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Recurrence of cardiac defects among siblings: Could this pose an urgent need for genetic and chromosomal analysis? Case report and review of literature.

Chinawa Josephat M[1*], Ujunwa FA[1], Aronu AE[1], Chinawa AT[2], Maduka NC[2], Obidike EO[2]

[1]Department of Paediatrics, College of Medicine, University of Nigeria, Enugu Campus, Nsukka, Enugu, Nigeria

[2]Department of Community medicine, Enugu State University, College of medicine, Nsukka, Enugu, Nigeria

Abstract

Background: Current trends in chromosomal analysis and genetic assay for cardiac anomalies have led to arising need for genetic cardiologists and counsellors.
Objectives: We present series of four cases that showed a very strong demand and need for genetic testing and counselling.
Results/Case Presentation: We report four cases of congenital familial disease, each pair consists of siblings with both congenital and acquired heart diseases. The first pair arise from same parents, both males, 8 years and 5 years respectively with both presenting with anomaly from cono-truncal origin.
The elder brother has pulmonary stenosis and the younger had truncus arteriosus. The former had surgery and was doing well but the former awaits surgery.
The second pair arise from same biological parent. Both are females, 8 years and 6 years old respectively, both had cardiomyopathy, they are now awaiting cardiac transplant.
Regrettably, none of the familial cases had any genetic assay or counselling because of lack of funds and facilities.
Conclusion: From these cases, it is very expedient to include genetic counselling and chromosomal analysis as part of our daily practice in our locale. Indications such as the presence of a syndromic phenotype, growth delays and a family history of cardiac lesion could be a tell-tale sign for genetic analysis.

Keywords: Genetic assay, Congenital heart disease, Acquired heart disease, Cardiac transplant.

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Introduction

Congenital Heart Defects (CHD) are the commonest cause of congenital malformations. Majority of families show only one person with CHD. Nevertheless, the risk increases in children who are born into families with congenital heart disease. Kristoffer et al. [1] noted a recurrence rate of 4.1% among younger sibling with a family history of congenital heart disease, compared to 1.1% of those without family history of congenital heart disease. The increase risk of recurrence is a pointer that familial risk factors are important in the aetiology of congenital heart disease [1]. Some genetic conditions arising from cardiac lesions couldshow an incomplete or age-related penetrance [2]. Example is cardiomyopathy which usually manifests at early adolescence. Cardiac lesions demonstrate variable expressivity: different family members with the same genetic mutation expressing the disease in different ways. Also they demonstrate clinical and genetic overlap which may complicate the interpretation of genetic results [3].

Despite these caveats, knowledge of the genetic nature of cardiovascular diseases will inform need for familial screening, help in early diagnosis and treatment in order to delay onset of disease, also aid in risk stratification for sudden cardiac death in affected individuals.

Roles of genetic counsellor in clinical care is very pivotal in handling issues of consanguinity. It involves risk assessment, education, genetic testing, result interpretation and disclosure of results [4]. Main principles of genetic counselling that will enable a well knitted and sound genetic counselling involve autonomy: where decision to make genetic testing is basically that of the counselee. Non-defectiveness: here, information should be correct and precise and an informed consent must be provided before blood tests. Other technique involve sampling right to know the genetic result and confidentiality [5]. We present a series of four cases that showed a very strong demand and need for genetic testing and counselling [6]. Problems arising from familial heart disease or consanguinity can be averted or reduced to the barest minimum by involving professionals in genetic counselling in our practise especially those that present with heritable cardiac disease or storage disorders. Genetic counselling is a cascade of events that starts from genetic counselling to library preparation then To Next Generation Sequencing (NGS) to genetic reading and processing of gene alignment to their respective genome and variant calling [7].

Results/Case Presentation

Case 1

OS an 8-year-old male who presented with a history of cough and breathlessness that started at 3 months of age, leg swelling and abdominal swelling that started 2 years ago. Examination showed a child in obvious respiratory distress withe raise jugular venous pressure, heave at the lower left sternal boarder and grade 3/6 ejection systolic murmur maximal at the second left inter-space and a grade 3 holo-systolic murmur located at the lower left sternal boarder. Apex was located the 6th intercostal space, mid clavicular line. There is also remarkable ascites and hepatomegaly of 8 cm. A diagnosis of congestive cardiac failure secondary to Pulmonary stenosis was made however, echo showed a very severe pulmonary stenosis extending into the pulmonary bifurcation and severe tricuspid regurgitation. He was place on continuous furosemide infusion in a syringe pump, dopamine infusion, digoxin and sildenafil and enalapril. Subsequently, he had surgery and spent about 2 weeks in the hospital and was discharged. He had since been coming for follow up.

Case 2

OD a 5-year old male presented with 2-month history of inability to gain weight and fast breathing. Examination showed an asthenic infant, afebrile, not pale, tachypneic with clear lung fields, displaced apex beat at 6th intercostal space, lateral to mid clavicular line with grade 3 ejection systolic murmur and hepatomegaly of 4 cm. Chest X-ray showed bilateral hilar vascular prominence with plethora and a widened mediastinum. He is the younger brother of case 1. Echocardiography showed a diagnosis of truncus arteriosus and pulmonary hypertension. Patient has been on anti-failure regimen and has remained stable. Currently awaiting corrective surgery.

