ORIGINAL ARTICLE

Congenital heart disease: Epidemiological, genetic and evolutive profil

Les cardiopathies congénitales: Profil épidémiologique et génétique

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Abstract

Introduction: Congenital heart disease is a heterogeneous group of malformations and one of the most common causes of mortality in children.
Aim: The aim of this study was to investigate the clinical, genetic and evolutive characteristics of congenital heart disease.
Methods: A retrospective, descriptive study was carried out between 2020 and 2023 at the pediatrics and neonatology department of Mongi Slim university hospital of Tunis. All children with confirmed congenital heart disease were included.
Results: Forty-five patients were included, representing 5.7‰ of all admissions. The sex ratio was 1.4. A prenatal diagnosis of congenital heart disease was established in 9% of cases. The median age at the time of discovery was 18 days. The initial symptomatology was respiratory distress in 64% of cases. The main reasons for performing a cardiac ultrasound were heart murmur in 38% followed by polymalformative assessment in 27% of cases. Most of the cardiopathies were atrial septal defects (42%) and ventricular septal defects (40%). Cyanotic heart diseases represented 29% of cases, conotruncal ones 13% and ductodependent ones 16%. Congenital heart disease was associated with a genetic anomaly in 53% of patients, including 15 cases of trisomy 21 and four Di-George syndromes. The treatment was mainly medical (38%), associated with surgery in 5 cases. Death occurred in nine patients, representing a mortality rate of 20%.
Conclusion: Efforts still need to be made to improve pre- and post-natal diagnosis and ensure rapid treatment in order to reduce morbidity and mortality in our country.

Key words: Congenital heart disease ; Epidemiology ; Newborn ; Pediatrics; Genetics ; Mortality

Résumé

Introduction: Les cardiopathies congénitales constituent un groupe hétérogène de malformations et une cause fréquente de mortalité infantile.
Objectif: décrire les caractéristiques cliniques, génétiques et évolutives des cardiopathies congénitales.
Méthodes: Étude rétrospective, descriptive réalisée entre 2020 et 2023 au service de pédiatrie et néonatologie de l'hôpital universitaire Mongi Slim de Tunis. Tous les enfants hospitalisés et présentant une cardiopathie congénitale durant la période d'étude ont été inclus.
Résultats: Quarante-cinq patients ont été inclus, représentant 5,7‰ de l'ensemble des admissions. Le sex-ratio était de 1,4. Un diagnostic prénatal de cardiopathie congénitale a été établi dans 9% des cas. L'âge médian au moment de la découverte était de 18 jours. La symptomatologie était faite principalement de détresse respiratoire dans 64% des cas, suivie du souffle cardiaque dans 38 % des cas. Une anomalie génétique était associée dans 53% des cas, dont 15 cas de trisomie 21 et quatre syndromes de Di-George. Les cardiopathies les plus fréquentes étaient les communications interauriculaires (42%) et les communications interventriculaires (40%). Les cardiopathies cyanogènes représentaient 29% des cas, les cardiopathies conotronculaires 13% et les cardiopathies canal-dépendantes 16%. Le traitement était principalement médical (38%), associé à une chirurgie dans 5 cas. Le décès est survenu chez neuf patients, soit un taux de mortalité de 20%.
Conclusion: Des efforts restent à faire pour améliorer le diagnostic pré et post-natal et assurer un traitement rapide afin de réduire la morbidité et la mortalité dans notre pays.

Mots clés: Cardiopathie congénitale ; Épidémiologie ; Nouveau-né ; Pédiatrie ; Génétique ; Mortalité

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Introduction

Congenital heart disease (CHD) is the most common malformation in children, accounting for around a third of all congenital anomalies [1,2]. The incidence is estimated at around 8 per 1,000 births [3]. CHD encompass a heterogeneous group of malformations of the various cardiac structures and/or large vessels, developed during embryonic or fetal life [1,2,4]. As they are extremely diverse, ranging from simple benign anomalies to severe malformations incompatible with life, their prevalence remains underestimated [1]. The most common congenital heart defects in children are ventricular septal defects, followed by atrial septal defects, with a total prevalence of 4.8 per 1000 live births [5]. The causes of congenital heart disease (CHD) are diverse, reflecting the complexity of heart development. These causes include environmental factors, genetic influences (such as single-gene disorders, chromosomal anomalies, and pathogenic copy number variations), and multifactorial origins. As a result, CHD can present as isolated defects or alongside other organ malformations and genetic abnormalities [6,7]. The diagnosis of congenital heart defect may be made antenatally, at birth or later [3,8]. Improved prenatal diagnosis and advances in medical and surgical management have influenced the current epidemiology of heart disease. However, mortality and morbidity associated with CHD remain significant, particularly in developing countries [9]. While the epidemiological, etiological and prognostic data on CHD have been well defined in developed countries, few studies on the subject were published in Tunisia.

