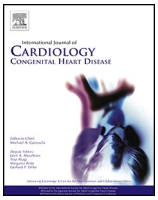
International Journal of Cardiology Congenital Heart Disease 17 (2024) 100529

Contents lists available at ScienceDirect

International Journal of Cardiology Congenital Heart Disease

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-congenital-heart-disease



Congenital heart defects and consanguinity: An analysis of the Sidra cardiac registry data in Qatar☆

Mange Manyama [a], Dana Al Sayegh [a], Khalifa Al-Sulaiti [a], Muna Almasri [a], Omna Sharma [a], Aya El Jerbi [b], Zakariya Al-Riyami [b], Padma Kumari Sarada [a], Samir Gupta [b], Hesham Al-Saloos [a,b], Kholoud N. Al-Shafai [b,*]

[a] Weill Cornell Medicine – Qatar, Doha - Qatar
[b] Sidra Medicine, Doha - Qatar

ARTICLE INFO

Keywords:
Congenital heart diseases
Consanguinity
Sidra Medicine
Qatar
Cardiology

Congenital heart disease (CHD) is among the most commonly diagnosed congenital disorders, impacting approximately 0.8 %–1.2 % of live births worldwide [1]. Among the different types of CHDs, Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD) and Patent Ductus Arteriosus (PDA) are the most frequent types [1]. Epidemiological studies indicate that etiology of congenital heart diseases is multifactorial, with both genetic and environmental risk factors being implicated [2]. Our previous study on patients with CHD in Qatar identified cytogenetic abnormalities, pathogenic Single-Nucleotide Variants, and some recessive variants, such as c.884A > G in SMYD6 as potential genetic factors contributing to CHD [3]. Parental consanguinity is one of the risk factors that has been associated with occurrence of CHD, especially in regions where endogamy is a common practice [4]. Consanguineous marriages are prevalent practices in Arab countries, especially among first cousins, and are widely accepted and practiced. In this study, we describe the epidemiologic characteristics of patients with congenital heart diseases in Qatar and the association between CHD and consanguineous marriages using data from the Cardiac Registry Database at Sidra Medicine.

Data for this study was obtained from the Cardiac Registry Database at Sidra Medicine that was established July 2019 for research purposes, in accordance with the Declaration of Helsinki (IRB #1500769) and informed consent was obtained from each study subject. This study was approved by the Institutional Review Boards of Sidra Medicine (IRB# 1796639) and Weill Cornell Medicine-Qatar (IRB #1687460) since this was collaborative research involving the two institutions. Extracted de-identified information for each subject included nationality, gender, CHD specific diagnosis, maternal history of diabetes mellitus and history of parental consanguinity. Diagnosis of CHD in each patient was either diagnosed prenatally or in infancy, confirmed by an experienced cardiologist utilizing one or more of the following diagnostic tools: echocardiogram, cardiac Magnetic resonance imaging (MRI), computerized tomography (CT) angiography, or diagnostic catheterization. All CHD cases were classified using ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification). Data was analyzed using SPSS ® statistical software *(Version 27.0, International Business Machine Corporation ®, 2020)*.

At the time of data collection for this study, the Sidra Cardiac Registry Database had data for 85 patients with CHD, channelopathies and cardiomyopathies collected between July 2019 and October 2022. Out of the 85 patients, 9 patients were excluded because of having either cardiomyopathy or channelopathy without CHD. The final sample size used in the analysis was 76 subjects, which included 43 males (56.6 %) and 33 females (43.4 %). Most of the subjects (52.6 %) were from the Middle East and North Africa (MENA) region (excluding Qatar), followed by South Asia (30.3 %) and Qatar (14.5 %). The three most

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author. PhD P.O. Box 26999, Doha, Qatar.
E-mail address: kalshafai@sidra.org (K.N. Al-Shafai).

https://doi.org/10.1016/j.ijcchd.2024.100529
Received 28 February 2024; Received in revised form 15 July 2024; Accepted 17 July 2024
Available online 20 July 2024

Table 1
Subjects' Demographics.

