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Heart Murmur among Lebanese Children: A Retrospective Study to Evaluate Epidemiological Features and Risk Factors

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Abstract

Objective: This retrospective study aims to evaluate the influence of different variables incriminated as risk factors for pathological heart murmur (HM).

Methods: The study is conducted among 277 children aged between 0-14 years old referred to pediatric cardiology consultation upon a new finding of an isolated heart murmur. Therefore, they were divided into two groups (Case Group=pathological HM and Control group=Innocent HM) through the Doppler echocardiography diagnosis. A questionnaire was used later on to study all the socio-demographic factors and compare them between the two groups.

Results: Of 277 patients, pathological heart murmurs were found in 178 cases (64.26%). A statistically significant difference is found among seven variables: Consanguinity, Age<1 year, Low socio-economical status, Family history of congenital heart disease, North Region, Poly-malformation Syndrome, and presence of other clinical findings and abnormal symptoms associated to the murmur.

Conclusions: These results show that genetic factors are recognized as the ultimate risk factor for congenital heart diseases (CHD), whereas environmental factors play a decreasing role through prevention policies adopted worldwide such as control of maternal diabetes, alcohol use during pregnancy, teratogenic drugs and rubella.

Keywords: Heart Murmur; Congenital heart disease; Lebanon; Consanguinity

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Introduction

A heart murmur is a continuous sound that is audible with a common stethoscope, produced by turbulent blood along its passage through heart cavities. Often heart murmurs are innocent and do not underline a structural lesion.

Heart murmurs are so frequent and touch almost 80% of neonates and 1/3 of infants and children. Therefore, it shall remain the chief cause of consultation in pediatric cardiology clinics [1-3]. Congenital heart diseases (CHD) are also known for their high prevalence with an incidence reaching 0.5 to 0.8%; most cases being diagnosed during infancy and accounting only 1 to 2/1000 cases in school-aged children later on.

Innocent heart murmurs are isolated murmurs with no other clinical or historical findings and no underlying structural cardiovascular disease. McCrindle et Al identified six auscultatory characteristics found in functional or innocent HM, which may help the clinician to establish the diagnosis without a cardiac ultrasound in almost 50% of cases [4].

In general, 40 to 70% of heart murmurs in children, all ages combined, are due to functional murmurs [3,5-7], knowing that pathological heart murmurs (also referred as organic HM) are most likely to be found among infants aged less than a year. A heart murmur heard first at 6 months is associated to a higher risk of congenital heart disease; 1:7 vs. 1:50 if it is first heard at the age of 1 year. Cardiac ultrasound provides an accurate diagnosis and remains the gold standard test for evaluation of HM. However, it is suspected not to be cost-effective especially since innocent heart murmurs represent a great part of heart murmurs in school-aged children. Referral to pediatric cardiologist seems to be reasonable since he is aware of risk factors of pathological murmurs and master the art of cardiac auscultation.

Due to the multitude of etiologies of congenital and acquired heart diseases, we reviewed the literature to identify them clearly. This study aimed to compare the influence of these main factors compared between two groups of children selected randomly presenting either pathological or innocent heart murmur.

In fact, multiple university hospitals conducted studies to evaluate heart murmurs in children. For example, the study done in Charles de Gaulle University Hospital (CHUP-CDG) in Burkina Faso published in 2015 showed upon 109 patients followed among 23 months that 39% of cardiac ultrasounds are done for a newly heard heart murmur, in which 28.26% corresponded to Ventricle Septal Defect (VSD) [8]. Furthermore, an observational study conducted in Egypt within the year of 2015 and enrolling 183 patients showed that 53% of heart murmurs are innocent with no statistically significant difference between pathological and innocent murmurs regarding age, consanguinity and family history of congenital heart disease. Recurrent respiratory tract infections seem the main significant factor for pathological heart murmur [9]. An another study made in the Middle-East region was done in Saudi Arabia in 2009 and showed that age represents a major factor in evaluating heart murmur, for what 42.5% of heart murmurs during neonatal period are due to structural heart disease [10]. As for our study, we managed to distribute our enrolled patients into two groups after a complete cardiac examination and adequate echocardiography for all children aged between 0-14 years old referred for a newly heard heart murmur, with no anterior cardiac symptoms. The two groups are compared for common variables listed in the literature by adequate statistic tests and we finally established the main risk factors for pathological heart murmur.

