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CHARGE syndrome and congenital heart diseases: systematic review of literature

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Abstract

CHARGE syndrome (CS) is a rare genetic disease that affects many areas of the body. The aim of the present systematic review was to evaluate the prevalence and types of congenital heart diseases (CHDs) in CS and their impact on clinical outcome. A systematic review from 1981 to September 2022 was conducted. Clinical studies that reported the association between CS and CHDs were identified, including a case report of a rare congenital anomaly of the aortic arch (AA) with persistent fifth AA (PFAA). Demographic, clinical and outcome data were extracted and analyzed. A total of 68 studies (44 case reports and 24 case series; n=943 CS patients) were included. The prevalence of CHDs was 76.6%, patent ductus arteriosus 26%, ventricular 21%, atrial septal defects 18%, tetralogy of Fallot 11%, and aortic abnormalities 24%. PFAA has not been previously reported in CS. Cardiac surgery was performed in more than half of CS patients (150/242, 62%). The in-hospital mortality rate was about 9.5% (n=86/900) in case series studies and 12% (n=5/43) in case reports, including cardiovascular (CV) and non-CV causes. CHDs and feeding disorders associated with CS may have a substantial impact on prognosis. CHDs were usually associated with CS and represent important causes of morbidity and mortality. PFAA, although rare, may also be present. The prognosis is highly dependent on the presence of cardiac and non-cardiac developmental abnormalities. Further studies are needed to better identify the main causes of the long-term outcome of CS patients.

Introduction

"CHARGE" is the acronym that describes a rare genetic syndrome (estimated incidence of 1-3/10,000 births) characterized by a constellation of clinical findings, including coloboma, heart defects, choanal atresia, retardation of growth and/or development, genitourinary malformation, and ear abnormalities. Additional possible features consist of cranial nerve anomalies, cleft lip/palate, distinctive facial features, renal anomalies, omphalocele/umbilical hernia, scoliosis/hemivertebrae, immune deficiency, hand, and limb anomalies [1] (Figure 1).

Clinical diagnostic criteria for CHARGE syndrome (CS) were first proposed in 1998 by Blake *et al.* [2], and then revised in 2005 by Verloes *et al.* [3]. The *CHD7* (chromodomain helicase DNA-binding protein 7) gene, located on 8q12, which regulates the transcription of tissue-specific genes involved in different developmental stages, is the only one associated with this syndrome [4]. It should be noted that a broad CS phenotypic spectrum may occur along with

highly variable clinical presentations. In this regard, about 20% of patients with a *CHD7* mutation do not fulfill the clinical diagnostic criteria and are referred to as atypical CHARGE cases [5].

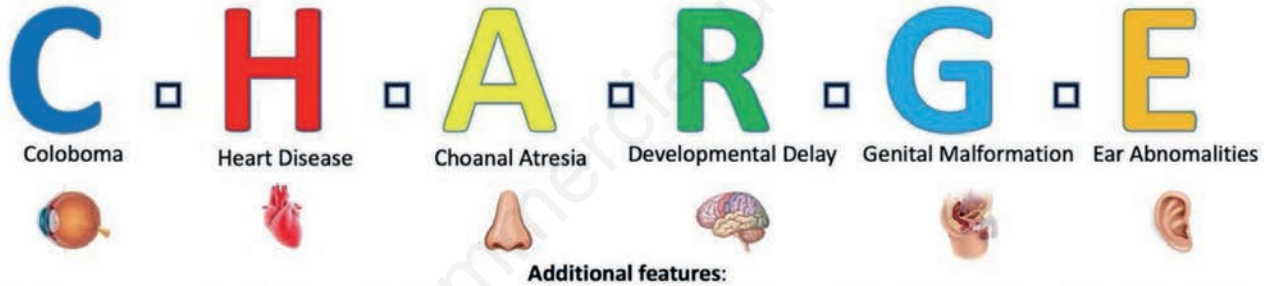
Herein, the present systematic review of the literature aims to investigate the prevalence and types of congenital heart diseases (CHDs) in CS and their impact on clinical outcomes. A rare case report of persistent fifth aortic arch (PFAA) in a child with genetically confirmed CS is also described.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Diagnostic Test Accuracy (PRISMA) Statement [6].

