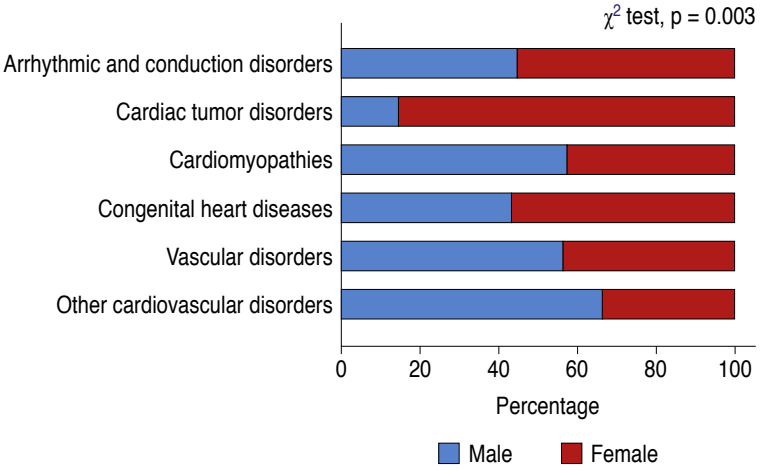

Figure 2: Distribution of sex of patients with rare genetic cardiovascular diseases among cardiovascular phenotype groups.

A curated database initiative (PhenoDis)[5] has annotated the existence of 327 rare cardiac diseases so far,[5] without counting those that affect the vascular system or other rare cardiovascular diseases. The present study detected the broad spectrum of rare genetic cardiovascular diseases that can occur in cardiovascular clinical practice. The spectrum includes rare genetic cardiovascular diseases affecting the heart structure and functioning, blood vessels, cardiac conduction, autonomic systems, and others. A total of 104 different rare genetic cardiovascular disease diagnoses were identified, not limited to a few widely known syndromes. We should be aware that a great proportion of the rare genetic cardiovascular diseases found in the present study have an unknown prevalence or are considered ultrarare diseases with an extremely low prevalence (≤ 1/50,000 - < 1/1'000,000) in the general population.[10] Ultrarare diseases are routinely excluded from public health policies and comprise highly heterogeneous phenotypes with complex molecular mechanisms. Therefore, it is essential to highlight the importance of its recognition to promote comprehensive diagnostic approaches, the formation of doctors specialized in them, drug development, novel therapies, and the creation of health policies consistent with the needs of the patients suffering from these diseases.[18]

The cardiovascular phenotype distribution observed among rare genetic cardiovascular diseases showed some expected results, such as a higher frequency of congenital

heart diseases[19] and a lower frequency related to rare genetic disorders with cardiac tumors.[20] Unexpectedly, cardiomyopathy disorders had a lower frequency compared to other cardiovascular phenotypes. In this regard, it is widely known that hypertrophic cardiomyopathy as a composite is one of the most common genetic diseases, with a prevalence between 1/200 and 1/500 in the general population.[21] Although not all the subtypes of hypertrophic cardiomyopathies are rare,[12] a higher proportion of cases was expected than observed. Several factors related to characteristics inherent to these types of rare genetic cardiovascular diseases, such as variable expressivity, attenuated phenotypes, incomplete or reduced penetrance, atypical phenotypes, absence of genetic family history, or lack of genomic diagnosis that could make its recognition, referral, and diagnosis difficult may be contributing to this.[21-23] A finding to consider was the proportion of cases corresponding to thoracic aortic aneurysms and dissection disorders (Marfan syndrome, Loeys-Dietz syndrome, and others) that represented almost a third of all cases with rare genetic cardiovascular diseases in the outpatient clinic. The early recognition and diagnosis of these diseases are crucial to conducting proper follow-up, genetic counseling, treatment, and surgical procedures to prevent fatal outcomes.

The retrospective design has well-known limitations, and probably some rare genetic cardiovascular diseases could have been masked among highly prevalent diseases or were not suspected yet.[22,23] Nevertheless, the retrospective design offers a good alternative for detecting low-prevalence disorders in the absence of registries, insufficient epidemiological data, and missing specific International Classification of Diseases (ICD) codes for rare diseases.[3] Moreover, no studies have been conducted regarding the prevalence of rare genetic cardiovascular disease in a cardiovascular clinical setting or other hospitals. Although the cardiology hospital studied is a cardiovascular reference in Mexico, the prevalence per disease in the outpatient clinic reported in the present study remained as newly descriptive data to inform about the situation of these diseases and could not be compared with the general population or regional disease prevalences. However, the number and prevalence observed in the present study could increase in the future with the improvement and implementation of more diagnostic technologies and the incorporation of cardiogenetics clinics. Despite the limitations, the present study sets a step forward to close knowledge gaps concerning rare cardiovascular disease prevalence and, hopefully, encourage further research.

CONCLUSIONS

Rare diseases face considerable challenges because of their low prevalence in the general population. Scarce studies have focused on knowing the number and distribution to delineate the magnitude in different clinical contexts. The current study has provided the first estimate of the overall prevalence of rare genetic cardiovascular diseases in a cardiovascular hospital. In this hospital, almost one in forty patients was affected. Moreover, the present study identified the vast spectrum of rare genetic cardiovascular diseases and their most common cardiovascular phenotype in a cardiovascular clinical setting.

Further research in other cardiovascular hospitals and the general population is needed to achieve a global panorama concerning these diseases. Recognition and visibility of rare diseases are the first steps toward better clinical care. Also, it is imperative to create comprehensive clinical registries for rare genetic and nongenetic cardiovascular diseases. This study reminds us that rare genetic cardiovascular diseases are rare, complex, and not easy to recognize but not invisible.

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Correspondence:
Blanca Rebeca Ibarra-Ibarra, MD, MSc, PhD
E-mail: blanca.ibarra@cardiologia.org.mx