Associated factors of congenital heart disease among children in a rural health care setting in Sri Lanka

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Abstract

Introduction: Congenital heart disease (CHD) is the commonest congenital abnormality worldwide and carries a high mortality. To determine preventive strategies, information regarding the aetiological factors of CHD in Sri Lanka is essential.

Objectives: To determine the associated factors of CHD in a rural healthcare setting in Sri Lanka.

Method: A case-control study was carried out at Teaching Hospital Anuradhapura (THA) Sri Lanka, from July–December 2019 including 146 participants. Children under 5 years of age, who were diagnosed to have CHD following 2D-echocardiography, were included as cases. A community-based control selection was done including children who had normal 2D-echocardiography. A total of 73 cases and 73 controls were selected. The parents were interviewed using a structured questionnaire after obtaining informed written consent. Data were analysed using SPSS version 23.0. The odds ratio (OR) was used to determine the associated risk factors and the 95% confidence interval (95% CI) was used to determine the statistical significance.

Results: Mothers who used non-steroidal anti-inflammatory drugs (NSAIDs) showed risk associations with CHD (OR 2.02, 95% CI=1.71 – 2.37). Anti-epileptic drug use during the first trimester (OR 2.02, 95% CI=1.71–2.39), exposure to fire wood smoke (OR 3.39, 95% CI=1.04–11.2) and paternal exposure to paints (OR 3.39, 95% CI= 1.04-11.2) emerged as significant risk factors of CHD.

Conclusions: In this rural healthcare setting in Sri Lanka, use of antiepileptic drugs, NSAIDs, exposure to firewood smoke and different types of paint during the antenatal period were significantly associated with CHD.

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(Key Words: Congenital heart disease, risk factors)

Introduction

Congenital heart disease (CHD) is the most common congenital abnormality identified around the world[1]. CHD constitutes 28% of all congenital defects[2]. Between 2500 to 3500 live births which occur in Sri Lanka are associated with CHD[3,4]. The management of major CHD imposes an economical challenge for a lower-middle income country such as Sri Lanka[5]. In addition, children with CHD and their families face many socio-economic and psychological challenges[6].

Lack of information regarding the modifiable risk factors for CHD has become a drawback when designing preventive strategies. There are several definitive risk factors such as maternal rubella, phenylketonuria, pre-gestational diabetes, exposure to thalidomide and vitamin A congeners or retinoids. However, for other potential risk factors such as maternal and paternal illnesses, drug exposures and environmental exposures inadequate evidence exists[7,8,9]. Individual variation of these identified risk factors and minimal availability of interventional options during the antenatal period are other identified problems. A health condition with such characteristics requires researches conducted at different settings and populations[10].

North-Central Province is the biggest province in Sri Lanka and is ranked 8th by the number of populations. Anuradhapura District is recognized as an area with an agricultural lifestyle, a low rainfall and relatively a poor socio-economic background. It is situated quite a distance away from the capital. Natural water is hard in nature and it is difficult to find clean drinking water. Wood and other fuel are used to generate energy rather than gas and electricity. Despite these deficiencies, the maternal and child health care service indicators of this area

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are compatible with other districts. Anuradhapura is the major city of the province and is the home for Teaching Hospital Anuradhapura (THA). A total of 3485 children with suspected CHD had presented to the paediatric cardiology clinic at THA in 2018 and out of them 1011 (29%) were confirmed to have CHD. There is minimal amount of published data regarding the aetiological factors of CHD in Sri Lanka. Hence, there is a distinct requirement for periodical studies on this topic.

Objectives

To determine the antenatal and peri-conceptional associated factors of CHD among children born in a rural healthcare setting in Sri Lanka.

Method

This study was designed as a case-control study to achieve aforesaid objectives. Children less than 5 years of age and who had a confirmed cardiac abnormality on 2D-echocardiography were included as cases in this study. Cases were selected from the children who presented to the cardiology clinic at THA from July 2019 to December 2019.

Age and sex matched controls were selected from the same 'Grama-Niladhari' (GN) division from where the cases had been selected. The sample size for the single arm was calculated by using the equation $N = [k \times P_1 (1-P_1) + P_2 (1-P_2)/ (P_1-P_2)^2]$ where P_1 (expected proportion of variables in cases) and P_2 (expected proportion of variables in controls) were taken as 80% and 95% respectively.

Alpha (α) and Beta (β) were set at 0.05 and 0.2 respectively to calculate the 'k' (constant which is a function of α and β)[11]. Calculated sample size for a single arm of the study was 73. Children who were diagnosed with chromosomal abnormalities and less than 37 weeks of gestation at birth were excluded from the study.

Definition of cases: Children who were diagnosed with a CHD by a consultant cardiologist through an echocardiogram.