Literature search, study selection and data extraction

A systematic literature search was performed using PubMed (MEDLINE), Embase, and Scopus from 1981 to September 2022. The following medical subject headings were used separately: "CHARGE syndrome" and "cardiovascular disease", "CHARGE syndrome" and "congenital heart disease", "CHARGE syndrome" and "aortic disease". English-language, peer-reviewed original publications were searched. Observational studies and case series reporting CS and CHDs were included. In addition, case reports were also considered to provide more comprehensive results. Abstracts, conference presentations, editorials, expert opinions, animal studies, and those with full text not available online were excluded. Reference lists of relevant studies and reviews were screened to identify further studies not detected by the electronic search. Eligibility criteria were as follows: i) CS according to well-defined diagnostic criteria described within original data manuscripts [2,3]; ii) CHDs reported in CS patients. Two cardiologists (AN and MF) evaluated study eligibility and quality independently. They also performed data extraction by using standardized data collection sheets. Disagreements were resolved by consensus with a third cardiologist (MVP). A flow diagram of the selection process is shown in *Supplementary Figure 1*. The data extracted from included studies were as follows: study design, genetically confirmed CS diagnosis, patient characteristics, the type and percentage of CHDs, the need for cardiac surgery and clinical in hospital, and long-term outcome. All statistical analyses were performed with tailored software.



Clinical criteria

	Major criteria	Minor criteria	Clinical diagnosis
Blake et al. [2]	1. Coloboma, microphthalmia	1. Cardiovascular malformation	Typical CHARGE: four major or three major + three minor
	2. Choanal atresia or stenosis	2. Tracheo-esophageal defects	
	3. Characteristics ear anomalies: external ear, middle ear, inner ear, mixed deafness	3. Genital hypoplasia or delayed pubertal development	
	4. Cranial nerve dysfunction	4. Cleft lip and/or palate	
		5. Developmental delay	
		6. Growth retardation	
		7. Charateristic facial features	
Verloes et al. [3]	1. Ocular coloboma	1. Heart or esophagus malformation	Typical CHARGE: three major or two major + two minor
	2. Choanal atresia	2. External or middle ear anomalies	
	3. Hypoplastic semicircular canals	3. Rhomboencephalic dysfunction including sensoneural deafness	
		4. Hypothalamo- hypophyseal dysfunction	
		5. Mental retardation	

Figure 1. Clinical criteria for CHARGE syndrome diagnosis.

Results

A total of 1271 records were identified in PubMed, Scopus, and EMBASE. Of these, 510 were excluded because duplicates. After the screening of the title and abstract, 514 papers were also excluded because they did not fulfill the inclusion criteria. 247 papers were assessed for eligibility and 179 were further excluded. Of these, 34 were reviews, 21 were written in non-English language, 14 were abstracts, and 7 did not have the full text not available. In addition, 103 did not provide cardiovascular (CV) data. Finally, full-text analysis was made in 68 studies of CS patients with CHDs, of which 24 case series and 44 case reports. The PRISMA flow diagram is depicted in *Supplementary Figure 1*.

Case Series

The comprehensive case series data are reported in Table 1 [4-28]. The overall population consisted of 900 CS patients (52% males, age range = 0-69 years). Caucasians were more prevalent (61%) than Asians (39%). In most cases (≥80%; mostly in more recent studies), CS diagnosis was made according to molecular testing. The prevalence of CHDs was about 76.6% (*Supplementary Table 1*). Cardiac surgery was performed in more than half of CS patients (150/242, 62%) and often required multiple and staged repairs.

Outcomes

The in-hospital mortality rate was about 9.5% (n=86/900), ranging from 4 to 50% (Table 1) [29]. Specifically, causes of in-hospital mortality were reported in 71 patients, including CV (38%) and non-CV deaths (62%). Aspiration of secretions due to feeding problems was the most common cause of non-CV death, described in about 50% of deaths. In the study of Blake *et al*. [7], 26% (13/50) of CS patients (9 male and 4 female) died: 3 immediately after birth, 7 between 1 month and 1 year of age, and 3 between 1 and 5 years of age. Most CS patients (7/13, 54%) died from aspiration of secretions. The other causes of death were: 3 sudden deaths, 1 coagulation intravascular dissemination, 1 withdrawal of treatment. In another study [27], the in-hospital mortality rate was 34% (20/59), including CV (11/20, 55%) and non-CV deaths (9/20, 45%). In-hospital complications were reported in about 33% (73/220) of CS patients, ranging from 20 to 60%. Among them, non-CV in-hospital complications were most frequently described (ranging from 51 to 100%), including, in most cases, feeding problems for tracheoesophageal atresia/fistula, pharyngeal incoordination, choanal atresia, gastroesophageal reflux, and respiratory problems/infections. In-hospital CV complications were reported only in two studies (37/109, 34%) [7,27] (Table 1). In most case series, long-term outcome data were missing. Long-term mortality rates were reported only in two studies [7,18].