Methods

Patients

Patients included in our study were selected among thousands of children seen as outpatients in Nini hospital (Tripoli-North Lebanon), Hammoud Hospital (Saïda-South Lebanon), and two main hospitals in Beirut (Hôtel-Dieu de France and Abou-Jaoude hospitals); all seen by the same cardiologist.

On a period of 9 months (June 2015-February 2016), all children presented for heart murmurs and getting an echocardiography in these hospitals were selected. A questionnaire form was filled later on and final considerations were taken through inclusion and exclusion criteria **(Table 1).**

On a second hand, the records collected via the questionnaire and the data of cardiologist clinics were completed by calling parents for their approval to be enrolled in this study and to fulfill all the remaining required information. Therefore, many cases (n=42) were excluded by lack of accessibility and failed contact. The final number of patients enrolled in the study is 277 patients among 319 legitimate to be cases in the study.

Table 1 Final considerations through inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Age : 0-14 years old	Prior cardiology consultation/ Echocardiography
Referral for isolated heart murmur	-
Lebanese Nationality	-

Statistical analysis

Our retrospective study aim to compare two groups of children: those diagnosed with pathological heart murmurs (n=178) and those who had innocent heart murmur (n=99).

All the data, obtained via the questionnaire and phone calls with one of the parents, were transferred into excel sheets and statistical analysis is made by SPSS system.

Student's T-test is used to determine the differences in cases of normally distributed data and chi-square test (χ^2 test) is adopted to compare variables between the two groups.

A statistically significant difference is fixed for a p-value<0.05, or a confidence level at 95%.

Results

Epidemiological and demographic characteristics

Among 277 patients, 53% are male with a mean of age at the consultation time at 34 months; distributed as shown in **Table 2**.

Socio-economical status and educational level

Low levels corresponded to low incomes <500 000 L.L per month or lack of any academic degree, high levels are related to university degrees or monthly income twice the minimum pension **(Table 3).**

Consanguinity

Consanguinity of first or second degree is found in 55 couples (20%), but 220 couples are not consanguine (80%).

Family history of heart diseases

27of 277 children (10%) have a family relative diagnosed with CHD.

Sibling Age gaps

134 children were first-born, 84 are at the second rank, 40 the third rank and 19 had more than three older siblings.

Personal history of infections

Only eight have had a history of Strep throat while 6 had rheumatic fever as complications.

Context of murmur diagnosis

Heart murmur was discovered in routine examination in 209 children with no other clinical finding (75.45%).

Heart Murmur type

The study revealed that 64.26% corresponded to pathological heart murmur *v/s* 99 cases (35.74%) have innocent murmur.

Maternal factors

See **Table 4.**

Table 2 Epidemiological and demographic characteristics.

Some epidemiological and demographic characteristics					
Sex	130 F	147 M	-	-	-
Age	151<1 years old	67 [1-5 years]	42 [5-10 years]	17 [10-14 years]	-
Region	139 Beirut	85 South	53 North	-	-
Paternal age at childbirth	38 <25 years old	51 [25-30 years]	90 [30-35 years]	47 [35-40 years]	51>40 years old
Maternal age at birth	85<25 years old	102 [25-30 years]	74[30-35 years]	13 [35-40 year]	3>40 years old

Table 3 Socio-economic status and educational level.

Fathers	28 (10%)	118 (43%)	131 (47%)
Mothers	37 (13%)	134 (49%)	106 (38%)

Table 4 Maternal factors.

Some maternal factors				
Miscarriage	59 previous miscarriage	218 no		
Maternal habits	60 tobacco	74 coffee	164 exposed to varnish, hair dyes, disinfectants and pesticides	35 alcohol
Pregnancy complications	10 upper respiratory infection	8 Gestational Diabetes	8 Hypertension	1 rubella
Drug use during pregnancy	23 : yes	254:no	-	-
Mode of delivery	63:C section	214 : vaginal delivery	-	-
Gestational Age	267 normal GA	10 premature	-	-

Delivery and postnatal Complications

30 children presented a post-natal complication and/or NICU admission.

Poly-malformative syndrome

15 children presented different malformations: 7 cases of Down syndrome, 2 cases of Noonan Syndrome and one case of Turner syndrome.

Age distribution within the different regions studied

See **Table 5**.

Consanguinity distribution within different regions

-In Beirut: 13 consanguine marriages (9%).

