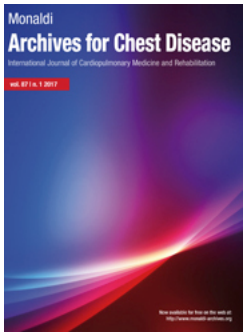

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CHARGE syndrome and congenital heart diseases: systematic review of literature

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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 aortic arch (PFAA). Demographic, clinical and outcome data were extracted and analyzed. Sixty-eight studies (44 case reports and 24 case series; n=943 CS patients) were included. The prevalence of CHDs was 76.6%, patent ductus arteriosus (PDA)

26%, ventricular (VSD) 21%, atrial septal defects (ASD) 18%, tetralogy of Fallot 11%, 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%). 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.

Key words: CHARGE syndrome; persistent fifth aortic arch; congenital heart disease; aortic disease.

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]. 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 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 CHDs in CS and their impact on clinical outcome. 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 (MESH) 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 in order 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 [2,3] described within original data manuscripts; 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 of cardiac surgery and clinical in hospital and long- term outcome. All statistical analyses were performed with tailored software.

Results

A total of 1271 records were identified in PubMed, Scopus and EMBASE. Of these, 510 were excluded because duplicates. After the screening of title and abstract, 514 papers were also excluded because they did not fulfill inclusion criteria. Assessed for eligibility were 247 papers and 179 were further excluded. Of these, 34 reviews, 21 written in non-English language, 14 abstracts, 7 with full text not available. In addition, 103 did not provide cardiovascular (CV) data. Finally, full-text analysis was made in 68 studies of CHARGE syndrome 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 [4,5,7-28]. The overall population consisted of 900 CS patients (52% males, age range = 0-69 years). Caucasians were more prevalent (61%) than Asians (39%). In the large majority of cases (≥80%; mostly in more recent

studies) CS diagnosis was made according to molecular testing. The prevalence of CHDs was about of 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

In-hospital mortality rate was of 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 death, 1 coagulation intravascular dissemination, 1 withdrawal of treatment. In other study [27] in-hospital mortality rate was 34 % (20/59) including CV (11/20, 55%) and non-CV death (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 five years was 70% (13/50 deaths) with most of 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. 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) were described in Table 2 [30,72]. 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. Interestingly, right 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 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 undergone major non-CV surgery (i.e. genitourinary, ophthalmic, plastic otolaryngology, gastric surgery) requiring general anesthesia.

Outcomes

The in-hospital mortality rate was of 12% (5/43). Specifically, 4 patients died within two 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 for pulmonary infections and acute respiratory distress.

Follow-up data were available in only 26 case reports. 1 death (4%) occurred at 11 months after discharge for unknown reasons. Long term complications were reported in about 73% (19/26) of cases. Among them CV complications (left ventricular 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 two-dimensional 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 SDs), 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 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 the 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, definitive diagnosis of CS was already made at the Children's National Hospital of Rome, Italy. Electrocardiogram showed sinus rhythm and incomplete right branch block. TTE documented mildly increased left ventricular (LV) end diastolic diameter (60 mm, Z score= + 2.2) and LV ejection fraction within normal limits (LV EF = 55%). A single posterolateral papillary muscle and a cleft of anterior mitral leaflet associated with mild mitral regurgitation were detected (Figure 2). Atrial and ventricular septal defects were not found and ductal shunts were excluded. Right heart dimensions, function (tricuspid annular plane systolic excursion – TAPSE = 26 mm), and systolic pulmonary artery pressures (sPAP=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 non-significant peak gradient 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. In Type 1 PFAA (double-lumen/double-barrelled aortic arch) 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 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, 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 patient 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 [73]. The pattern of cardiac malformations varies among individuals and was described only in small case series and case reports. Although the CS is a rare disease, the high prevalence and the heterogeneity of CHDs associated with the CS should be taken into account 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 outcome with a detailed and accurate systematic review.

