European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 9, Issue 6, 2022

ECHOCARDIOGRAPHY BASED APPROACH TO THE DIAGNOSIS OF CARDIOVASCULAR GENETIC DISEASES: CASE SERIES AND REVIEW OF LITERATURE

Rajesh Nandal[1], Kuldip Singh Laller[2], Ashwani Kumar[3], Saurabh Biswas[4], Meenakshi Lallar[5]

1-Assistant professor, Department of Cardiology, Post Graduate Institute of Medical Sciences, Rohtak
2-Sr. Professor and Head, Department of Cardiology, Post Graduate Institute of Medical Sciences, Rohtak
3-Associate Professor, Post Graduate Institute of Medical Sciences, Rohtak
4-DNB cardiology student, Post Graduate Institute of Medical Sciences, Rohtak
5- Consultant Geneticist, Prime Diagnostics, Chandigarh and MedGenome Labs, Bengaluru.

Corresponding author: Dr. Rajesh Nandal

Abstract:
Cardiovascular genetic diseases include syndromic and non-syndromic congenital structural heart diseases and cardiomyopathies, arrhythmic disorders, vascular disorders in connective tissue diseases, lipid disorders such as familial hypercholesterolemia, storage disorders etc. We aim to discuss spectrum of genetic diseases seen in cardiology practise while performing routine echocardiography and also try to propose and highlight a simple approach to identify such patients to prioritise for genetic testing to aid further management. Out of total 930 patients seen in the OPD (from July 2021 to July 2022), 65 patients were suspected to be affected with genetic disease. Out of these 65, only 25 underwent genetic testing (38%). Amongst these 25 patients, a genetic diagnosis was possible in 11 patients (yield -44%). Authors concluded that lack of suspicion and training, or resources cardiac genetic disorders are often diagnosed late or sometimes never diagnosed and this leads to missed opportunities to treat and prevent recurrences in the same family, either through reproductive counseling or cascade screen of at-risk relatives. As seen, any genetic disorders ranging from chromosomal to single gene defects have characteristic cardiac lesion and a cardiologist doing echocardiography can play a pivotal role in diagnosis. A multidisciplinary approach and basic sensitization of cardiologist when to suspect and refer for genetic work up/testing becomes important for clinical management of all such patients and cascade screening in at-risk relatives.
Keywords: Cardiovascular genetic diseases, echocardiography, fetal medicine.

Introduction

Cardiovascular genetic diseases include syndromic and non-syndromic congenital structural heart diseases and cardiomyopathies, arrhythmic disorders, vascular disorders in connective tissue diseases, lipid disorders such as familial hypercholesterolemia, storage disorders etc [1]. With increasing awareness, imaging and genetic testing resources more cardiac genetic conditions are being routinely diagnosed [2]. These diseases can present from fetal to adult life, with isolated or multisystemic complaints, and hence may present primarily to the cardiologist or to allied health care personnel like general physicians, paediatricians, fetal medicine specialist or geneticist. Most such patients will require a multidisciplinary involvement for accurate diagnosis and management, wherein a cardiologist will play an integral role in diagnosis and management. Hence, cardiologists need to maintain a high index of suspicion when encountering such patients, especially when finding anomalies on echocardiography. This is imperative to diagnose cardio genetic disorders early and accurately timely diagnosis helps not only in disease management but also timely genetic counselling helps prevention of similar recurrences in family and cascade screening in at-risk relatives can be offered.

In this case series, we describe the common cardiac genetic disorders that we encountered in clinical practice while doing echocardiography. Hence stressing the role of echocardiography, clinical history and physical examination as key to diagnosis of these common cardiac genetic disorders. We aim to discuss spectrum of genetic diseases seen in cardiology practise while performing routine

echocardiography and also try to propose and highlight a simple approach to identify such patients to prioritise for genetic testing to aid further management.

Methods

This is a cross -sectional retrospective case series. We included patients with abnormal echocardiographic results where an underlying genetic etiology was suspected, and finally genetic diagnosis was made. An informed consent was taken. All patients with suspected genetic etiology who did not underwent genetic testing were not included in the study.