-In South: 28 cou les consanguineous (33%).

-In North: 16 consanguine marriages (30%).

Family history of CHD distribution among regions

The study enrolled 12 cases (8.5%) in Beirut, 8 cases in the South (9.5%) and seven cases (13%) in the North region.

Socio-economical status distribution among regions

See Table 6.

Comparison of all variables between the two groups; pathological and innocent heart murmur

Through statistical analysis, 7 upon 19 studied variables showed a significant difference with a p value<0.05

Age

There is a significant difference in age between the two groups (p<0.0001) with a mean of age at 4 years 10 months in control group (innocent HM) and 20 months in the case group (pathological HM)

More findings in this same context:

- ≤ 1 years old: 151 children; 22 (15%) have innocent HM *v/s* 129 (85%) pathological HM.
- [1-5 years]: 67 children; 39 (58%) innocent HM *v/s* 28 (42%) pathological HM.
- [5-10]: 42 children; 27 (64%) innocent HM *v/s* 15 (36%) pathological HM.
- [10-15]: 17 children; 11 (65%) innocent HM *v/s* 6 (35%) pathological HM.

Therefore, 61% of children aged >1 years old have innocent heart murmur and 85% of children less than one year old have pathological heart murmur.

Distribution among regions

There is a significant difference between regions (p<0.0001). Effectively, there are 139 children living in Beirut with only 54% having a pathological HM *v/s* 85 children from the south with 66% of them having a pathological HM. Then the north regions, among 53 children, 89%have pathological HM.

Socio-economical status and educational level

Table 7 showed a significant statistic difference between the two groups.

Consanguinity

It also revealed a significant difference between two groups (p=0.038). 39% of children of 220 couples with no consanguinity have pathological heart murmur *v/s* 75.5% of children of consanguine parents have pathological HM.

Family history of CHD

Family history is a factor with limited significant difference p=0.048. There were 250 cases with no history of CHD, and 62% of them have a pathological HM. On the other hand, there were 27 cases with positive family history and 81.5% of them corresponded to pathological HM.

Malformations

We can establish a clear relationship between syndromic malformations and risk of pathological heart murmur (p=0.013).

There were 15 cases of polymalformative syndrome; only one had an innocent heart murmur.

Context of murmur diagnosis

The diagnosis of heart murmur was associated to other signs and symptoms in 68 cases, from which 76% had a pathological heart murmur. The other 209 cases (isolated heart murmur with no particular context) were divided into 83 (40%) with innocent HM and 126 (60%) with pathological HM. At this level of comparison, the p-value is also significant (p=0.016).

Those were the 7 variables that proved their implication as risk factors for pathological heart murmur: Age<1 years old, North region, Consanguinity, Family History of CHD, low socio-economic status, presence of other malformations and associated symptoms leading the diagnosis of murmur. However; sex, parental age, pregnancy and perinatal complications, maternal habits/drug use and alcohol consumption during pregnancy, gestational age, mode of delivery and childhood infections seem not to be significantly incriminated as risk factors. This table resumes all these results in **Table 8**.

Classification of frequent etiologies of pathological HM

Our two groups compared 178 children with pathological HM and 99 children with functional HM. VSD was the most frequent CHD found in 38% of cases, followed by pulmonary stenosis, atrial septal defect, tetralogy of Fallot and persistent atrial duct . Here is their distribution in all three regions in the table shown in **Table 9**.

Table 5 Age Distribution within the different regions studied.

	≤ 1 year	[1-5] Years	[5-10] Years	[10-15] Years
Beirut	67 (48%)	37 (27%)	24 (17%)	11 (8%)
South	42 (49%)	25 (18%)	14 (10%)	4 (3%)
North	41 (77%)	5 (9.5%)	5 (9.5%)	2 (4%)

Table 6 Socio-economic status distribution among regions.

Region	*B*			*S*			*N*		
Level	***L***	***M***	***H***	***L***	***M***	***H***	***L***	***M***	***H***
Father%	1	27	72	6	68	26	42	43	15
Mother%	1	39	60	10	76	14	53	28	19

Note: Region: B=Beirut, S=South, N=North; Level: L=low, M=medium, H=High

Discussion

After collecting all these data comparing children aged 0-14 years in three different areas in Lebanon, referred for isolated heart murmur heard in a routine examination; here is what we encounter

- The age of the child at the moment of diagnosis is critically important to evaluate and follow through; children aged less than one-year-old are at higher risk for pathological heart murmur and further evaluation and referral for cardiac ultrasound is fundamental. This observation comes along all other studies already mentioned [11,12] and is mainly correlated to the high prevalence of congenital heart disease that manifest early in life, by the time fetal circulation develops into postnatal circulation.
- Living in the North of Lebanon seems to be a major factor for pathological heart murmurs. This is mainly due to high rate of consanguinity, low socio-economic and cultural levels and family history of CHD, present in this region. All of these factors proved their relationship with

Table 7 Statistic difference between the two groups.