To the best of our knowledge, this is the first systematic review that comprehensively investigated in a largest population of 944 CS patients the prevalence (76.6%) and types of CHDs. Specifically, PDA emerged as the most frequent heart defect (26%), followed by VSD and ASD (21% and 18% of cases, respectively) (Figure 4A). Complex CHDs were also described, such as tetralogy of Fallot (TOF) (11%), pulmonary stenosis/atresia (5%), double outlet right ventricle/ double outlet left ventricle (DORV/DOLV) (4%), transposition great arteries (TGA) (2%), Ebstein's anomaly (1%), atrioventricular (AV) canal (0.9%), LV hypoplasia (0.6%) and total anomalous pulmonary venous connection (TAPVC, 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 aortic arch (IAA) in 1.4% and aortic coarctation in 3% of cases. 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 [73] and demonstrated the over-representation of conotruncal defects (31-42%) and AVSDs (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% *vs* 3.4%) and AA abnormalities (33.6% *vs* 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 aortic arch (a derivative of the fourth embryological arch) and the pulmonary artery (a derivative of the sixth

aortic arch 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 aortic arch was 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 require intervention. Occasionally, it is single finding and the symptoms and the clinical course are mostly affected by associated CHDs and by hemodynamic consequences. Undoubtedly, a comprehensive and standardized TTE remains the first-line diagnostic tool for PFAA and associated CHDs [77], even if in 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, aortic arch 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 aortic arch dissection.

Outcomes

The available literature of the case series showed a wide range of in-hospital mortality rate (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% *vs* 12%, respectively). In case series studies non-CV causes of deaths 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 of 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 nonsyndromic 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, trachesophageal 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 potential risk of selection bias. However, the estimated prevalence of CHDs was similar with data reported in the largest case series of 299 patients with CS (76.6 % *vs* 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 test, 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 outcome of CS patients.

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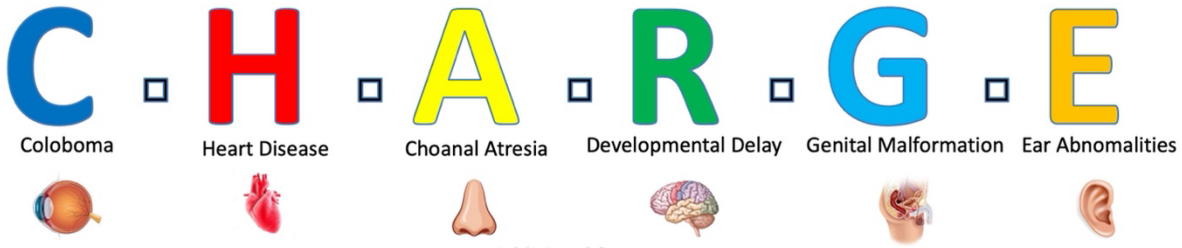
Figure 1. Clinical criteria for CHARGE syndrome diagnosis.



