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Prevalence of Critical Congenital Heart Disease During Surgical Mission Trips to Low-Middle Income Countries. What to Expect

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Abstract

Background: The incidence of congenital heart disease (CHD) is nearly 8 per 1000 live births and about 20% of those patients diagnosed with CHD will present early after birth with signs of Critical Congenital Heart Disease (CCHD) requiring a catheter-based or surgical intervention during the neonatal period.
These numbers are based exclusively on Western literature and Western countries. Little is known about the actual prevalence of CCHD at the time of clinical assessment and treatment during surgical missions in low- and middle-income countries (LMICs).

Methods: This is a retrospective study comparing the prevalence of CCHD at the time of presentation for surgery during humanitarian missions in LMICs. We compared the results to published data for similar cohorts in the USA. Proportions were compared using OR and 95% CI and significance was set at $p<0.01$
We discuss potential causes for epidemiological discrepancies. Classification of CCHD was in 4 groups according to the number of functional ventricles (2 or 1) and the presence of Aortic Arch Hypoplasia (No and Yes)

Results: Between February 2008 and June 2019, our organization operated on 5767 patients in 27 countries. Of these, 243 Neonates were presented to our cardiologists with CCHD. After excluding simple PDA ligations in Preterm newborns, 239 neonates surgically treated for their CCHD, or 4% of the total. Most of our patients were in Group I (2 ventricles and normal aortic arch), while the USA predominant group was IV (1 ventricle and arch hypoplasia)

Conclusions: The prevalence of Critical CHD is significantly lower during humanitarian missions to LMICs than the one observed in Western Countries (4% vs. 20%).
Conditions on the ground such as pregnancy termination laws, gender bias, geographic bias, and length of short-term missions play a strong influence on types of CHD diagnosis seen during humanitarian surgical missions.

Introduction

Congenital heart disease (CHD) accounts for at least 50% of congenital malformations.[1] About 20% of those children born with CHD will present early after birth with what is known as Critical Congenital Heart Disease (CCHD).[2] This severe form of CHD presentation has been described as the specific group of cardiovascular malformations that will likely result in the death of a child in the first year of life unless some type of invasive intervention (catheter or surgery based) takes place.[3]

The expected prevalence of diagnoses among patients presenting with CCHD in the newborn period has been thoroughly described in the Western literature, but it is solely based on the statistics of Western countries. Very little is known about the actual prevalence of CCHD and its variants at the time of clinical assessment and surgical treatment during humanitarian missions to low- and middle-income countries (LMICs).

Objectives

This observational study attempts to assess the prevalence of different diagnoses in newborns with CCHD presenting to surgery during surgical mission trips to LMICs with limited cardiology/cardiac surgery services. We also compare CCHD prevalence during surgical humanitarian missions to the published data for similar cohorts in the USA and discuss potential causes for epidemiological discrepancies.

Methods

All newborns screened, diagnosed, and treated for CCHD during surgical missions to low-and middle-income countries by a single specialized NGO were included in this retrospective analysis.

The proportion of patients diagnosed with specific CCHD diagnosis at the time of assessment for treatment are compared to Western published data. We used Odds Ratio calculations with 95% confidence intervals to assess any differences between patients. Significance was set at $p<0.01$

Classification of Critical Congenital Heart Disease

Critical congenital heart disease encompasses several cardiac defects: Hypoplastic left heart syndrome, pulmonary atresia, transposition of the great arteries, tricuspid atresia, truncus arteriosus, total anomalous pulmonary venous return, coarctation of the aorta, double outlet right ventricle, Ebstein's anomaly, interrupted arch, single ventricle, aortic stenosis and some critical presentations of Tetralogy of Fallot and pulmonary stenosis.

While a clear diagnosis is the basis for an accurate estimation of the true incidence of CCHD, when confronted with over a dozen different entities, a way to cluster them by similarities becomes necessary to facilitate the comparative effort.