Maternal Level	*Innocent HM*	*Organic HM*	*Total*
Low	2 (5%)	35(95%)	37
Medium	49(37%)	85(63%)	134
High	48(45%)	58(55%)	106
Paternal Level	***Innocent HM***	***Organic HM***	***Total***
Low	2 (7%)	26(93%)	28
Medium	33(28%)	85(72%)	118
High	64(49%)	67(51%)	131

Table 8 Risk factors for pathological heart murmur.

1.	Age <1year old	p<0.0001
2.	Sex	p=0.32
3.	Region (North)	p<0.0001
4.	Paternal age at birth	p=0.67
5.	Maternal age at birth	p=0.23
6.	Socio economic status	p=0.003
7.	Consanguinity	p=0.038
8.	Family history of CHD	p=0.048
9.	Sibling age gaps	p=0.35
10.	Childhood infections	p=0.41
11.	Context of murmur diagnosis	p=0.016
12.	Previous miscarriages	p=0.12
13.	Maternal use of alcohol	P=0.11
14.	Pregnancy complications	p= 0.28
15.	Drug use during pregnancy	P= 0.33
16.	Mode of delivery	p=0.56
17.	Maternal exposure to varnish, hair dyes, disinfectants and pesticides	p=0.22
18.	Maternal use of coffee and maternal smoking	p=0.13
19.	Malformations	p=0.013

Table 9 Classification of frequent etiologies of pathological HM.

CHD	Beirut	North	South	Total	Total in (%)
VSD	32	18	18	68	38
Pulmonary Stenosis	11	5	8	24	13.5
ASD	6	4	3	13	7.3
TOF	6	3	4	13	7.3
PDA	3	2	2	7	4
OTHERS	17	15	21	53	30

Note: CHD: Coronoray Heart Disease; ASD: Atrial Septal Defect; TOF: Tetralogy of Fallot; PDA: Patent Ductus Arteriosus

pathological heart murmur. In fact, 77% of children in this area were aged less than one year old, 42% of parents have low socio-economical status, 30% of the couple was consanguine and family history of CHD was positive in 13% of cases. Those factors mainly reflect the regional difference that we found.

- In controversy to other studies, low socio-cultural level is associated to a higher risk for pathological heart murmur [13]. This may be related to consanguinity and exposure to environmental risk factors in these categories. A further lineal regression analysis is needed to identify correlations between these factors.
- Genetics seem to play a major risk factor for pathological heart murmur. Both consanguinity and family history of CHD reflect a higher risk for pathological HM: in consanguine marriages 75.5% of the children with heart murmur seem to have a CHD while 81.5% of children with a family history of CHD also have a pathological HM. While reviewing literature, consanguinity was incriminated as risk factor due to hereditary transmission of some CHD [14-18]. For example, there is an autosomal dominant transmission for some polymalformative syndrome associated with birth defect and family history of CHD is thereby also a risk factor [12,14]. Furthermore, we have only determined 10% of CHD etiologies, hereditary factors account of 3% of all identified causes. Nevertheless, 90% of undetermined etiologies are probably due to more genetic factors not yet established [15].
- Otherwise, the presence of malformations in a child with heart murmur, whether this malformation is part of a syndrome or no and the risk of congenital heart disease is higher. 14 out of 15 children having a malformation came to have also a pathological heart murmur. This also reflects the incriminated role of hereditary and genetic factors in CHD [15].
- The context of murmur diagnosis guides also the clinician to the possibility of organic heart murmur. A child that manifests other symptoms then the heart murmur (past recurrent infections, development delay, short breathiness…) is at higher risk to present a CHD.

As for the other variants that we could not establish a causality relationship, we mention

Maternal habits during pregnancy showed no significant effect on CHD, as cited in literature [16,17-20]. A remarquable observation is noted: women who drank coffee seem have a protection against CHD however this relationship is probably due to pure coincidence since no other study had established a protective role of caffeine against birth defects.