Definition of controls: Children who were confirmed as not having a CHD through an echocardiogram. Selected controls were referred to a consultant cardiologist for 2D echocardiogram for exclusion of CHD.

Data were collected from the parents of the child by using an interviewer-administered questionnaire. Data on socio-demography, ante-natal, environmental and substance abuse were collected both subjectively and objectively by trained data collectors. Weights and heights of the mothers were measured and mothers with BMI more than 30 were grouped as obese. Environmental exposures of the parents were measured subjectively using 'yes' and 'no' scale. Data verification was done using antenatal records and other relevant medical documents available with parents.

Ethical Issues: Ethical clearance was obtained from the Ethical Review Committee of the Sri Lanka College of Paediatricians (No. SLCP/ ERC/ 2019/ 13). Written informed consent was obtained from the parents of the participating children

Statistical analysis*:* Descriptive statistics and calculation of odds ratios (OR) were done to describe the variables and to determine risk factors of CHD.

Results

All the participants were collectively included to describe the socio-demographic characteristics. They were then compared with the associated risk factors. Age of the children with CHD ranged from 1 to 58 months (Mean=5.53 months: SD=8.29 months). Majority of children represented the age group below 2 years of age (n=140:95.8%) and were males (n=76:52.1%). Majority of the parents were Sinhalese. Most of them were educated only up to the GCE Ordinary Level or below (Table 1).

We studied the relationship of the recreational substances with the occurrence of CHD. Only one mother in the control group was reported as using alcohol and all the mothers in this study were non-smokers. Mothers who were chewing betel were found to be equally divided between the cases and control groups. Among fathers, 45.2% were current users of alcohol among cases and controls. According to the study, fathers' alcohol usage, cigarette smoking and betel chewing habits were not associated with CHD (Table 2).

According to the table 3, obesity, pre-gestational diabetes mellitus and gestational diabetes mellitus were not significantly associated with CHD in this sample (Table 3).

One mother who had received anti-epileptics and two who had received NSAIDs were present and their offspring had CHD. Odds of developing CHD in offspring's of the mothers who had received anti-epileptics or NSAIDS during the 1st trimester were 2 times greater than those who had not. This finding was statistically significant at 5% level. There was no significant association between erratic use of folic acid and a past history of miscarriages with the occurrence of CHD, though, the OR is greater than one (Tables 3 and 4).

Table 5 shows the environmental exposures of fathers.

Table 1: ***Socio-demographic characteristics of parents of the children***

Parent	Cases	Cases	Total (%)
Mother			
Ethnicity: Sinhalese	63	68	131 (89.7)
Tamil	02	-	02 (01.3)
Muslim	08	5	13 (08.9)
Education: Up to O/L	49	46	92 (63.1)
Up to A/L	21	26	47(32.2)
Graduated	03	03	06 (04.1)
Age (years): <25	25	19	44 (30.1)
25-35	37	43	80 (54.8)
>35	11	11	22 (15.1)
Father			
Ethnicity: Sinhalese	63	67	130 (89.1)
Tamil	02	-	02 (01.3)
Muslim	08	05	13 (08.9)
Other	-	01	01 (0.68)
Education: Up to O/L	56	55	111 (76.1)
Up to A/L	14	13	27 (18.5)
Graduated	03	05	08 (05.4)

Table 2: ***Usage of alcohol, smoking and betel chewing among fathers (n=73)***

Substance	Cases	Controls	OR	95% CI
Alcohol				
Yes	32	34	0.895	0.46-1.72
No	41	39		
Smoking				
Yes	15	19	0.735	0.34-1.59
No	58	54		
Betel chewing				
Yes	19	28	0.565	0.28-1.14
No	54	45		

Table 3: ***Distribution of maternal nutritional and endocrinological conditions related to gestation (n=73)***

Condition	Cases	Controls	OR	95% CI
Obesity				
Yes	14	12	1.21	0.52-2.82
No	59	61		
Pre-conceptional diabetes mellitus	03	01	3.09	0.32-30.5
Yes	70	72		
No				
Gestational diabetes mellitus	19	28	0.565	0.28-1.14
Yes	54	45		
No				
Miscarriages				
Yes	18	13	1.51	0.678 – 3.37
No	55	60		

Table 4: ***Distribution of drug exposures of mothers during antenatal period (n=73)***

Environmental factor	Cases	Controls	OR	95% CI
Cooking with firewood				
Yes	69	61	**3.39**	**1.04-11.2**
No	04	12		
Proximity to factories				
Yes	01	04	0.24	0.062-2.20
No	72	69		
Exposure to vehicle emission				
Yes	21	15	1.56	0.73-3.34
No	52	58		
Pipe borne water				
Yes	13	22	0.52	0.23-1.09
No	60	51		
Domestic source of water				
Yes	13	16	0.772	0.34-1.75
No	60	57		
Filtered water				
Yes	55	59	0.72	0.39-1.59
No	18	14		