The aims of this study were to investigate the epidemiological, clinical and genetic characteristics of CHD and the mortality associated in a Tunisian pediatrics and neonatology department.

Methods

A retrospective, descriptive study was carried out between 2020 and 2023 at the

the pediatrics and neonatology department at Mongi Slim Hospital, La Marsa. We included all children under 15 years of age hospitalized during the study period with CHD confirmed on cardiac ultrasound. The diagnosis was either previously established or made during hospitalization. We excluded septal hypertrophies, patent foramen ovale (PFO), and persistent ductus arteriosus in the context of prematurity to focus on significant congenital heart defects no related to secondary conditions.

Patients were selected from the database of the Neonatology and Pediatrics Department at Mongi Slim Hospital, La Marsa. Patients' medical records and hospitalization reports were used to collect the necessary data. For each patient, the following data were recorded: demographic and epidemiological data, age and circumstances of CHD diagnosis, initial clinical data, paraclinical data (biological, radiological), cardiac ultrasound data and genetic study. Medical, interventional and/or surgical treatment and outcome were recorded. In the event of death, the age, circumstances and main cause were specified. Anonymity and confidentiality of data were respected.

We used SPSS software version 25 to collect and process our data. Qualitative variables were expressed as simple frequencies (absolute numbers) and relative frequencies (percentages). Quantitative variables were expressed as means, medians and standard deviations with determination of the range (extreme values).

Results

During the study period, 7926 patients were admitted to the neonatology and pediatrics department of the Mongi Slim Hospital in La Marsa. We collected 45 children with congenital heart disease, representing a hospital prevalence of 5.7‰. The sex ratio was 1.4. The median age was 40 days [1day-11years]. Newborns accounted for 49% of patients. Consanguinity was noted in 5 cases (11%). A pathological family history in the siblings was found in 6 patients, including 2 cases of heart disease, 1 case of encephalopathy, 1 case of hepatopathy, 1 case of DiGeorge syndrome and one death in infancy. The mean maternal age at conception was 34 years [20-40], with 38% of mothers over 35. Pregnancy was complicated by dysgravidia in 17 cases (38%), including 10 cases (59%) of gestational diabetes, 2 cases (12%) of toxemia gravidarum and 5 cases (29%) where both pathologies were associated. Morphological ultrasound, performed in 31 parturients (69%), was pathological in 29%. The anomalies detected antenatally were cerebral malformations in 3 cases, renal abnormalities in 2 patients and 2 with skeletal anomalies (table 1).

A fetal karyotype analysis on amniotic fluid was performed on four women (9%) who had high-risk results from the triple test or presented with morphological anomalies. The analysis identified aneuploidies: two cases of trisomy 21, one case of trisomy 18, and one case of Turner syndrome. Four cases of heart disease were diagnosed antenatally but not genetically studied : Conotruncal heart disease, ventricular septal defects, Tetralogy of Fallot (TOF) and single ventricle with mitral valve atresia..

The mean gestation age (GA) of our patients was 37 weeks + 6 days ± 2.3 [30-41]. Eleven patients (24%) were premature and 16% had low birth weight. The median age of CHD diagnosis was 18 days [1 day-24 months]. Nineteen patients (42%) were diagnosed after 1 month of life. The most frequent reason for admission was neonatal respiratory distress (33%), followed by acute bronchiolitis (31%). Hypoxia was observed in 14 cases (31%). A heart murmur, perceived in 65% of cases, was the main reason for requesting cardiac ultrasound. Acute heart failure and cyanosis were found in 4% and 2% of cases respectively. Femoral pulses were absent in 2 patients. Hepatomegaly was found in 11 patients (24.4%). Sixteen patients had cardiomegaly on chest X-ray. Other abnormalities are summarized in Table1.