Smoking and alcohol did not also show a significant difference between the two comparative groups. The implication of those two environmental factors cannot be totally declined in our study because of biases: women are aware of health issues related to tobacco and alcohol use, and tend to not use them/or deny using them during pregnancy.

As for exposure to varnish, dye, pesticides and disinfectants, those factors are not incriminated as like all published studies

- Pregnancy complications are not significant in our study, as other publications [21]. Most of these complications are not known to be associated with birth defects, except for gestational diabetes [14] and rubella [22]. In our database, 8 cases of diabetes and only one case of rubella were reported. Due to this small number, a conclusive statement cannot be made concerning these two factors. However, it is a good sign of effectiveness of preventive measures through rubella vaccination and control of gestational diabetes.
- Drug use during pregnancy is also another well-controlled factor that does not affect anymore the risk of congenital diseases; due to public awareness and gynecologist guidance for the use of limited safe drugs.
- Alcohol consumption is a factor that may be bias in our study with a small number of women admitting to drinking alcohol due to religious expectations or fear of guilt.
- Tonsillitis during infancy did not seem to increase the risk for pathological heart murmur. This is mainly explained by the systematic use of antibiotics to treat infections and prevent Strep group A complications (rheumatic fever), knowing that tonsillitis is not a reliable predictor of later rheumatic heart disease.
- Parental age at the time of birth does not seem to be a risk factor for congenital heart diseases. However, we observed that CHD are mostly present in children of mothers aged between 35-39 years old and fathers aged less than 25 years old. All of this joins the results of cited publications [14,23].
- A history of miscarriages does not implicate a risk of CHD, as many studies proved [24]. However, we cannot deny that cardiac malformations may cause some of these miscarriages and raise a hidden risk for CHD.
- Gestational age, mode of delivery, rank between siblings, sex and postnatal complications are not significant as cited in literature. [15]

The methodology of this study required a close follow-up in pediatric cardiologist clinics in three different regions of Lebanon on a period of 9 months, to enroll all children referred for heart murmur. 277 patients respond to criteria after parental approval and were grouped into cases and control group for evaluation of genetic, demographic and environmental factors. The questionnaire used was done by the same interlocutor to minimize the risk errors.

Our study shows many advantages: it consumed a little time in comparison of other observational studies and used an easy measurement tool (questionnaire) to collect all the data. It is inexpensive, the costs being limited to making phone calls to complete the database and having the statistical analysis done. There was no indication to have the same number of patients in the two comparative groups.

It is the first retrospective study done in Lebanon to evaluate factors of heart murmur in children and it did encounter a large amount of patients among a short period of time (277 children in 9 months *v/s* 183 children in one year in the observational study of Egypt). The risk of errors and limitations of this study include the recall bias (the accuracy and completeness of participant recollections of past events as for environmental exposures during pregnancy or family history of CHD). In this same perspective, the recall bias incriminates patterns of parents with sick children that tend to emphasize all factors *v/s* parents with a healthy child that will neglect major history factors. There is also the random sampling error or bias of selection, since three regions of Lebanon are not enough to present all Lebanese population variability. They are a main reflect of outpatients in private clinics that do not share the same demographic characteristics of all population. There is also the exclusion bias since patients whom no contact number was available or were not reachable (42 among 319 patients) were automatically excluded from the study. It is not a highly significant amount but it may have excluded patients with a rather low socioeconomic status.

Conclusion

While evaluating characteristics of heart murmur in Lebanese children, we managed to identify seven risk factors for pathological heart murmur, in order to establish new preventive measurements against controllable factors.

Those factors are child age <1 year old, region where he comes from, socioeconomic status, consanguinity, family history of CHD, malformations, and context of diagnosis.

Since genetic factors are widely incriminated, genetic counseling seems the remaining hope to limit risk of transmission of hereditary heart diseases; along with limitation of consanguine marriages by managing some awareness campaigns.

In parallel, some environmental factors must be totally eradicated such as rubella by immunizing all girls and more strict policies for drug prescriptions during pregnancy and organizing more awareness campaign against fetal alcohol syndrome and a strict control of gestational diabetes.

Finally, we should know the prevalence and characteristic features of innocent heart murmurs so we can limit parental anxiety in front of a newly heard heart murmur.

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