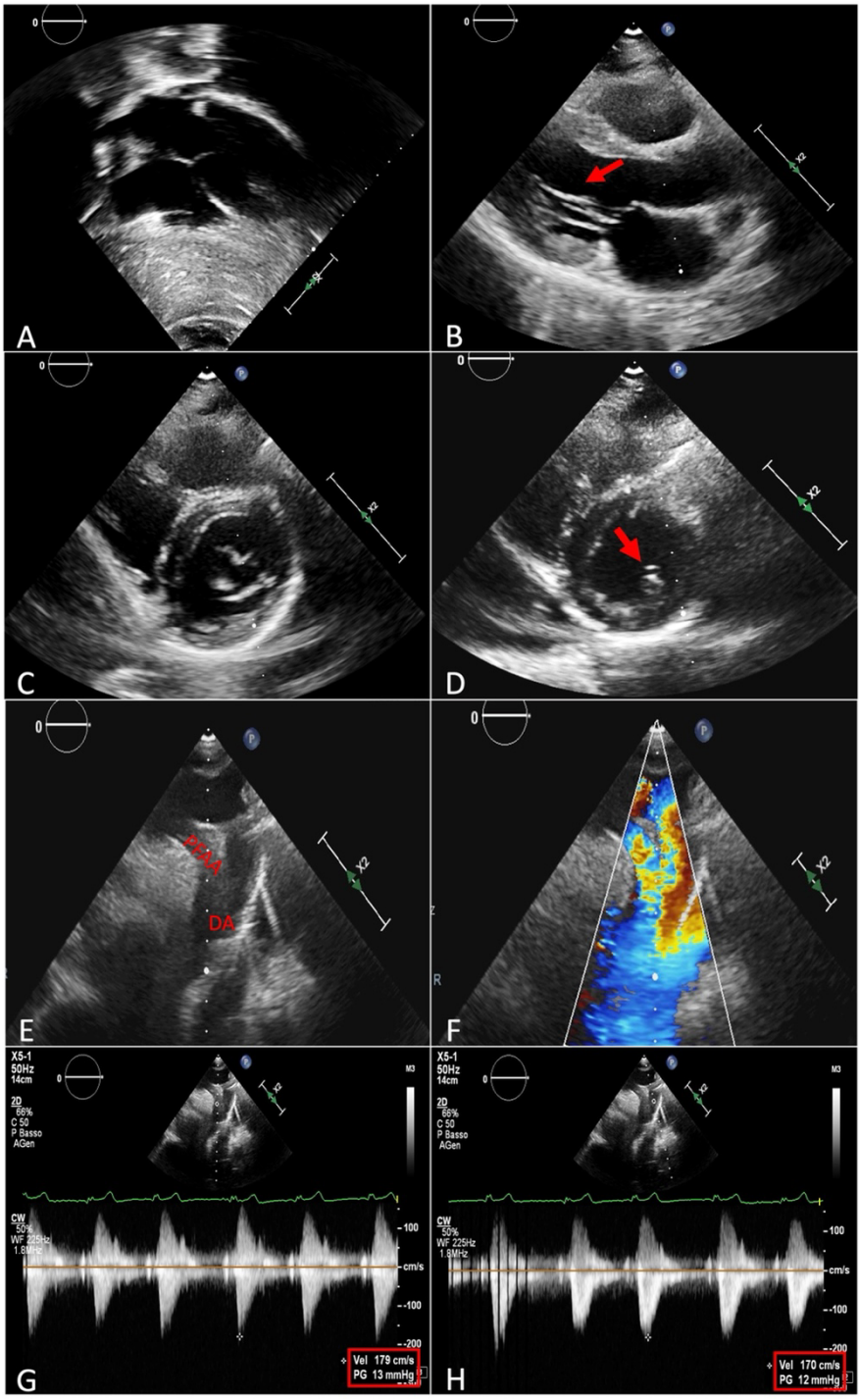
Additional features:

cranial nerve anomalies, cleft lip/palate, distinctive facial features (square face, prominent forehead), omphalocele/umbrilical hernia, scoliosis/hemivertebrae, renal anomalies, hand and limb anomalies, short neck, nipple anomalies, immune deficiency.

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 2.



Subxiphoid long-axis view showing situs solitus and levocardia (A); at parasternal long axis view, single papillary muscle was detected (red arrow) (B); short axis view showing cleft of anterior mitral leaflet (C) and single papillary muscle (red arrow) (D). Suprasternal views showing Freedom type 1 PFFA (E). In F Color doppler flow imaging shows the "double-lumen aortic arch", in which AA is divided into superior and inferior channel. The lower arch is a 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. In G and H continuous wave Doppler showing non-significant peak gradient of 13 and 12 mmHg on PFAA and fourth arch, respectively.