Table 1. Anomalies associated with congenital heart disease

Ultrasound morphological abnormalities :	**N**
Cerebral anomalies :	3
Complete vermian agenesis	1
Intraplexialis fluid collection	1
Left occipital ventriculomegaly	1
Renal anomalies: Bilateral pyelectasis	2
Skeletal anomalies :	
Club feet/ Curved shape of femur and humerus	2
Clinical abnormalities :	**N**
Facial dysmorphia:	27
Trisomy21	15
Trisomy 18	1
Di-George syndrome	4
Alagille syndrome	2
Other non-specific	5
Hypotonia :	13
Trisomy 21	11
Trisomy 18	1
Morsier syndrome	1
Hypotrophy :	14
Trisomy 21	8
Trisomy 18	1
Turner	1
Panhypopituitarism	1
Alagille syndrome	1
Other non-specific	2
Birth tooth	1
Sexual ambiguity	1
Ophthalmological abnormalities :	2
Bilateral posterior embryotoxan	1
Blepharophimosis	1
Limb anomalies :	3
Hexadactyly	1
Overlapping toes	1
Varus feet	1
Esophageal atresia	1
Anal atresia	1
Psychomotor retardation	1
Congenital hypothyroidism	6
Severe hypocalcemia	1
Cholestasis	1
Immune deficiency	2
Butterfly vertebra associated with Alagille syndrome	1

Twenty-six patients (68%) had left-right shunt pathologies. They were represented primarily by atrial septal defects, followed by ventricular septal defects. Conotruncal heart diseases were found in six patients: tetralogy of Fallot (TOF) (n=3); Pulmonary atresia with ventricular septal defect (PAVSD) (n=2) and double outlet right ventricle (n=1). Duct-dependent ones were recorded in seven cases (16%): Coarctation of the aorta (n=2); TOF (n=3) and PAVSD (n=2). Amongst the CHD, we noted 13 cases of cyanogenic heart disease (29%). The main types of CHD found on cardiac ultrasound are reported in Table 2.

Genetic studies were carried out in 29 patients (64%). A genetic anomaly was detected in 24 cases (53%). The different syndromes encountered and the associated heart disease are described in Table 3.

Therapeutic management was based on medical treatment in 17 patients (38%). Six neonates received prostaglandin infusion. Diuretics were prescribed in 14 patients. Surgical management was required in 5 patients, and percutaneous dilatation in 2 others. For 11 patients, no treatment was prescribed and regular monitoring was recommended.

Table 2. Congenital heart disease diagnosed by cardiac ultrasound

Congenital heart disease	**n (%)**
Atrial Septal Defect (ASD)	19 (42)
Ventricular Septal Defect (VSD):	18 (40)
Perimembranous	11 (24)
Conotroncale	6 (13)
Admission	1 (2)
Patent Ductus Arteriosus (PDA)	10 (22)
Complete Atrioventricular Canal defect (CAVC)	3 (7)
Tetralogy of Fallot	3 (7)
Pulmonary atresia with open septum	2 (4)
Double outlet right ventricle	1 (2)
Aortic Valve Stenosis with aortic bicuspidism	1 (2)
Pulmonary stenosis (PS)	4 (9)
Transposition of the Great Arteries (TGA):	3 (7)
TGA	1 (2)
TGA + double mismatch + PS + VSD	1 (2)
TGA + PS + TA + VD hypoplasia + VSD	1 (2)
Coarctation of the aorta	2 (4)
Dilated cardiomyopathy	1 (2)
Complex heart disease :	4 (9)
TGA+ double mismatch + PS + VSD	1 (2)
TGA + PS + TA + Right ventricular hypoplasia + VSD	1 (2)
Pulmonary atresia + VSD	1 (2)
Uni ventricle on situs ambigus + Pulmonary atresia + TAPVC	1 (2)

ASD : Atrial Septal Defect; **VSD** : Ventricular Septal Defect ; **PDA** : Patent Ductus Arteriosus ; **CAVC** : Complete Atrioventricular Canal defect ; **PS** : Pulmonary stenosis ; **TAPVC** : Total Anomalous Pulmonary Venous Connection ; **TGA**: Transposition of the Great Arteries ; **TA** : Tricuspid atresia ; **DCM**: Dilated cardiomyopathy;

The evolution was marked by re-hospitalization in 25 patients (55.6%), including 10 for cardiac decompensation, one for Fallot's malaise and the others for respiratory pathology.