Blake *et al*. [7] reported that 3/13 (23%) patients died between 1 and 5 years of age for CV causes. Interestingly, survival at 5 years was 70% (13/50 deaths) with most deaths within the first year of life (10/13, 77%). In the study of Issekutz *et al*. [18], one death was reported at 9 years and another one at 8 months (Table 1).

Long-term complications were reported in about 15% (54/370) of CS patients, ranging from 5 to 50%. Among them, non-CV complications were most frequently described including swallowing problems (59%), recurrent respiratory infections (18%), retinal detachment (9%), and single reports of hydronephrosis and epileptic seizures. Long-term CV complications were missing. The hospital readmission rate was about 10% (10/100 CS patients), ranging from 6.5 to 50%.

Case Reports

Patients' characteristics of the 44 CS case reports (61% males; age range = 0-6 years) are described in Table 2 [30]. *CHD7* mutation was confirmed in 66% (29/44) of cases. The most common type of cardiac defect was the patent ductus arteriosus (PDA) (22/44; 50%). Ventricular septal defect (VSD) and atrial septal defect (ASD) were described alone or in association in 41% (18/44) and 29% (13/44) of cases, respectively. Other associated CHDs are reported in Table 2 [31-54]. Interestingly, the right aortic arch (AA) was described with and without signs of aortic coarctation among 27% (12/44). Aberrant subclavian artery (SA) was reported in 25% (11/44) of cases while PFAA was only in our case report. Of note, about half of the cases (21/44, 48%) underwent cardiac surgery, mostly performed within 1 year from birth. Furthermore, nearly three-quarters of the patients have undergone major non-CV surgery (*i.e*., genitourinary, ophthalmic, plastic otolaryngology, gastric surgery) requiring general anesthesia.

Outcomes

The in-hospital mortality rate was 12% (5/43). Specifically, 4 patients died within 2 weeks of life, 2 patients at 7.5 and 22 months, respectively. In-hospital CV death occurred in 4 cases, while non-CV mortality was reported in 1 patient. In-hospital complications were mostly non-CV (15/19, 79%), of which 9 were for pulmonary infections and acute respiratory distress.

Follow-up data were available in only 26 case reports. One death (4%) occurred 11 months after discharge for unknown reasons. Long-term complications were reported in about 73% (19/26) of cases. Among them, CV complications [left ventricle (LV) dysfunction, acute heart failure] occurred in 37% (7/19), while non-CV complications were reported in 63% (12/19), including pulmonary infections, gastrointestinal and neurological complications, urinary infections, and immunodeficiency.

Case Report

A 12 years-old child was referred for 2D color Doppler echocardiography (TTE) follow-up examination at the Cardiology Division, "Cava de' Tirreni" Hospital. He was born at term *via* normal spontaneous vaginal delivery. Height was 9 cm below the third percentile (-2.9 standard deviation), weight at the third percentile and body mass index at the 25th percentile. Hemodynamic parameters were normal (blood pressure = 120/80 mmHg; heart rate = 75 bpm; oxygen saturation on room air = 98%). Family history was negative for short stature, endocrine or autoimmune conditions, and CHDs. Feeding disorders during the neonatal period or convulsions were not referred. Medical clinical history consisted of bilateral ocular coloboma, left hypoacusis, scoliosis, mild motor impairments, nocturnal enuresis, genitourinary anomalies such as micropenis and retractile testicles, facial dysmorphisms with narrow bifrontal diameter, small mouth and dysplasia of the pinnae. These malformations met Blake's diagnostic criteria of CS (three majors and three minors) for which he underwent molecular diagnostic testing that identified a de novo mutation (variant c.5290_5300+10del) in the *CHD7* gene. However, a definitive diagnosis of CS was already made at the Children's National Hospital of Rome, Italy.

Table 1. Data from case series (1981-2020).