All the patients that were included in the study (with cardiac echocardiographic findings and suspected genetic diagnosis), for them a basic history taking, examination was done, and they were investigated in collaboration by pediatrician/cardiologist and geneticist whenever need be. Genetic testing was phenotype based and varied from karyotyping, cytogenetic microarray to next generation sequencing based panels and exome.

Results

Out of total 930 patients seen in the OPD (from July 2021 to July 2022), 65 patients were suspected to be affected with genetic disease. Out of these 65, only 25 underwent genetic testing (38%). Amongst these 25 patients, a genetic diagnosis was possible in 11 patients (yield -44%). Table 1 shows the demographics, presenting complaints, echocardiographic findings, genetic testing and final diagnosis in these 11 patients.

Discussion

In recent years, with advent of next generation sequencing, the utility, availability and cost-effectiveness of genetic testing has increased and increasingly we are being able to diagnose many genetic conditions. Genetic testing is informative and useful for clinical management, reproductive counselling and cascade screening of at-risk relatives. Genetic testing is phenotype based and depending upon the etiology suspected (chromosomal or single gene defect) testing options vary from karyotype, microarray to NGS based panel or exome analysis. Given the cost and complexity of genetic testing, involvement of a clinical geneticist or genetic counselor may be helpful [3]. Clinicians should be aware that genetic testing might not reveal a cause or confirm a diagnosis of the patient's disease because the yield of genetic testing for any inherited cardiovascular disease remains <100% [4]. In our study the yield was only 44%, though the sample size is quite small and varied. In this regard, American Heart Association (AHA) has issued a statement summarizing current best practices with respect to genetic testing and its implications for the management of inherited cardiovascular diseases [1]. Also, AHA has released a statement regarding establishment of specialized clinical cardiovascular genetics programs recognizing the unmet need, utility and advances in genetic testing in cardiology [5].

As seen from the study echocardiography detects various cardiac disorders encompassing from structural congenital heart defects (PDA, ASD, TOF and Supravalvular aortic stenosis) to different cardiomyopathies. They can be either syndromic (Trisomy 13, 22q11.2 syndrome, William syndrome, Holt Oram syndrome, Noonan, Marfan and Fabry syndrome) to isolated non syndromic cardiac genetic disorders like non hypertrophic cardiomyopathy and ARVD. As seen from the Table 1, the cardiogenetic disorders present from neonatal to adult ages and vary from chromosomal disorders like trisomy 13, 22q11.2 microdeletion to single gene disorder. The single gene disorders can be multisystemic like Noonan and Fabry or purely cardiac involvement like ARVD and other cardiomyopathies.

Based on our series in this series we can suggest an approach. We observed 27% (3/11) patients presented with developmental delay and dysmorphism and were later diagnosed with chromosomal anomalies. Firstly, this reiterates the need for the person performing echocardiography to ask few questions about development and do basic physical examination. Secondly, One must remember syndromic association of some common cardiac lesions as seen in our case series like Supravalvular aortic stenosis, TOF, ASD , PDA are seen in William syndrome, 22q11.2 microdeletion, Holt Oram and Trisomy 13 respectively and in all these cases there are positive physical examination findings (Table 1). Thirdly, in cases of sudden deaths in family and cardiomyopathy findings in echo genetic testing should be done to guide not only for treatment (in patient 11-ARVD, Pacemaker insertion was

done) but also to diagnose storage diseases like Fabry (Patient 4) where enzyme replacement therapy is available and renal surveillance is important to prevent and treat renal failure. Fourthly, genetic diseases are important for reproductive counselling as they can recur in the family. Timely diagnosis in cases of all the cases provided opportunity for genetic counselling and can lead to prevention of disease and diagnosis in other asymptomatic family members. As seen in our series, when family pedigree, history and examination of close family members was done, we found that in case 3 (Marfan syndrome) the condition was inherited from mother, who was then screened with echo and put on beta blocker prophylaxis. Depending upon the mode of inheritance AD (Noonan, Marfan syndrome, Cardiomyopathies), or X-linked (Fabry) the risk to the families were conveyed with respect to other at -risk members and reproductive risks to the case and parents/siblings. Taking in all above learning points a simple step wise approach in case of abnormal echocardiography findings which should alert one to presumptive genetic diagnosis and further testing/referral of patient can be presumed (Fig 1).