Case 3

UU is a 6-year-old female. She presented with cough, fever, breathlessness, ascites and chest pains. Physical examination revealed grade 3/6 pan-systolic murmur located maximally at the lower left sternal boarder. A clinical diagnosis of congestive cardiac failure was made. Echocardiography revealed dilated cardiomyopathy (Ejection fraction of 20.1%) with severe left ventricular dysfunction. Patient was commenced on dopamine and enalapril. She awaits cardiac transplant

Case 4

UC is an 8 year old female. She is the elder sister of case 3. She presented with cough, fever, breathlessness, ascites and chest pains. Examination also revealed grade 3/6 pan systolic murmur maximal only at lower left sternal boarder. Diagnosis was dilated cardiomyopathy with severe left ventricular dysfunction and ejection fraction of 20.1%. Patient was also commenced on dopamine and enalapril. She had an abdominal paracentesis due to worsening respiratory distress caused by ascites. Both siblings are on cardiac transplant list.

Discussion

Genetic counselling among parents with children who had hereditary cardiovascular disease has been included in treatment guidelines of children with congenital heart disease. [8-10]. Some countries have promulgated policies of genetic counselling for patients undergoing genetic testing for specific hereditary conditions especially those of cardiac origin. Most familial cases are inherited as complex traits. Several studies have shown patterns of familial risk for congenital heart disease [4]. It is estimated that the risk of occurrence for congenital heart disease is 3%-4% in siblings of affected patients and 4%-10% in offspring of affected patients [4]. We had two children in a family of three affected in our case; this puts the risk at more than 4%. It is not clear what the risk will be in the future generation of the affected case. This therefore makes it very ideal for genetic assay among the parents and sibs to really know the risk and the chromosome that is affected. Risk of recurrence vary by the congenital heart disease sub-group. For instance, recurrence risk was observed to be highest in the subgroup with left-sided cardiac defects as compared to other forms of congenital heart disease [11,12].

Outflow tract and aortic arch anomalies are the second commonest familial heart disease and accounts for 20%-30% of congenital heart disease [12]. Deletions affecting the 22q11.2 chromosomal loci and the TBX 1 gene account for much of the phenotype [13]. Our cases with congenital heart disease may have the same locus of chromosome 22q11.2. However, this is inferred as genetic assay was not done for them due to lack of facility and funds. Congenital pulmonary valve malformation could also re-occur in families with associated high consanguinity rate. However, this could not be established in our patients. The prevalence is about 4/1000 live births and accounts for 10% of children with congenital heart defects. About 10% of patients with pulmonary stenosis have additional cardiac anomalies associated with Noonan, LEOPARD and multiple lentiginous syndromes. They are mainly autosomal dominant and rarely autosomal recessive. Again the importance of chromosomal analysis in these series would have helped confirm this assertion and possibly avert recurrence. A study by Peyvandi et al. [13] in 2014 to determine the risk of congenital heart disease in relatives of 1620 Probands with Cono-truncal Cardiac among various parents and siblings. Defects showed that the risk of congenital heart disease was higher in siblings than in parents. About one third of affected parents and three fifth of affected siblings had a concordant lesion. This shows that recurrence risk varies by lesion and relationship of great vessels. We could not ascertain the frequency of distribution of risk among parents and sibs of our cases. Viasta et al. [14] in 2011 reported a total recurrence rate of one out of 52 cases, after one previously affected child and 1/10 after two previously affected children. Tynan et al. [15] reported a recurrence rate of 7.7% in fetuses with one or more first degree relatives with congenital heart diseases. The recurrence rate in our patient whose lesion were from

conotruncal origin was 1:3. It is important to note that with Mendelian inheritance pattern, recurrence risks are 50% and 25% for autosomal dominant and recessive genes respectively. We had a frequency of 33% in ours but we could not prove if it is autosomal or recessive, However, our risk frequency could be affected by the issue of variable penetrance. Difficulties in estimating recurrence risks are compounded by the absence of clear genetic diagnosis due to variability's in penetrance. Estimates are therefore based on detailed family tree and literature. Two subjects from our series who are from the same parents also presented with dilated cardiomyopathy. Dilated cardiomyopathy and hypertrophic cardiomyopathy are genetically and phenotypically heterogeneous. In a study of 120 cases in Japan, 20 and 13 cases had TTN and LMNA genes implicated respectively [16]. TTN variant were the major cause of sporadic dilated cardiomyopathy and LMNA variant were most implicated of the familial dilated cardiomyopathy. In same study of 52 children with Hypertrophic Cardiomyopathy (HCM), MYH7 and MYBPC3 variants were the most common. We could not detect any genetic implication or variant in our sibs for obvious reasons [17]. Penetrance can be complete (100%) in instances where all carriers develop the cardiac anomaly, it could also be incomplete if the mutated carriers never develop the cardiac lesion [18]. It is necessary to note that most autosomal recessive cardiomyopathies are linked with complete penetrance before adulthood, however majority of autosomal dominant cardiomyopathies are associated with incomplete penetrance [17-22]. As a result of agerelated penetrance of most cardiomyopathies, evaluation of families may take place when these children show no symptoms. If these children are not followed up adequately, they may develop symptoms at adulthood. The extent of cardiac examination varies depending on the type of cardiomyopathy. More often than not, additional investigations may include exercise testing, signal-averaged ECG, and cardiac magnetic resonance imaging may be necessary. Our series were diagnosed with echocardiography alone [23].

Conclusion

From these cases, it is very expedient that genetic counselling, need for detailed family history and chromosomal analysis should be part of our daily practice in our locale. Indications such as the presence of a syndromic phenotype, growth delays, developmental delay, defects with variable expressivity, and context of multiplex family *i.e.* a diagnosis having afflicted first-or second degree relative, a family history of cardiac lesion could all be a telltale sign for genetic assay.

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***Correspondence to:**

Chinawa Josephat M

Department of Paediatrics,

College of Medicine,

University of Nigeria Enugu Campus

Enugu, Nigeria

Tel: +234 803 722 1864.

E- mail: josephat.chinawa@unn.edu.ng