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

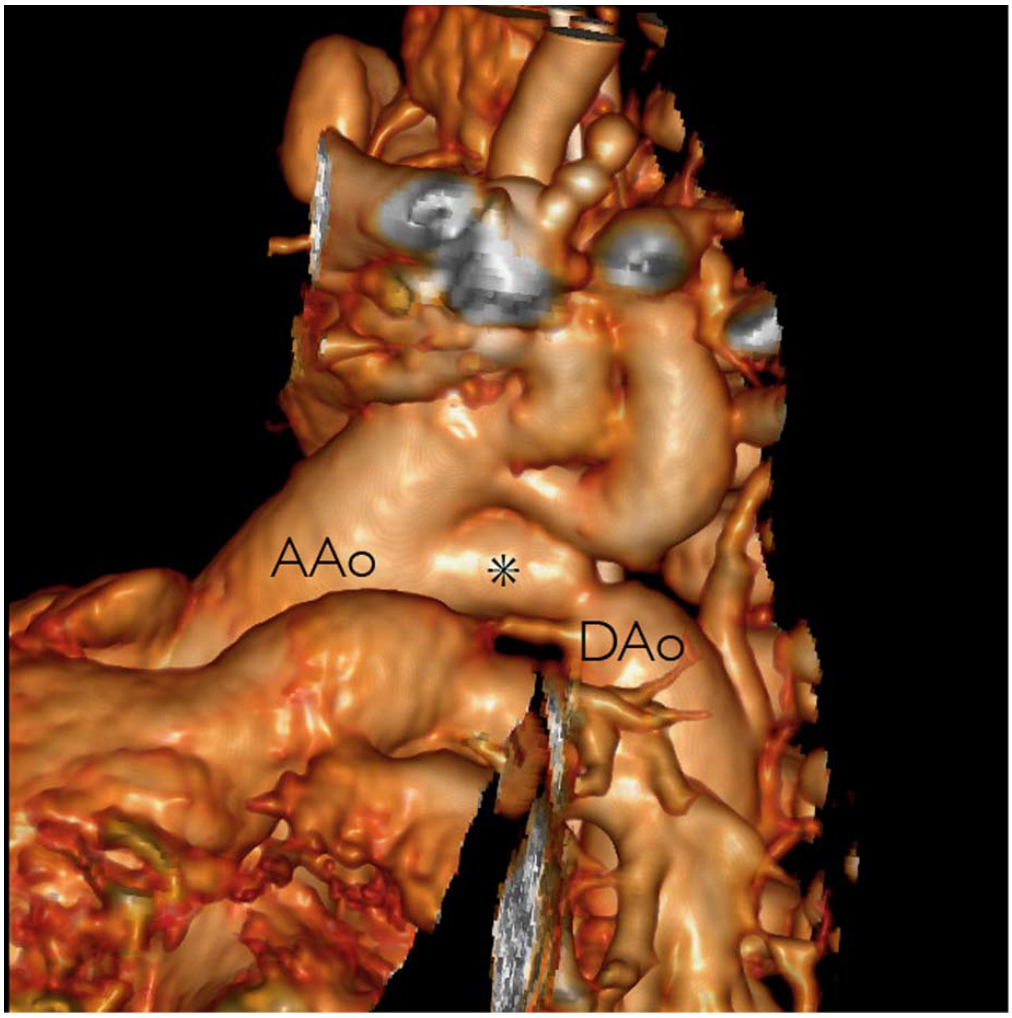


Figure 4. Distribution of CHDs (A) and aortic and vessel abnormalities (B) in CHANGE syndrome by the cumulative analysis of case reports and case series (944 patients). VSD, Ventricular septal defect; ASD, Atrial septal defect; TOF, Tetralogy of Fallot; PS, Pulmonary stenosis; DORV, Double outlet right 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.