It is a general dictum that highest diagnostic yield is in individuals with extracardiac features and/or a family history, due to an increased chance of a syndromic or inherited form. The diagnostic yield and primary types of causative variants differ across CHD categories. Various studies have shown yield of genetic testing 39% in those with multiple congenital anomalies and 20% in those with isolated congenital heart disease. They found right ventricular obstructive defects were highly associated with abnormal genetic test results [6]. When we review the diagnostic yield of genetic testing, which was low around 44% in our series. It agrees with previous studies, but we need larger sample sizes for more accurate account.

We see that in our cohort, 45% cases (5/11) were diagnosed with cardiomyopathy, both syndromic and isolated. This could be due to larger proportion of adult population in the clinic. This implores us to take important family history and following a positive genetic diagnosis cascade family screening in siblings and at-risk relatives should be initiated to diagnose and prevent fatal events in the asymptomatic individual of the family who harbor the same mutations. Previous studies also recommend a family history of at least 3 generations should be obtained for all patients with a primary cardiomyopathy. Genetic counseling is recommended for all patients with cardiomyopathy and their family members [7].

Conclusion

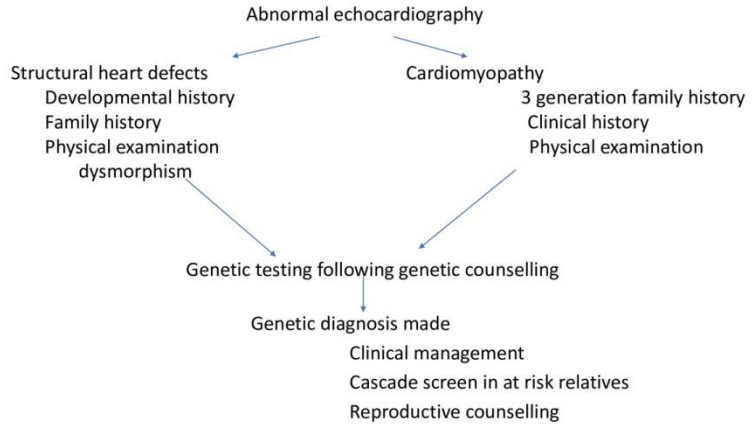
Given that the genetic disorders are rare, there is lesser knowledge amongst the clinicians regarding diagnosis and clinical management. Hence, either due to lack of suspicion and training, or resources cardiac genetic disorders are often diagnosed late or sometimes never diagnosed and this leads to missed opportunities to treat and prevent recurrences in the same family, either through reproductive counseling or cascade screen of at-risk relatives. As seen, any genetic disorders ranging from chromosomal to single gene defects have characteristic cardiac lesion and a cardiologist doing echocardiography can play a pivotal role in diagnosis. A multidisciplinary approach and basic sensitization of cardiologist when to suspect and refer for genetic work up/testing becomes important for clinical management of all such patients and cascade screening in at-risk relatives.

Table 1: Description of genetic etiology and presenting features

S.No	Age sex	Echocardiography findings	Presented to	Presenting complaints	Genetic test	Final diagnosis
1.	1 day, Male	PDA	Pediatrician, referred for echocardiography	IUGR, cutis aplasia, respiratory distress	Karyotype	47, XY, +13 (Trisomy 13)
2.	12 year , Male	Moderate pulmonary valve stenosis, normal biventricular function	Pediatrician, referred for echocardiography	Short stature, fatigue and failure to thrive	Targeted Exome	Noonan syndrome Heterozygous *PTPN11*, c.317A>C
3.	10 year, Male	Aortic root 28 mm, Z score (+2.39)	Physician, referred for echocardiography	Marfanoid habitus	Connective tissue panel	Marfan syndrome heterozygous *FBN1*, c.6388G>A