We elected to group our patients utilizing the CCHD classification published by Schultz[3] and Clancy[4]. This simple form of classification considers the number of ventricles (1or 2) combined with Aortic Arch obstruction (Yes/No) resulting in a CCHD classification consisting of 4 categories. Class I (Biventricular, no arch obstruction); Class II (Biventricular with arch obstruction); Class III (Single ventricle, no arch obstruction) and Class IV (Single ventricle with arch obstruction).

Results

Between Feb 2008 and June 2019 our organization, in collaboration with our local colleagues, diagnosed and surgically treated 5767 pediatric patients born with CHD at 27 pediatric heart centers distributed among 17 LMICs (Ukraine, North Macedonia, Belarus, Honduras, Iraq, Russia, Libya, Iran, Ecuador, Pakistan, Egypt, Paraguay, China, India, Dominican Republic, Kuwait, Morocco).

Among all the patients operated on, there were only 256 neonates (4.2% of the total) presenting with critical congenital heart disease. After excluding all pre-term newborns diagnosed with hemodynamically significant isolated patent ductus arteriosus, data on the remaining 243 neonates (M/F: 151/92) were collected for this epidemiological review, with 238 of them matching within the four categories of CCHD used for com-

parison. The overall surgical mortality among the 243 neonates operated in LMIC for their CCHD was 19.7% (n=48).

The first significant finding was in the proportion of neonates diagnosed with CCHD in our cohort when compared to published data (4.2% vs. 20% respectively). There were also discrepancies in the proportion of cases in each sub-group, particularly in Classes 1 and 4. For instance, Class 1 patients in our cohort represented 63% of all CCHD treated, while Class 4 neonates represented only 4.2% of our total.

Several cyanotic (e.g., Tetralogy of Fallot and Hypoplastic Right Ventricle in all its variants) as well as non-cyanotic diagnoses (e.g., Critical Aortic Stenosis) were less common among our patients than usually described. (**Tables 1** and **2)**. There was an over-representation of transposition of the great arteries (TGA) (n=106/243 cases) in our cohort of patients with CCHD. Furthermore, 32.7 % of all our transposition diagnoses were from a single center (Nasiriyah, Iraq). **Table 3**.

Table 1. Comparison between our data (NCA) and Schultz published data[3]

CHD Class	Schultz et al. (n)	%	NCA (n)	%	OR (95% CI)	P-Value
I	159	32.5	150	63	**3.55** (2.57-4.91)	**<0.0001**
II	90	18.4	38	15.8	**0.84** (0.56-1.28)	0.42
III	73	14.9	40	16.8	**1.15** (0.76-1.76)	0.51
IV	168	34.3	10	4.1	**0.084** (0.043-0.16)	**<0.0001**
	490		239			

Table 2. Comparison between our data (NCA) and Clancy published data[4]

CHD Class	Clancy et al. (n)	%	NCA (n)	%	OR (95% CI)	P-Value
I	102	32.1	150	63	**3.61** (2.53-5.14)	**<0.0001**
II	28	8.8	38	15.8	**1.97** (1.17-3.31)	0.01
III	8	2.5	40	16.8	**7.83** (3.59-17.1)	**<0.0001**
IV	180	56.6	10	4.1	**0.034** (0.017-0.066)	**<0.0001**
	318		239			

Table 3. Our cohort by country and CCHD Class prevalence. The last column shows the prevalence of Transposition of the Great Arteries in each country and overall.
CCHD= Critical Congenital Heart Disease
TGA= Transposition of the Great Arteries