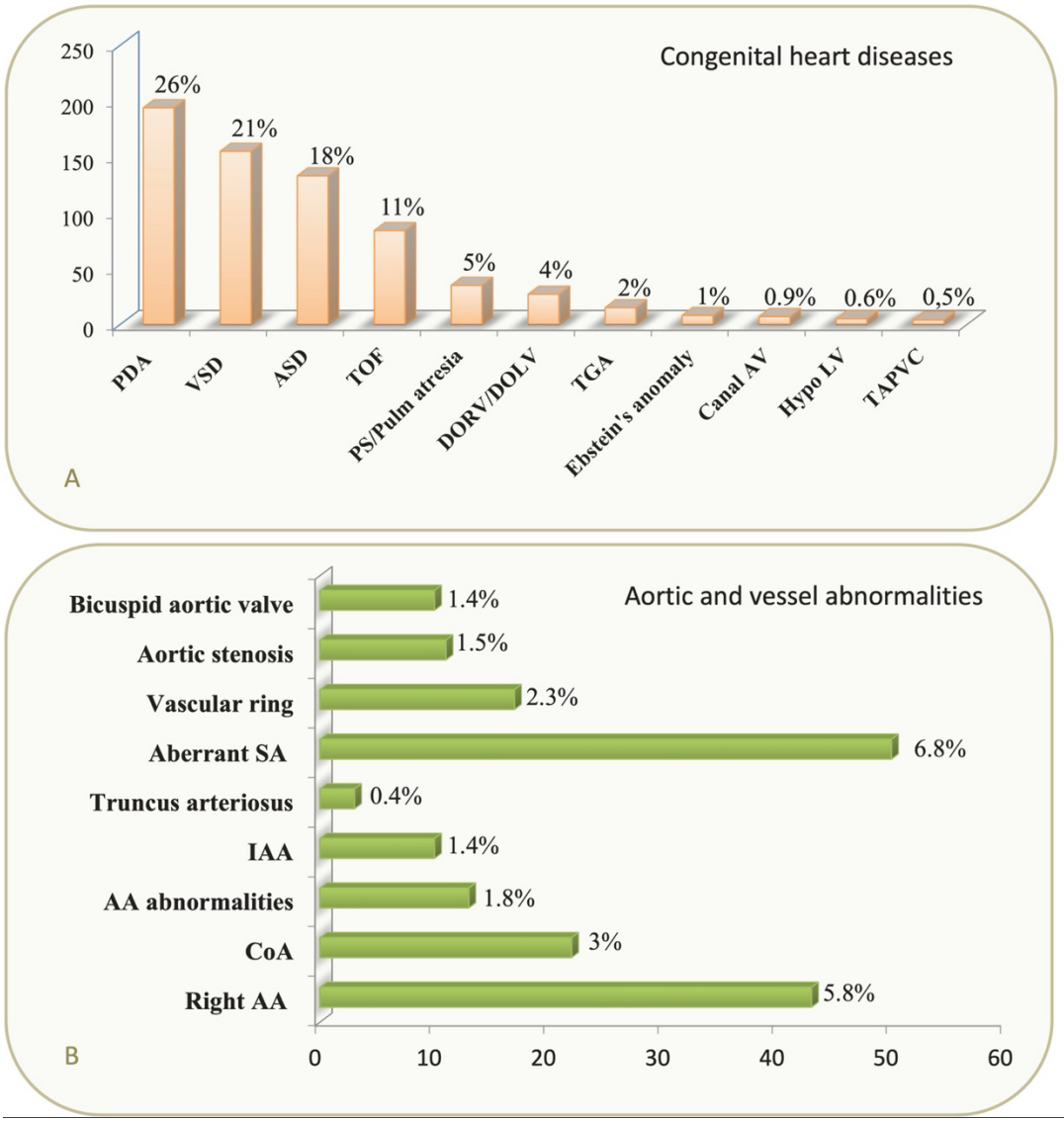


Table 1. Data from case series (1981-2020).

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 (%)	In-hospital complications n (%)	Long-term death n (%)	Long-term complications n (%)
									CV/non-CV death n/n (%)	CV/non-CV n/n (%) Hospital stay	CV/non-CV death n/n (%)	Hospital readmission n (%)
Aramaki M, 2006	17	8 (47)	0-18 6 ± 6	0	100%	17 (100)	-	-	-	-	-	-
Blake KD, 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)	0-69 13 ± 13	-	100%	46 (100)	-	-	-	-	-	-
Davenport, 1986	15	8 (53)	1-27 7 ± 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)	0-11 3 ± 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)	0-7 1.5 ± 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	0-2 0 ± 1	-	100%	3 (100)	-	-	-	-	-	-
Lee, 2009	4	3 (75)	3-10 5.7 ± 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)	1-29 9 ± 7	0	80%	19 (76)	-	-	-	-	-	-
Sohn, 2015	18	8 (44)	0-19 1.7 ± 1.9	0	100%	13 (72)	11/13 (84)	-	-	5 (27%) non CV 5 (27%)	-	-
Stroemland, 2005	31	15 (48)	0-31 1.5 ± 0.6	31 (100)	-	16 (52)	16/16 (100)	-	-	-	-	-
Tellier, 1998	47	17 (36)	0-9	47 (100)	-	40 (85)	-	17 (36)	17 (36%)	11 (23%)	-	-

									non CV death 17 (36%)	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)	-	-	-	-	-	-

- not available; *data on death were reported in 14 of only 42 patients with congenital arch vessel anomaly; √ 26 of 220 patients with CHD.

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 ɳ
Long-term death, n (%) ϕ CV/non-CV death, n/n (%)	1 (4) ς -

Long-term complications, n (%)	19 (73) $^{\Delta}$
Hospital readmission, n (%)	8 (53) $^{\sigma}$

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.

$\propto$ 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