Table 5: ***Environmental exposures of fathers (n=73)***

Environmental factor	Cases	Controls	OR	95% CI
Exposure to motor painting				
Yes	02	01	2.02	0.18-22.8
No	71	72		
Exposure to wood painting				
Yes	04	03	**1.35**	**1.04-11.2**
No	69	70		
Exposure to agrochemicals				
Yes	20	25	0.725	0.36-1.47
No	53	48		
Proximity to factory				
Yes	01	05	0.189	0.02-1.69
No	72	68		
Exposure to vehicle emission				
Yes	23	17	1.51	0.72-3.15
No	50	56		
Pipe borne water				
Yes	13	22	0.52	0.23-1.09
No	60	51		
Domestic source of water				
Yes	13	16	0.772	0.34-1.75
No	60	57		
Filtered water				
Yes	55	58	0.79	0.36-1.72
No	18	15		

Discussion

Studies on risk factors for CHD are in the form of a continuum, since emergence of new risk factors is always a possibility. Behaviour of risk factors could be different in a given context. Hence, the need of studying risk factors of CHD will never be saturated. This study was conducted to identify the risk factors of CHD in the context of a rural population in the dry zone of Sri Lanka.

We identified risk factors under the groupings of socio-demography, ante-natal, gestational, exposures to medications and chemicals and expert opinions. Most of the subjective data were verified by cross checking with valid documents. Environmental exposures were evaluated subjectively and considered as appropriate proxy measurements for this study according to the expert opinion[7,8,10,12,16].

The Baltimore and Washington study states that exposure to pesticides and other agrochemicals directly affects the occurrence of CHD[10]. However, a contributory association with exposure to agrochemicals for CHD was not demonstrated in our study (OR=0.725, 95%CI=0.36-1.47). This could be due to the fewer incidences of CHD that were reported where the father was exposed to agrochemicals (Table 5). None of the mothers admitted exposure to agrochemicals during pregnancy.

Mills *et al*[12] have reported that heavy alcohol intake by mothers during pregnancy is significantly associated with congenital malformations; however, only a single mother admitted use of alcohol during our study. Similarly, Alverson *et al*[13] have reported that first trimester maternal cigarette smoking is a modest risk factor for select CHD phenotypes; however none of the mothers were smokers in this study. Accepted factors for CHD in developed countries cannot be applied directly to the rural settings in Sri Lanka. The odds ratios for smoking, alcohol consumption, betel chewing and exposure to agrochemicals by the father demonstrated that they had no statistically significant associations with CHD in this study (Tables 2 and 5), though these factors were identified as risk factors during previous studies[2,7,8,14].

An observation of note is the risk association with CHD among mothers who had used firewood for domestic cooking and among parents who were exposed to vehicle emission, paint and solvents during their occupation. These findings demonstrate that ambient air pollution has a risk association with CHD. Gilboa *et al*[15] have demonstrated a risk association between exposure of mothers to particulate and gaseous air pollutants during the first trimester of pregnancy and selected CHD.

Several studies have demonstrated the teratogenic effects of maternal obesity and pre-gestational diabetes[7,8]. In our study there was no statistically significant association between maternal obesity, pre-gestational diabetes mellitus or gestational diabetes mellitus and CHD. The Atlanta birth defects case-control study demonstrated that peri-conceptional multivitamin use was associated with a reduced risk of CHD[16]. Therefore, by commencing folic acid intake from 3 months before pregnancy and continued use through the first trimester, incidence of both neural tube defects and that of CHD could be reduced. However, in our study there was no statistically significant risk association between folic acid intake and CHD.

The study findings indicate that the use of NSAIDs (OR=2.02:95% CI=1.72-2.39) and anti-epileptics (OR=2.02:95% CI=1.72-2.38) during pregnancy is directly associated with the incidence of CHD. It is best to create an awareness regarding this matter among medical practitioners[17]. Water contamination may be an important source of human pesticide exposure. Animal studies and observational studies in humans have reported associations between CHD in offspring and pesticide exposure[18]. However, in our study drinking clean pipe borne, domestic or filtered water was not significantly associated with CHD.

This study was limited to a rural setting due to financial and time constraints. The study findings were deprived of sufficient information to include all the expected variables. This reduced the heterogeneity of the study sample and reduced the external validity of the study findings.

Conclusions

In this rural healthcare setting in Sri Lanka, use of antiepileptic drugs, NSAIDs, exposure to firewood smoke and different types of paint during the antenatal period were significantly associated with CHD.

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