We deplored 9 deaths (20%) during hospitalization. Four were attributable to heart disease, including the patient with septo-optic dysplasia. Five children had a chromosomal aberration : four Trisomy 21 and one Trisomy18. The types of CHD in the deceased patients comprised one case of univentricular heart with ambiguous situs and pulmonary atresia, one patient with dilated cardiomyopathy, three infants with complete atrioventricular defect, two patients with combined atrial septal defect and ventricular septal defect, one case of double-outlet right ventricle, and one neonate with transposition of the great vessels that was not diagnosed antenatally and could not be managed promptly.

The median time from diagnosis to death was 6.7 months [2 days-27 months].

Discussion

This study aimed to determine the epidemiologic characteristics of congenital heart disease and the mortality associated in children referred to a pediatrics and neonatology department of Mongi Slim Hospital , Tunisia.

Table 3. Type of congenital heart defect among cases with genetic syndromes

Genetic syndrome	*number*	*Genetic study*	*Heart disease*
Trisomy 21	15	Karyotype : 47, XX, +21 (n=6) 47, XY, +21 (n=9)	ASD+ PDA (n= 3) ; ASD (n=5) ; CAVC (n=1) ; CAVC+VSD+ASD (n=1); CAVC+ PDA (n=1) ; PDA (n=3) ; TOF (n=1)
Trisomy 18	1	Karyotype : 47, XX, +18	ASD+ VSD
DiGeorge Syndrome	4	FISH 22q11.2 microdeletion	TOF (n=2); TGA + PS + TA + RV hypoplasia (n=1); Aortic stenosis and bicuspidism (n=1)
Turner	1	Karyotype : 45,X	Coarctation of the aorta
Alagille	2	WES: Mutation in JAG1 gene	PS (n=1) PS + aortic bicuspidism (n=1)
Panhypopituitarism	1	NGS: Heterozygous GLI2 mutations	VSD+ASD
Morsier syndrome (septo-optic dysplasia)	1	- not available -	ASD+ CAP

CAP: patent ductus arteriosus; **DCM**: dilated cardiomyopathy; **ASD** : Atrial Septal Defect; **VSD** : Ventricular Septal Defect ; **PDA** : Patent Ductus Arteriosus ; **CAVC** : Complete Atrioventricular Canal defect ; **PS** : Pulmonary stenosis ; **TAPVC** : Total Anomalous Pulmonary Venous Connection ; **TGA**: Transposition of the Great Arteries ; **TA** : Tricuspid atresia ; **DCM**: Dilated cardiomyopathy; **T18**: Trisomy 18; **T21**: Trisomy 21; **TOF**: Tetralogy of Fallot; **RV**: right ventricle. **FISH** : Fluorescence in situ hybridization, **WES** : Whole exome sequencing ; **NGS** : Next Generation Sequencing

We identified 45 children with congenital heart disease, corresponding to a hospital prevalence of 5.7‰. The prevalence of congenital heart disease varies considerably between studies worldwide between 2.7 ‰ in Tunisia and 10.8 ‰ in the USA [9-14]. According to a meta-analysis including 114 epidemiological studies worldwide, the lowest rate is recorded in Africa around 1.9‰ [5]. This is explained by ethnic and genetic factors as well as available means and skills. In our series, the overall prevalence of CHD, all types combined, was 5.7‰. Our results can be explained by the exclusion of certain minor cardiopathies, as well as non-malformative cardiac anomalies such as tumors and rhythm disorders. In addition, a number of newborns died with a highly suggestive symptomatology of congenital heart disease, but unconfirmed due to a lack of resources and the remoteness of the cardiopediatric department.

A male predominance was noted in our study. This has also been noted in many series [15-17]. Consanguinity were found in 11% of cases in our study, is one of the recognized factors associated with CHD This rate of consanguinity is significantly lower than that reported in other Tunisian study by Hammami et al. (30.5%) [12]. Therefore, in this study, consanguinity cannot be considered a risk factor for CHD.

In our work, pregnancy was complicated by dysgravidia in 38% of cases. Studies have shown that gestational toxemia and gestational diabetes are significantly associated with cardiac malformations [18-19].

The benefits of antenatal diagnosis have been clearly demonstrated, particularly in optimizing management and reducing mortality [20]. Despite improved monitoring of pregnancies and the considerable contribution of fetal morphological ultrasound, less than 10% of our patients were diagnosed antenatally, which remains low. This is in line with some Tunisian studies, where the reported rate was 11%, whereas it reaches 71% in some countries, such as the Haute-Normandie region [9,21].