First author, year	Total patients, n	Male, n (%)	Age, range Mean±SD	Caucasian race, n (%)	Genetically confirmed diagnosis, (%)	CHD n (%)	Cardiac surgery, n (%)	Death n (%)	In-hospital death, n (%) CV/non-CV deathn/n (%)	In-hospital complications, n (%) CV/non-CV n/n (%) hospital stay	Long-term death, n (%) CV/non-CV deathn/n (%)	Long-term complications, n (%) Hospital readmission n (%)
Aramaki, 2006	17	8 (47)	0-186±6	0	100	17 (100)	-	-	-	-	-	-
Blake, 1990	50	29 (58)	-	-	-	42 (84)	30/42 (71)	13 (26)	13 (26%) non-CV death 13 (26%)	26 (52%) CV 21 (42%) / non-CV 25 (50%)	3 (23%)-	-
Corsten-Janssen, 2014	46	29 (63)	0-6913±13	-	100	46 (100)	-	-	-	-	-	-
Davenport, 1986	15	8 (53)	1-277±9	-	-	5 (33)	2/5 (40)	1 (7)	1 (7%) CV death 1 (7%)	2 (13%) non-CV 2 (13%)	-	4 (26%) 2 (13%)
Husu, 2013	18	6 (33)	0-113±4	18(100)	100	14 (78)	11/14 (78)	3 (17)	3 (17%) CV death 3 (17%)	-	-	-
Ahn, 1998	3	1 (33)	0-2	0	-	3 (100)	1/3 (33)	-	-	-	-	-
Chang, 2013	2	1 (50)	0	0	-	2 (100)	0	1 (50)	1 (50%) non-CV death 1 (50%)	1 (50%) non-CV 1 (50%)	-	- 1 (50%)
Farquhar, 2002	2	1 (50)	0	2 (100)	-	2 (100)	1/2 (50)	0	0	0	-	1 (50%) 1 (50%)
Cheng, 2019	9	7 (78)	0	0	100	8 (89)	6/8 (75)	-	-	-	-	-
Chestler, 1988	6	4 (67)	0-71.5±2.8	6 (100)	-	4 (67)	-	1 (17)	1 (17%) non-CV death 1 (17%)	-	-	3 (50%) 2 (33%)
Corsten-Janssen, 2016	299	-	-	299 (100)	100	220 (73)	-	14 (33) *	14 (33%) -	-	-	26 (12%) √ -
de Lonlay-Debeney, 2015	5	3 (60)	0	5 (100)	100	4 (80)	1/4 (75)	2 (40)	2 (40%) non-CV death 1 (20%)	1 (20%) non-CV 1 (20%)	-	-
Issekutz, 2005	77	-	-	77 (100)	-	65 (84)	15/65 (23)	9 (12)	9 (12%) CV death 4 (5%)/ non-CV death 5 (6,5%)	-	1 (1,3%) non-CV 1 (1,3%)	14 (18%) 5 (6,5%)
Larson, 1995	3	0	0-20±1	-	100	3 (100)	-	-	-	-	-	-
Lee, 2009	4	3 (75)	3-105.7±3	0	100	4 (100)	-	-	-	-	-	-
Oley, 1987	20	14 (70)	0-14	20 (100)	-	20 (100)	18/20 (90)	1 (5)	1 (5%) CV death 1 (5%)	7 (35%) non-CV 7 (35%)	-	1 (5%) -
Pagon, 1981	20	-	-	20 (100)	-	12 (60)	-	4 (20)	4 (20%) CV death 3 (15%) / non-CV death 1 (5%)	6 (30%) non-CV 6 (30%)	-	5 (25%) -
Qin, 2020	5	4 (80)	0	-	100	4 (80)	-	-	-	3 (60%) non-CV 3 (60%)	-	-
Shoji, 2014	25	13 (52)	1-299±7	0	80	19 (76)	-	-	-	-	-	-
Sohn, 2015	18	8 (44)	0-191.7±1.9	0	100%	13 (72)	11/13 (84)	-	-	5 (27%) non-CV 5 (27%)	-	-
Stroemland, 2005	31	15 (48)	0-311.5±0.6	31 (100)	-	16 (52)	16/16 (100)	-	-	-	-	-
Tellier, 1998	47	17 (36)	0-9	47 (100)	-	40 (85)	-	17 (36)	17 (36%) non-CV death 17 (36%)	11 (23%) non-CV 11 (23%)	-	-
Wyse, 1993	59	33 (56)	-	-	-	50 (85)	38/50 (76)	20 (34)	20 (34%) CV death 11 (19%) / non-CV death 9 (15%)	33 (56%) CV 16 (27%) / non-CV 17 (29%)	-	-
Legendre, 2017	119	57 (48)	1-21	119 (100)	90%	76 (64)	-	-	-	-	-	-

SD, standard deviation; CHD, congenital heart diseases; CV, cardiovascular; -, not available; *data on death were reported in 14 of only 42 patients with congenital arch vessel anomaly; √26 of 220 patients with CHD.