4.	42 year, Male	Concentric hypertrophy of the left ventricle with near-normal systolic function.	Cardiologist	Dyspnea, chest pain.	Cardiomyopathy panel	Fabry Hemizygous *GLA* , p.Try236Ter
5.	31 year, Female	Moderate MR, concentric LV hypertrophy, LVEF-60%	Cardiologist	Dyspnea and chest pain, family history of sudden death	Cardiomyopathy panel	Noonan *PTPN11*, c.1484C>T
6.	1 month, Female	Tetralogy of Fallot with right sided aortic arch	Pediatrician referred for echocardiography	Cyanotic baby with dysmorphism	Cytogenetic microarray	DiGeorge syndrome/ 22q11.2 deletion
7.	3 year, Female	Supravalvular aortic stenosis	Pediatrician referred for echocardiography	Developmental delay and dysmorphism	Cytogenetic microarray	William syndrome/ 7q11.23 deletion
8.	66 year Male	ECHO findings showed no provokable gradient, decreased left ventricle GLS and left atrium strain and enlarged left atrium and was suggestive of hypertrophic cardiomyopathy.	Cardiologist	Hypertension and dyspnea	Cardiomyopathy panel	Hypertrophic cardiomyopathy-4, Heterozygous, *MYBPC3*, c.3569G>T
9.	30, year Female	LVEF- 65%, Mild MR, Mild Septal hypertrophy	Cardiologist	Dyspnoea, fatigue , family history of sudden death	Cardiomyopathy panel	Cardiomyopathy, hypertrophic, MYH7, heterozygous variant, c.2146G>A (p.Gly716Arg)
10.	12 year Female	Small ASD left to right shunt	Geneticist	Bilateral digitalized thumbs, small and tag like	Targeted exome	Holt Oram syndrome Heterozygous *TBX5*, p.Gly125Arg
11.	27 year Female	Regional wall motion abnormalities and dyskinesia with small outpouching. Echocardiogram showed dilated right atrium and ventricle	Cardiologist	Syncope episodes Family history of sudden death.	Cardiac cardiomyopathy panel	Arrhythmogenic right ventricular cardiomyopathy/ dysplasia Heterozygous *PKP2*, p.Arg735Ter
		Channelopathy				

Figure 1 : Simplified approach to genetic diagnosis on abnormal echocardiography



References

1. Musunuru K, Hershberger RE, Day SM, Klinedinst NJ, Landstrom AP, Parikh VN, Prakash S, Semsarian C, Sturm AC; American Heart Association Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. 2020 Aug;13(4):e000067.
2. Payne K, Gavan SP, Wright SJ, Thompson AJ. Cost-effectiveness analyses of genetic and genomic diagnostic tests. Nat Rev Genet. 2018 Apr;19(4):235-246. doi: 10.1038/nrg.2017.108. Epub 2018 Jan 22. PMID: 29353875.
3. Courtney L. Scherr, Kerstin Kalke, Sanjana Ramesh, Hoda Fakhari, Lisa M. Dellefave-Castillo, Maureen E. Smith, Callie Kalny, Elizabeth M. McNally, Laura J. Rasmussen-Torvik, Integrating clinical genetics in cardiology: Current practices and recommendations for education, Genetics in Medicine, Volume 24, Issue 5, 2022, Pages 1054-1061, ISSN 1098-3600, https://doi.org/10.1016/j.gim.2022.02.003.
4. Hathaway, J., Heliö, K., Saarinen, I. *et al*. Diagnostic yield of genetic testing in a heterogeneous cohort of 1376 HCM patients. *BMC Cardiovasc Disord* **21**, 126 (2021). https://doi.org/10.1186/s12872-021-01927-5
5. Ahmad F, McNally EM, Ackerman MJ, Baty LC, Day SM, Kullo IJ, Madueme PC, Maron MS, Martinez MW, Salberg L, Taylor MR, Wilcox JE. Establishment of Specialized Clinical Cardiovascular Genetics Programs: Recognizing the Need and Meeting Standards: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. 2019 Jun;12(6):e000054. doi: 10.1161/HCG.0000000000000054. Epub 2019 May 23. PMID: 31117808.
6. Chaix MA, Andelfinger G, Khairy P. Genetic testing in congenital heart disease: A clinical approach. World J Cardiol. 2016 Feb 26;8(2):180-91. doi: 10.4330/wjc.v8.i2.180. PMID: 26981213; PMCID: PMC4766268.
7. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic evaluation of cardiomyopathy: a Heart Failure Society of America practice guideline.J Card Fail. 2018; 24:281–302. doi: 10.1016/j.cardfail.2018.03.004