Antenatal investigation of CHD by a doctor skilled in fetal echocardiography is essential for detecting heart disease, identifying any associated malformations, and developing an effective treatment plan.

Early diagnosis of CHD is crucial. Any delay in diagnosis carries a serious risk of morbidity, mortality and disability [22]. In our study, the median age of diagnosis was 18 days, and 42% were diagnosed after 1 month. The free interval of detection varied significantly according to the type of CHD, its impact, the associated extracardiac manifestations and the availability of prenatal diagnosis. In addition, echocardiography performed by especially trained neonatologists may help to estalish rapid diagnosis specially in complex heart diseases causing morbidity and high mortality. This can only succeed with the involvement of neonatologists in pediatric cardiology training, as they are the first to examine the newborn and often suspect the diagnosis.

The predominant clinical signs revealed in our study were respiratory distress, heart murmur and hypotrophy, in line with the literature [8,10,23]. Clinical presentations and severity of CHDs depend on their types or sub-types. In our study, consistent with findings in the literature, the most prevalent congenital heart defects (CHDs) were ventricular septal defect (VSD) and atrial septal defect (ASD). Specifically, our results indicated that ASD and VSD were the most common CHDs among children, affecting 42% and 40% of patients, respectively. Similarly, Abid et al.'s study in Tunisia reported ventricular septal defects (31%) and ostium secundum atrial septal defects (12.9%) as the most frequent conditions [10,13,21].

Syndromic CHD represent a significant proportion, accounting for between 7% and 50% of all congenital cardiopathies [24-26]. In our study, 53% of congenital heart diseases were associated with a malformative syndrome. The rate of association with extracardiac malformations is variable: 11% for Hoang et al. in the USA and 45.9% for Güçer et al. in Turkey [26,27]. This could be linked to better antenatal screening for congenital malformations, with the possibility of medical termination of pregnancy, which could explain this low prevalence. T21 was the dominant genetic anomaly in our series (33%), followed by DiGeorge syndrome. These findings were close to those in the literature, where the most frequently observed aneuploidies are trisomy 21, trisomy 18, trisomy 13, and monosomy X [16,27]. According to the study by Robert et al, 20% of fetuses with conotruncal heart disease carry a 22q11 microdeletion [4]. Concerning Alagille syndrome, the two cases identified can be attributed to the selection bias of

patients with chronic hepatopathy who were referred to our department, which is one of the leading centers in Tunisia for the diagnosis and treatment of liver diseases in childrens.

In our work, medical treatment was initiated in 17 patients (38%) and surgical treatment in 5 cases. Depending on the study, recourse to surgical treatment varied between 7.8% and 42% [3,13,32]. Very few cardiac centers exist in developping countries including Tunisia, which can explain the low rate of surgical treatment. Recent improvements of treatment and diagnostic procedures have improved the survival of patients with CHD, however, it is still considered as a leading cause of neonatal mortality. This rate ranged from 2% in developed countries to 38% in low- and middle-income countries [32]. In comparison with the literature, the mortality rate observed in our study was high at 20%, closely aligning with the 23.8% rate reported in the Tunisian study by Hammami et al.[12]. Another Tunisian study indicated a significant decline in CHD-related mortality, from 44% in 2014 to 27% in 2017 [9]. These variations in mortality rates are influenced by the quality of health infrastructure, the severity of the heart disease, and the availability of specialized facilities and trained medical professionals [9,28,31,32]. In addition, the availability of bedside cardiac echocardiography equipment is now an indispensable tool: it enables us to quickly and non-invasively provide valuable information for life-saving treatment. Nevertheless, more needs to be done to improve the management of congenital heart disease and reduce associated mortality [32]

Conclusion

Despite the limited size of our study population, our research is distinguished by its etiological diversity, encompassing a range of genetic syndromes. The mortality rate observed in our study was high. While significant progress has been made in managing congenital heart disease in developed countries, there is still a need for improvement in Tunisia. Enhancing early antenatal and postnatal diagnosis and ensuring timely surgical intervention are crucial steps forward. This underlines the importance of collaboration between obstetricians, neonatologists, cardiopediatricians, cardiovascular surgeons and geneticists. Such teamwork is essential for early diagnosis, establishing effective management protocols, and ultimately improving outcomes for children with CHD. Additionally, we emphasize the need for a national registry to accurately document and estimate the prevalence and associated morbidity of CHD in Tunisia.

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