Gender	N	%
Male	43	56.6
Female	33	43.4
Nationality		
Qatari	11	14.5
Middle Eastern/North African (Non-Qatari)	40	52.6
Southeast Asian	23	30.3
Other	2	2.6
Living status		
Living	64	84.2
Deceased	12	15.8
Congenital heart defect types		
Ventricular Septal Defect	26	34.2 %
Atrial Septal Defect	24	31.6 %
Transposition of the Great Arteries	17	22.4 %
Patent Ductus Arteriosus	17	22.4 %
Pulmonary Stenosis	17	22.4 %

**Only top five types of CHD are shown. Some patients had >1 CHD type, thus total % may exceed 100.*

common CHD types were VSD, ASD, and TGA (Table 1). It is importnant to note that a significant number of patients in the registry had multiple CHD types. Majority of patients in this study had other diseases in addition to the underlying CHD lesion. The pattern of distribution of CHD types in this study is comparable with findings from previous studies [3]. At least one comorbidity was present in each of the 62 patients (81.6 %). The most common comorbidities were circulatory system disorders and endocrine diseases.

We explored the association between CHD and parental consanguinity in patients who had dequate maternal information on this factor. Out of the 76 subjects, 32 (55 %) were born from consanguineous marriages. The higher proportion of consanguinity was found among CHD patients whose parents are non-Qatari Arabs (52.6 %). Consanguineous marriages among Qataris with CHD accounted for 14.5 %. Patients with CHD born by first-degree cousins accounted for 41.4 %, while second- and third-degree parental cousins accounted for 12.1 % and 1.7 % of the patients respectively (Table 2). The highest proportion of parental consanguinity was found among patients with VSD followed by PDA. Significant associations were found between parental consanguinity and patients with PDA and between first degree consanguineous marriage and occurrence of congenital heart defects ($P < 0.05$). Previous studies have reported that, in populations characterized by a high level of inbreeding, consanguinity can amplify underlying genetic risk factors, potentially attributing to the prevalence of recessive components as causative factors in certain cardiac defects [4,5]. First-degree cousins' marriage increases the risk for cardiac malformation to 5–8% [6]. Recessive gene mutations may play a role in the causation of CHD in first-cousin marriages, even though the exact mechanism is not fully understood [7].

This study also explored the presence of other known risk factors icluding maternal diabetes mellitus among parents of patients with CHD. About 38 % of the patients in this study were born to mothers who had Gestational Diabetes Mellitus, while 6.9 % to mothers with Pre-Gestational Diabetes Mellitus. No significant statistical association between CHD and either pre-gestational or gestational diabetes mellitus was found. Both pre-gestational and gestational diabetes mellitus are detrimental for the fetus. The first 6–8 weeks of human developmental are extremely crucial for the cardiac development, and elevated levels of HbA1c or fasting serum glucose during this time may be associated with a higher likelihood of CHD in the neonate [8]. Women with pre-existing diabetes mellitus, therefore, are at a slightly higher risk of giving birth to newborns with CHD than those with gestational diabetes [8]. Experimental-supported mechanisms by which maternal diabetes mellitus alters cardiac development include glucose-mediated disturbances of left-right patterning, increased apoptosis due to oxidative or other cellular stress, nitric oxide signaling deficiencies, and alterations of neural crest cell formation and migration [9,10].

Table 2
Parental consanguinity and CHD.

Parental consanguinity and degree. N (%)	P value	
1st Cousins	24 (41.4)	<0.001
2nd Cousins	7 (12.1)	0.072
3rd Cousins	1 (1.7)	0.447
No parental consanguinity	26 (44.8)	0.084

In conclusion, the most common CHD type in this study was VSD followed by ASD and TGA. The association between subjects born by first-degree parental cousins and congenital heart defects, was significant. Our findings reinforce previous research indicating that consanguineous marriages significantly increase genetic risks for offspring due to the inheritance of identical chromosomal segments from both parents.