The electrocardiogram showed sinus rhythm and incomplete right branch block. TTE documented mildly increased LV end-diastolic diameter (60 mm, Z score= + 2.2) and LV ejection fraction within normal limits (=55%). A single posterolateral papillary muscle and a cleft of anterior mitral leaflet associated with mild mitral regurgitation were detected (Figure 2). ASD and VSD were not found, and ductal shunts were excluded. Right heart dimensions, function (tricuspid annular plane systolic excursion = 26 mm), and systolic pulmonary artery pressures (29 mmHg) were within normal range. Pericardial effusion was absent. Interestingly, AA had a double-lumen appearance without Doppler signs of coarctation. Continuous wave Doppler showed a non-significant peak gradient of 13 and 12 mmHg on PFAA and on the descending aorta, respectively. The upper lumen was giving rise to the head and neck vessels, while the lower one was extending from the ascending to the descending aorta with no branching (Figure 2). This case of PFAA (type 1, according to Freedom classification) was not associated with coarctation, resulting in systemic-to-systemic connection without hemodynamic impact and not requiring surgical repair. The diagnosis of PFAA was further confirmed by Children's National Hospital, Rome, Italy. Type 1 PFAA (double-lumen/double-barrelled AA) may also be associated with interrupted arch or coarctation (Figure 3), in which the presence of an additional vascular channel to the distal aorta was critical for survival. Other types of PFAA, according to Freedom classification, were: i) system-to-pulmonary (type 2), in which the arterial connection was between the ascending aorta and the pulmonary arteries,

Table 2. Data from case reports (1989-2022).

Variables	
Patients, n	44
Male, n (%)	27 (61)
Age, min-max (years)	0-6
Caucasian race, n (%)[∝]	6 (50)
Genetically confirmed diagnosis, n (%)	29 (66)
VSD, n (%)	18 (41)
ASD, n (%)	13 (29)
PDA, n (%)	22 (50)
TOF, n (%)	4 (9)
DORV, n (%)	3 (7)
DOLV, n (%)	1 (2)
AV canal defect, n (%)	3 (7)
Ebstein's anomaly, n (%)	2 (5)
CoA, n (%)	5 (11)
BAV, n (%)	5 (11)
Hypoplasia AA, n (%)	1 (2)
TAPVC, n (%)	1 (2)
Right AA, n (%)	12 (27)
Pulmonary atresia/stenosis, n (%)	2 (5)
Aberrant subclavian artery, n (%)	11 (25)
Persistent LSVC, n (%)	2 (5)
PFAA, n (%)[♦]	1 (2)
Others, n (%)*	8 (18)
Cardiac surgery, n (%)	21 (48)
Death, n (%)[$]	8 (18)
In-hospital death, n (%)[$] CV/non-CV death, n/n	6 (14) 4 CV/1 non-CV[ϑ]
In-hospital complications, n (%) CV/non-CV, n/n hospital stay	19 (56)[Ψ] 4 CV/15 non-CV[η]
Long-term death, n (%)[φ] CV/non-CV death, n/n (%)	1 (4)[ς] -
Long-term complications, n (%)	19 (73)[Δ]
Hospital readmission, n (%)	8 (53)[σ]

VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; DOLV, double outlet left ventricle; AV, atrioventricular; CoA, coarctation of the aorta; BAV, bicuspid aortic valve; AA, aortic arch; TAPVC, total anomalous pulmonary venous connection; LSVC, left superior vena cava; PFAA, persistent fifth aortic arch; CV, cardiovascular. [∝]available in 12 case reports; [♦]described in our case report; *others: tricuspid atresia, right ventricular rhabdomyoma, dysplastic mitral valve, single coronary artery, overriding aorta, bicuspid pulmonary valve, aortic atresia, abnormal origin of pulmonary arteries; [$]available in 43 patients; [φ]available in 27 patients; [ϑ]in one case the death occurred during fetal period for unknown causes; [Ψ]available in 34 patients; [η]of those 9 patients for pulmonary infections and respiratory distress; [ς]at 11-months for unknown cause; [Δ]available in 26 patients; [σ]available in 15 patients.