Country	Total Patients Operated	CCHD	CCHD as % of Total	Class 1	Class 2	Class 3	Class 4	TGA (as % of all CCHD operated)
Ukraine	765	57	7.4	31	16	6	4	14
Russia	354	31	8.7	18	6	6	1	12
Libya	856	20	2.3	10	5	5		8
Iraq	1151	47	4	45	1	1		44
Macedonia	209	15	7.1	6	2	6	1	3
Pakistan	164	7	4.2	6		1		6
India	228	7	3	5	1	1		2
Honduras	606	12	2	8	4			3
Ecuador	431	7	1.6	7				3
Dominican Republic	454	7	1.5	5		2		3
Belarus	89	11	12.3	8	1	2		2
China	222	2	0.9	1		1		1
Morocco	46	3	6.5	1		1	1	0
Egypt	56	3	5.3	2		1		2
Kuwait	11	2	18	2				0
Paraguay	7	1	14.2	1				1
Iran	118	10	8.4	8	1		1	5
Total	**5767**	**242**	**4.1**	**164**	**37**	**33**	**8**	**109 (45%)**

Discussion

According to an ongoing series of peer-reviewed publications by Hoffman et al. [5,6,7] focusing exclusively on the incidence of congenital heart disease in the previous decades, there has been a steady upward trend in the diagnosis of CHD and CCHD worldwide. Going from as low as 4 or 5 per 1000 live births in the 1960's up to 12 to 14 per 1000 live births in 2002.

The reasons for this upward trend seem to be multifactorial, with the most significant influence arising from improved diagnostic methods and the growing availability of specialists worldwide. The same authors conclude "there is no evidence for significant differences in the incidence of CCHD in different countries or times."[6] This concept seems to be somewhat in conflict with published data showing that the prevalence of CHD varies around the world, but what remains constant is the proportion of the different types of diagnoses within a given region.[2] Along those lines, a systematic meta-analysis on the prevalence of CHD at birth worldwide seems to be in agreement with the constant increment of CHD prevalence over time.[8] Bringing into question the concept of geographic uniformity, by showing a significantly higher prevalence of CCHD at birth in Asia, followed by Europe, North America, South America, Oceania and Africa. Whether these differences are due to the lack of diagnostic technology and specialists, particularly in Africa, it remains to be proven.

Critical congenital heart disease has a widespread occurrence with an estimated prevalence of 19 per 10,000 births [2] with geographic variations in prevalence but not in proportions of diagnoses. While variations do happen, they are likely related to local diagnostic capabilities and expertise, the methodology used to assess the diagnoses and factors foreign to the incidence of CHD per se, such as the ability to early terminate pregnancies in the country in question.[2] Further variations in incidence may be due to regional genetic predisposition, maternal diabetes or malnutrition and the use of alcohol and teratogenic drugs.[9]

The setting in which CHD is first recognized (diagnosed prenatally, after birth but before discharge from the hospital, or diagnosed after discharge home) does seem to exert an influence on preoperative condition.[10] Paradoxically, patients diagnosed with CCHD later in life (beyond day one of life or after discharge) seem to fare better[11] likely because more serious conditions tend to either be recognized immediately after birth and either be rapidly treated or die, depending on resources available.

There are several ways to cluster the universe of CCHD into comparable sets of lesions.

A commonly used classification system, different from the one we used in this study, is based on a combination of 3 major sub-group types (LVOT obstruction, RVOT Obstruction and Cono-truncal anomalies) and two isolated diagnoses (Single ventricle and Total anomalous pulmonary venous return) encompassing a total of five categories of CCHD.[10, 12] We chose the classification based on number of ventricles and the anatomy of the aortic arch purely based on the ease of comparison with previously published sets of data.

Potential causes for the prevalence of discordance

Neonatal cardiac surgery is an uncommon occurrence during humanitarian surgical trips, at least in our experience, and when it happens is ~~likely~~ due to chance rather than planning. Survivability beyond the first month of life while waiting for treatment constitutes a severely limiting factor regarding the chances of surgical treatment for most children born with CCHD in LMICs without fully functioning cardiology/cardiac surgery programs. This is particularly patent when even prolonged palliation with Prostaglandin cannot be secured in many centers.