This study was limited by small sample size and absence of control group which prohibited rigorous statistical analyses, potentially affecting the robustness of our findings.

Sources of funding

This study was supported by Sidra Medicine- Qatar, study number SDR600119. The publication of this article was funded by the Weill Cornell Medicine, Health Sciences Library, Qatar.

Ethics statement

Cardiac Registry Database at Sidra Medicine was established in accordance with the Declaration of Helsinki (IRB #1500769). Access to data of this database, for the purpose of this stuy, was approved by the Institutional Review Boards of Sidra Medicine (IRB# 1796639) and Weill Cornell Medicine-Qatar (IRB #1687460). The study complies with all required regulations.

Declaration of generative AI in scientific writing

The authors declares that generative AI was not used in writing this manuscript.

Submission declaration

The authors declare that this manuscript has not been published previously in any form, and it is not under consideration for publication elsewhere. This manuscript has been approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

CRediT authorship contribution statement

Mange Manyama: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Dana Al Sayegh:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Khalifa Al-Sulaiti:** Writing – original draft, Methodology, Investigation, Data curation. **Muna Almasri:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Omna Sharma:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Aya El Jerbi:** Project administration, Investigation, Data curation. **Zakariya Al-Riyami:** Investigation, Data curation. **Padma Kumari Sarada:** Writing – original draft, Methodology, Formal analysis. **Samir Gupta:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Hesham Al-**

Saloos: Writing – original draft, Project administration, Investigation, Data curation. **Kholoud N. Al-Shafai:** Writing – review & editing, Writing – original draft, Formal analysis, Project administration, Methodology, Student Supervision, Data curation, Conceptualization.

Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019;48(2):455–63. https://doi.org/10.1093/ije/dyz009.

[2] Blue GM, Kirk EP, Sholler GF, Harvey RP, Winlaw DS. Congenital heart disease: current knowledge about causes and inheritance. Med J Aust 2012;197(3):155–9. https://doi.org/10.5694/mja12.10811.

[3] Okashah S, Vasudeva D, El Jerbi A, et al. Investigation of genetic causes in patients with congenital heart disease in Qatar: findings from the Sidra cardiac registry. Genes 2022;13(8):1369. https://doi.org/10.3390/genes13081369.

[4] Gev D, Roguin N, Freundlich E. Consanguinity and congenital heart disease in the rural Arab population in northern Israel. Hum Hered 1986;36(4):213–7. https://doi.org/10.1159/000153628.

[5] Becker S, Al Halees Z. First-cousin matings and congenital heart disease in Saudi Arabia. Public Health Genom 1999;2:69–73. https://doi.org/10.1159/000016189.

[6] Yunis K, Mumtaz G, Bitar F, Chamseddine F, Kassar M, Rashkidi J, Makhoul G, Tamim H. Consanguineous marriage and congenital heart defects: a case-control study in the neonatal period. Am J Med Genet 2006;140:1524–30.

[7] Albesher N, Massadeh S, Hassan SM, Alaamery M. Consanguinity and congenital heart disease Susceptibility: Insights into rare genetic variations in Saudi Arabia. Genes 2022;13(2):354. https://doi.org/10.3390/genes13020354.

[8] Helle E, Priest JR. Maternal obesity and diabetes mellitus as risk factors for congenital heart disease in the offspring. J Am Heart Assoc 2020;9(8):e011541. https://doi.org/10.1161/JAHA.119.011541.

[9] Basu M, Zhu JY, LaHaye S, et al. Epigenetic mechanisms underlying maternal diabetes-associated risk of congenital heart disease. JCI Insight 2017;2(20): e95085. https://doi.org/10.1172/jci.insight.95085.

[10] Wang F, Fisher SA, Zhong J, Wu Y, Yang P. Superoxide dismutase 1 in vivo ameliorates maternal diabetes mellitus-induced apoptosis and heart defects through restoration of impaired wnt signaling. Circ Cardiovasc Genet 2015;8(5): 665–76. https://doi.org/10.1161/CIRCGENETICS.115.001138.