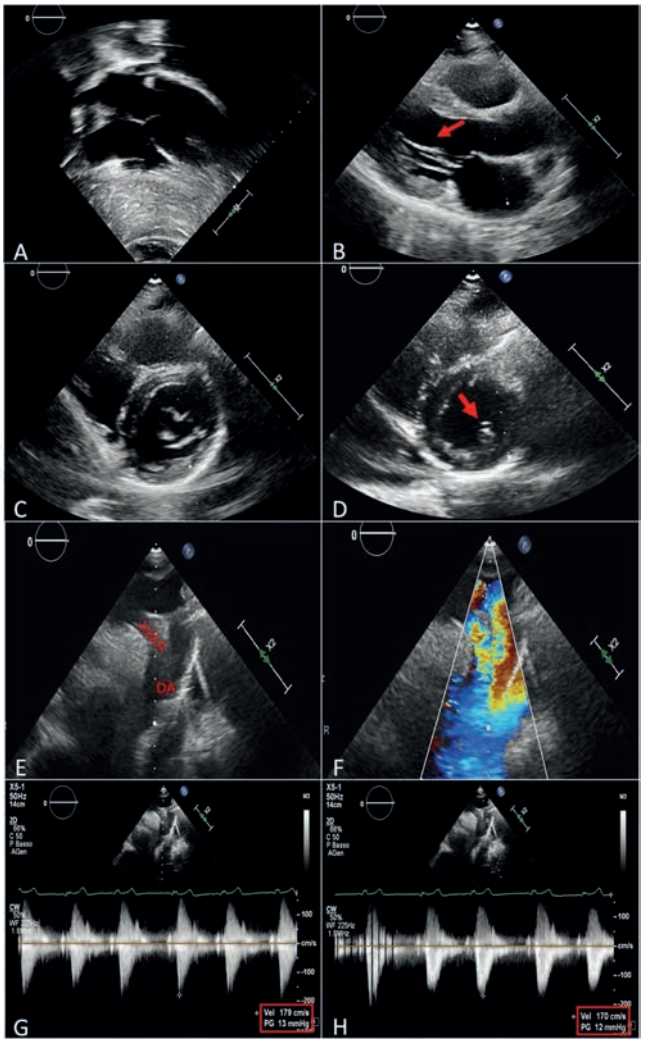


Figure 2. A) Subxiphoid long-axis view showing situs solitus and levocardia; B) at parasternal long-axis view, single papillary muscle was detected (red arrow); C,D) short axis view showing cleft of anterior mitral leaflet and single papillary muscle (red arrow); E) suprasternal views showing Freedom type 1 PFFA; F) color doppler flow imaging shows the "double-lumen aortic arch", in which aorthic arch is divided into the superior and inferior channel. The lower arch is a persistent fifth aortic arch (PFAA) that arises from the ascending aorta and is parallel with the fourth arch (aortic arch); the fourth arch and PFAA connect to the descending aorta together; G,H) continuous wave Doppler showed non-significant peak gradient of 13 and 12 mmHg on PFAA and fourth arch, respectively.

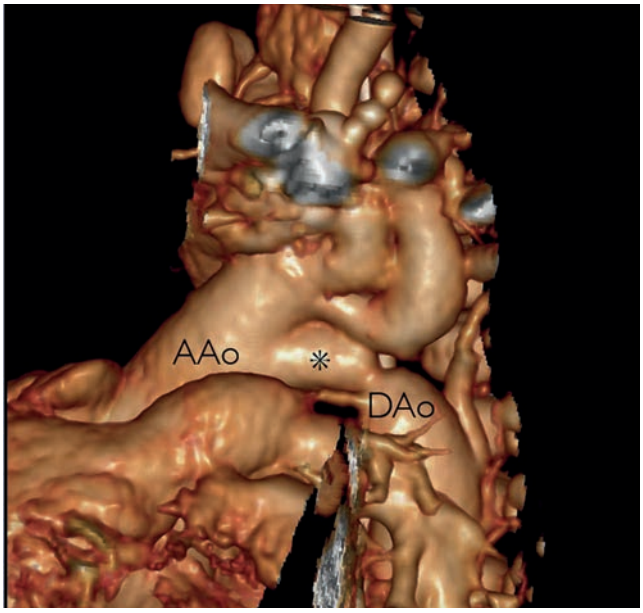


Figure 3. 3D reconstruction at computed tomography of a systemic-to-systemic persistent fifth aortic arch (asterisk) and interrupted aortic arch with distal coarctation in a 9-day-old neonate. AAo, ascending aorta; DAo, descending aorta. Reprinted from Lloyd *et al.* Cardiol Young 2018;28:175-81; with permission.

resulting in pathological left-to-right shunting with pulmonary hypertension. It may also be associated with critical right-sided obstructive lesions [such as pulmonary atresia, tetralogy of Fallot (TOF), isolated left pulmonary artery]; ii) pulmonary-to-system (type 3), in which blood flow was pulmonary to systemic in the opposite direction compared with type 2. It may be associated with any critical left-sided obstructive lesions; iii) bilateral (type 4) was rarely described in patients with double-outlet RV, subaortic VSD, and right AA.