When confronted with significant discordance between published data on CCHD among newborns in Western countries and those found in LMICs, we must first recognize that clinical prevalence of CCHD in Western countries closely follows prevalence at birth. Many, if not most, are antenatal or early after birth diagnosis. The continuum of cardiac care in those countries is well established and few patients, ~~if any,~~ are lost to the healthcare system. It would be difficult to know the true prevalence of CHD diagnoses at birth in most LMICs due to the unreliability of their public health statistical system, the unavailability of antenatal diagnosis, the frequency of deliveries at home and the geographic barriers presented to families that live far from a major specialty hospital when available, all conditions conductive to an early demise of the patient.

We believe variations in prevalence among different centers in low- and middle-income countries to be multifactorial. In some cases~~, just~~ the length of our team's presence in the country or the frequency of the surgical mission trips completely changed our ability to deal with newborns diagnosed with CCHD. Another decisive factor that seems to play a role is whether there was an established functioning program in place before our arrival. Undoubtedly many circumstantial reasons beyond the scope of this study also contribute to the differences. While neonatal cases are an uncommon occurrence during surgical trips lasting one or two weeks, a quite different picture arises when the assistance is provided on a more regular basis, such ~~it~~ was the case of our annual programs. For instance, nearly 20% of all our neonatal patients were diagnosed and treated at a single center (Nasiriyah, Iraq) where we were providing almost uninterrupted surgical and educational support to the local staff for 42 weeks a year.

Gender Bias

In contradiction to the accepted fact regarding

stating that CHD prevalence among newborns is gender-neutral, only 37.8 % of our patients diagnosed with CCHD were female. While lacking a verifiable explanation, we can only speculate that there were strong gender biases at work, perhaps due to cultural beliefs. Selective abortion of otherwise normal female fetuses is a well-documented occurrence in a few low-income countries.[13] Another plausible explanation could be a somewhat lesser effort on the part of families to search for a center and travel great distances to treat the heart-compromised female newborn.

Prenatal Diagnosis and Pregnancy termination

As prenatal ultrasound screening has increased globally, there has been a documented increase in early terminations of fetuses diagnosed with CHD.[14] In many ~~of the~~ countries where we work, we also confront the indiscriminate early termination of pregnancy in cases of inaccurate prenatal prognosis for some types of CHD. While accurate prenatal echocardiographic diagnosis is not widely disseminated in LMICs, in many instances routine pregnancy follow-up ultrasounds revealing a heart other than normal will trigger a reaction leading to early termination. In many cases, the specialist making the diagnostic is not clinically qualified to discriminate very simple forms of CHD with the result of fetuses that could have had a normal delivery and a normal life after surgical repair are being terminated. Pregnancy termination laws, Gross Domestic Product per Capita and Human Development Index for each country included in the study have been included as an **Appendix** to provide a better perspective.

Appendix

Country	GDP PER CAPITA (Median 2008-2019) ¶	Human Development Index ø	Pregnancy Termination Law
Russian Federation	USD* $11 392	0.824	On-Demand
Libya	USD* $7 781	0.724	Allowed with Exceptions[1]
Iraq	USD* $5 450	0.674	Allowed with Exceptions [1]
North Macedonia	USD* $5 195	0.774	On-Demand
Pakistan	USD* $1 229	0.557	Allowed with Exceptions [2]
India	USD* $1 515	0.645	Allowed with Exceptions [4]
Honduras	USD* $2 159	0.634	Unlawful
Ecuador	USD* $6 058	0.759	Allowed with Exceptions [2]
Dominican Republic	USD* $6 423	0.756	Unlawful
Belarus	USD* $6 368	0.823	On-Demand
China	USD* $7 020	0.761	On-Demand
Morocco	USD* $ 2 973	0.686	Allowed with Exceptions [2]
Egypt	USD* $2 905	0.707	Allowed with Exceptions [2]
Kuwait	USD* $38 074	0.806	Allowed with Exceptions [3]
Paraguay	USD* $5 354	0.728	Allowed with Exceptions [1]
I.R. Iran	USD* $5 647	0.783	Allowed with Exceptions [3]
Ukraine	USD* $3 100	0.779	On-Demand[5]