Discussion

CS is a rare genetic disorder that may affect many areas of the body, including heart defects. The pattern of cardiac malformations varied among individuals and was described only in small case series and case reports. Although CS is a rare disease, the high prevalence and the heterogeneity of CHDs associated with CS should be considered in real-life daily clinical practice for differential diagnosis. For this reason, this unique case described of PFAA inspired us to investigate the prevalence and types of CHDs in CS and their impact on clinical outcomes with a detailed and accurate systematic review.

To the best of our knowledge, this is the first systematic review that comprehensively investigated the prevalence (76.6%) and types of CHDs in a population of 944 CS patients. Specifically, PDA emerged as the most frequent heart defect (26%), followed by VSD and ASD (21% and 18% of cases, respectively) (Figure 4A).

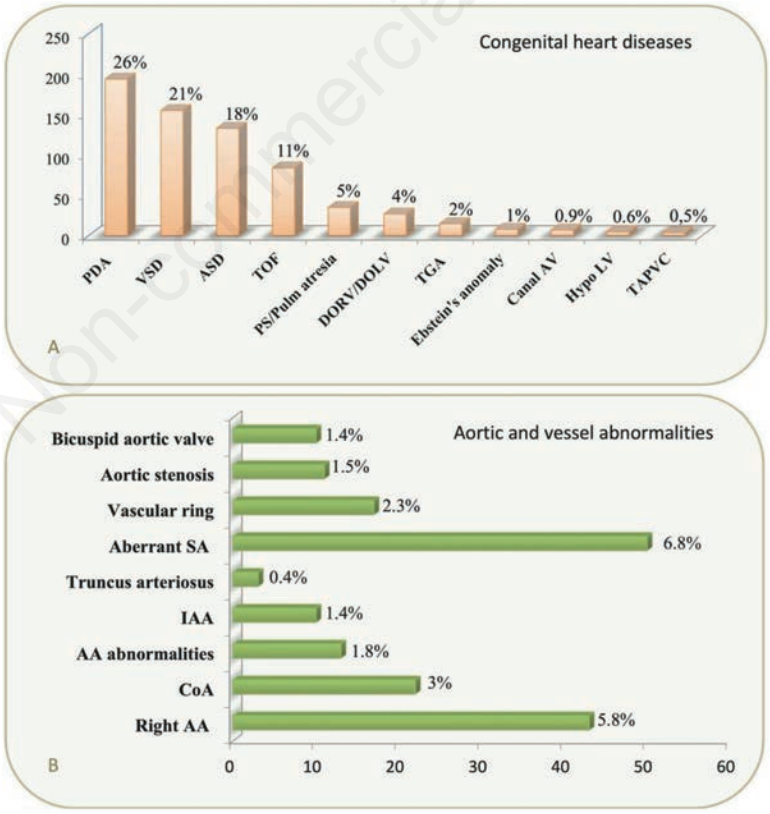


Figure 4. Distribution of congenital heart diseases (A) and aortic and vessel abnormalities (B) in CHANGE syndrome by the cumulative analysis of case reports and case series (944 patients). VSD, ventricular septal defect; ASD, atrial septal defect; TOF, tetralogy of Fallot; PS, pulmonary stenosis; DORV, double outlet right ventricle; DOLV, double outlet left ventricle; TGA, transposition great arteries; AV, atrioventricular; LV, left ventricle; TAPVC, total anomalous pulmonary venous connection; AA, aortic arch; IAA, interrupted aortic arch; SA, subclavian artery; CoA, coarctation of the aorta.

Complex CHDs were also described, such as TOF (11%), pulmonary stenosis/atresia (5%), double outlet right ventricle/double outlet LV (4%), transposition great arteries (2%), Ebstein's anomaly (1%), atrioventricular (AV) canal (0.9%), LV hypoplasia (0.6%) and total anomalous pulmonary venous connection (0.5%). Interestingly, aortic and vessel abnormalities were reported in a substantial number of cases (24%) (Figure 4B), ranging from 4 to 23% in all CS patients or from 5 to 36% in CS patients with other associated heart defects. Right AA was described in 5,8% [in association or not with aberrant SA (6.8%) and vascular ring (2.3%)], interrupted AA in 1.4%, and aortic coarctation in 3% of cases [55-73]. In some cases, vascular compression occurred with variable symptoms such as feeding difficulties, recurrent respiratory infections, cough, dyspnea, respiratory distress, dysphagia, and vomiting [74].

To date, the largest published study of CS patients examining the spectrum of CHDs included 299 individuals and demonstrated the over-representation of conotruncal defects (31-42%) and atrioventricular septal defect (13-17%) compared with patients with nonsyndromic heart defects and this difference was statistically significant between two groups ($p<0.001$). This finding was also documented by Meisner *et al*. [9] that reported AV septal defects (11.3% *versus* 3.4%) and AA abnormalities (33.6% *versus* 10.2%) more frequently in individuals with CS (n. 221) than the full population with CHDs [75].

Notably, our case is the first report of PFFA (in association with anterior mitral leaflet and subvalvular apparatus abnormalities without any hemodynamic impact) described in CS. PFAA, generally defined as the inferior channel located between the true AA (a derivative of the fourth embryological arch) and the pulmonary artery (a derivative of the sixth AA artery) [76], is usually diagnosed during the neonatal or infant period and is associated with aortic coarctation in 38% of cases. In our case, PFAA diagnosis was challenging because the double-lumen morphology of AA was the object of many debates. In some patients, such as ours, it may be an incidental finding, without Doppler signs of coarctation, completely asymptomatic and not requiring intervention. Occasionally, it is a single finding, and the symptoms and the clinical course are mostly affected by associated CHDs and hemodynamic consequences. Undoubtedly, a comprehensive and standardized TTE remains the first-line diagnostic tool for PFAA and associated CHDs [77], even if in the case of complex extracardiac anatomy, second-level imaging diagnostic techniques, such as CTA and/or cardiac magnetic resonance [78,79], are mandatory because more accurate for showing the origin, branching, the course, AA complexities as well as to investigate possible coexisting abnormalities of the pulmonary or systemic circulations. Missed and incorrect diagnosis are possible as well as it may be mistaken for AA dissection.

Outcomes

The available literature of the case series showed a wide range of in-hospital mortality rates (ranging from 4 to 50%), likely due to: i) missing outcome data; ii) different sample sizes (from 2 to 299 CS patients), and study population characteristics; iii) a great disparity of years of the studies (from 1981 to 2016) for which an improvement of the quality of care and the therapeutic approach may have a non-negligible effect on outcome data. However, the overall in-hospital mortality rate of the case series was not much different from the case reports (9.5% *versus* 12%, respectively). In case series studies, non-CV causes of death were more frequently reported (62%) than CV causes (38%). Aspiration of secretions due to feeding problems was the most common cause of non-CV death in about 50%. Instead, in case reports, in-hospital CV deaths were more frequently described (4/5, 80% of all deaths). It is possible that the potential risk of selection bias in the present systematic review (only studies reporting the association between CS and CHDs were included) was stronger in case reports. However, it is not possible to determine whether there are significant differences in terms of mortality between CS patients with and without associated CHDs. It is already known that individuals with CHDs and a genetic syndrome or association have an increased risk of poorer outcomes compared to non-syndromic individuals with CHDs [80]. Therefore, CS patients with CHDs may be considered undoubtedly "at high risk". Unfortunately, long-term mortality data were missing.

The broad spectrum of CHDs and developmental non-cardiac abnormalities (*i.e*., feeding disorders for choanal atresia, tracheosophageal fistula, gastroesophageal reflux) associated with CS may have a substantial impact on prognosis. These findings confirmed the need for a multidisciplinary approach to the different medical and surgical problems in CS patients.

Limitations

First, only studies reporting the association between CS and CHDs were included with a potential risk of selection bias. However, the estimated prevalence of CHDs was similar to data reported in the largest case series of 299 patients with CS (76.6 % *versus* 74%, respectively) [16]. Second, case series and case reports were often incomplete in terms of detailed in-hospital and long-term clinical outcomes data. Finally, the present systematic review covers a large time period (from 1981 to 2022), during which CS genetic diagnostic tests, imaging techniques, and the quality of care were significantly improved.

Conclusions

CHDs, namely PDA, VSD, ASD and aortic abnormalities, were usually associated with CS and represent important causes of morbidity and mortality. PFAA, although rare, may also be present. Cardiac surgery is required in more than half of cases. Prognosis is highly dependent on the presence of cardiac and non-cardiac development abnormalities. Further studies are needed to better identify the main causes of long-term outcomes of CS patients.

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Online supplementary material:

Supplementary Figure 1. Flow diagram illustrating study selection process.

Supplementary Table 1. Distribution of congenital heart diseases (number of cases) described from case series (1981-2020).