¶ World Bank Data: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD
Ø Human Development Index: https://hdr.undp.org/en/countries
* USD = United States Dollars
1 Allowed when risk to mother's life
2 Allowed when risk to mother's life or health
3 Allowed when risk to mother's life, health, or fetal defect
4 Allowed when risk to mother's life, health, fetal defect, or poverty
5 With restrictions after the 20th week

We have made the organization wide decision not to treat patients diagnosed with hypoplastic left heart syndrome (HLHS) except where the programs we are assisting fulfill the following criteria; 1- Serves as the sole source of pediatric cardiac surgery for the country, 2- Has a robust neonatal program with a survival for the arterial switch operation of 90% or more, 3- Has a critical care transport system capable of hospital to hospital transport of less than 6 hours, 4- Has historical birth records of at least 12 HLHS annually, and 5- There is country-wide availability of prostaglandins . The reasons behind this decision are multiple. Surgery for HLHS and ~~the~~ subsequent care is considered among the most demanding in neonatal cardiac surgery. Nowhere is the concept of total team excellence more apparent in our field. A major issue regarding treating children born with HLHS during a humanitarian mission is the limited assistance provided by the visiting team (one or two weeks), leaving a significant portion of the postoperative care to the local, unexperienced team. Another ethical consideration is the diversion of resources (material and human) taken away from children with other defects with relatively low operative mortality. To date, we have helped four heart centers with their HLHS management program, but only two continue to provide this surgery.

Transposition of the Great Arteries bias in our cohort

Several factors are likely contributing to this unbalance. Environmental issues such as oil and uranium contamination (see below) of soil and water, as well as public health issues~~,~~ (Nasiriyah Heart Center being the only fully functioning pediatric cardiac unit between Baghdad and Basra)~~,~~ are likely contributors to our biased experience in this center.

Use of Depleted Uranium ammunition in conflict zones and CCHD

This is an area of the world that has suffered prolonged and intense armed conflicts. Due to the type of ammunitions used, particularly during the second invasion of Iraq, the concentration of uranium in the soil is excessively high, particularly in areas of the country where the fight was the heaviest. This is the case in Fallujah, a town located west of Baghdad and about 400km north of Nasiriyah, where uranium contamination has been well documented.

The uranium concentration in the area surrounding Fallujah is around 1000 times the international allowed maximum uranium concentration in soil and 27 times higher than the international allowed uranium concentration in water.[15] The concentration of Uranium, among other heavy elements, in the hair of parents of children born with congenital defects in that area are several folds above the levels found in individuals of similar age in other countries.[16]

The number of congenital birth defects in general and congenital heart disease around Fallujah is much higher than international values. For instance, out of 6049 children born during an 11-month period at Fallujah General Hospital, 113 were diagnosed with congenital heart disease, which represents an incidence of 1.86%.[17] This could ~~well~~ be a strong contributing factor to the high numbers of neonates requiring surgical services for CCHD in the Iraq central area. It is not clear whether the specific incidence of transposition of the great arteries as a prevalent diagnosis is also directly related to this local phenomenon. However, it is certainly deserving of further investigation.

Conclusion

Our cohort of patients diagnosed and treated for critical congenital heart disease in low- and middle-income countries represent a small fraction of the total number of patients born with CCHD in these countries, yet some lessons can be drawn.

The prevalence of CCHD during humanitarian missions is always low since most patients are lost within weeks of birth. Consequently, while surgical missions may contribute in many ways to alleviate in part the heavy toll CHD places on society, they are unlikely to prevent significant losses from its most critical forms. Sustainable programs, with long-term assistance by international NGOs at least until fully established local services are a reality, are the only way to decrease the neonatal mortality related to CCHD in LMIC.

Discrepancies in specific diagnoses and prevalence between LMIC and their high-income counterparts are likely multifactorial, and management should be adapted to the conditions of each country and health system.

Proper prenatal diagnosis, specialized critical neonatal transportation systems, countrywide availability of Prostaglandins, and at least one highly functioning heart center are some of the most basic needs required to revert the current natural history of CCHD in countries with limited resources settings.

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