“A STUDY TO ESTIMATE THE PREVALENCE, RISK FACTORS AND NKX2-5 GENE CORRELATION OF CONGENITAL HEART DISEASES IN KANPUR AND PERIPHERY”

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Abstract

Congenital Heart Diseases (CHD) are structural anomalies of the heart arising from abnormal formation of the heart or major blood vessels. At least 18 distinct types of congenital heart defects are recognized, with many additional anatomic variations. These structural defects are the result of abnormal embryonic heart development and can be anatomically classified into abnormalities of the septa, the heart valves, and inflow or outflow tract of the heart. These structural defects most often have functional consequences, but of varying degree and significance. Some structural defects do not have important functional significance in early life such as the aortic valve with two leaflets, the prolapsing mitral valve, a small persistent patency of the arterial duct, small septal defects and patency of the oval foramen.²

The common defects are classified according to: a) side of the affected heart, b) communication or short circuit between both hearts chambers and c) Presence or absence of cyanosis.⁷ According to the Merck manual of Diagnosis the first eight CHDs are the common lesions, which account for 85% of all cases and the remaining (15%) account for variety of rare and complex CHDs

The environmental and genetic risk factors may play a key role in congestive heart diseases. They include having rubella during pregnancy, pregestational diabetes, Certain medications taken during pregnancy like( thalidomide, angiotensin-converting enzyme (ACE) inhibitors, statins, the acne medication isotretinoin and lithium),smoking, Drinking alcohol during pregnancy, and Heredity.

The NKX2-5 gene on chromosome 5q34 consists of two exons which encode a 324 amino acid protein. This homeobox transcription factor is expressed during early cardiac morphogenesis and serves as a master regulatory protein. Because of its critical role in cardiogenesis, NKX2-5 has
been a prime candidate in studies to identify the genetic basis of structural Congenital Heart Defects.\(^\text{15}\)

CSX/ NKX2.5 the earliest molecule marker of the cardiac lineage is NKX2.5 in vertebrates. It is one of the members of NK2 family of homeobox genes and a homolog of the Drosophila tinman. It has highly conserved regions of DNA binding, protein-protein interactions, nuclear translocation, and regulation of other transcription factors. Their homeodomains have a tyrosine at position 54, making it the most unambiguous feature of this class and is a useful classification tool. Homeobox genes have been found to play a crucial role in regulating tissue specific gene expression. Mutations in this gene have been reported to cause ASD, VSD with atrial ventricular block, TOF and Tricuspid valve abnormalities.

NKX2-5 mutations display diverse cardiac abnormalities that include septal defects, conotruncal malformations, hypoplastic left heart, dilated cardiomyopathy, and atrioventricular conduction block.\(^\text{17}\) Most reported NKX2-5 mutations were in the homeodomain, a critical part of the protein that interacts with deoxyribonucleic acid (DNA), and were typically associated with cardiac conduction anomalies.

Kathy J. Jenkins et al.,\(^\text{41}\) 2007 states that periconceptional multivitamin or folic acid intake, which may reduce the risk of cardiac disease in the fetus, and for additional types of potential exposures that may increase the risk, including maternal illnesses, maternal therapeutic and nontherapeutic drug exposures, environmental exposures, and paternal exposures. Information is highlighted regarding definitive risk factors such as maternal rubella; phenylketonuria; pregestational diabetes; exposure to thalidomide, vitamin A cogeners, or retinoids; and indomethacin cotocolysis.

Kapoor R, et al.,\(^\text{14}\) 2008 states that to study the prevalence, age-wise distribution, and clinical spectrum of congenital heart disease (CHD) at a multi-specialty corporate hospital in North India, Kanpur. A retrospective analysis of records of 10,641 patients over a five-and-a-half years. Clinical examination, echocardiography and color Doppler were used as diagnostic tools.\(^\text{14}\) A prevalence of 26.4 per 1000 patients was observed. VSD (ventricular septal defect) was the
commonest lesion (21.3%), followed by ASD (atrial septal defect) in 18.9% and PDA (patent ductus arteriosus) in 14.6%. Tetralogy of Fallot was the commonest cyanotic heart disease (4.6%). Maximum number of children with heart disease (82.9%) was diagnosed between 0-3 years of age.

Denise van der Linde et al., 40 2011, states that total CHD birth prevalence increased substantially over the last century, reaching a stable estimate of 9 per 1,000 live births in the last 15 years. This corresponds to 1.35 million newborns with CHD every year, representing a major global health problem. Significant geographical differences were found. It remains uncertain whether detected differences in CHD birth prevalence represent true or merely methodological differences. In the future, the etiology of CHD needs to be further clarified and population wide prospective birth defect registries covering the entire world population are needed to determine the exact birth prevalence.

Ritu Bhardwaj et al., 4 2014 states that the incidence of CHD varies with the age group studied. Although the majority of CHDs were diagnosed within the first few weeks of life, nearly one-third of CHDs were detected after the first birthday. This study not only covered the pediatric population but also adults (>18 years) with congenital heart defects, the latter category consisting of 83 out of 661 patients (12% of the cases), with a prevalence of 2.4/1000 adult CHDs in the population. In addition to this, in 6% of cases, ASD and VSD were present simultaneously, and in 6% of cases, VSD was present in combination with a variety of other cardiac defects (PS, PDA, PFO, and BAV), showing a very high occurrence rate of this lesion. Out of 220 VSD cases, 64% were detected in patients in the 0–5-year age group, 17% in patients of 6–10 years, 12% in patients 11–17 years, and 5% in adults. Advanced maternal age and multiple pregnancies are believed to be associated with perimembranous and muscular VSD; however, such a correlation could not be identified in the present cohort. ASD was the second most frequent CHD (19%), followed by TOF (16%). The ostium secundum type of ASD was the most predominant one.

IM Chung and Govindasamy Rajakumar., 46 2016, states that cardio genesis is a complicated process, comprising of numerous intricate pathways, where NKX2-5 plays a pivotal role.
Aberrations in the NKX2-5 transcription factor have been reported in various types of congenital heart defects and are spread across various domains on the gene. Functional studies have shed light on the mechanism of action of these mutations but more analysis will be needed to understand the entire picture of cardiac malformation.

**Methodology**

The study will be carried out in Central Research Laboratory, Rama Medical College, Rama University, Kanpur, U.P, India. The ethical clearance will be obtained from the Institute Ethical Committee (IEC).

**Patient Selection**

Total 200 cases of CHD will be taken from Rama Medical College, Rama University, Kanpur, U.P, during the period of 2018 to 2019. The consent of the patients and their parents will be taken.

**Data Collection**

The common parameters like age, sex and stage of heart disease will be taken. The age at the time of diagnosis of heart defects will be recorded. All cases will be thoroughly examined by chest x-ray, electrocardiogram, and 2D echocardiography. Family history of any heart abnormality, history of multiple abortions, nutrition and drug intake, any other pathophysiological conditions, and parity status of mother will be recorded for analysis. Age of below 5 years is included in this study. The normal children of equivalent age group will be taken as control. Parents are also to be investigated wherever possible.

**Inclusion criteria.**

1. Below 5 years of age groups are included in this study.

2. Only Kanpur and peripheral region CHD cases are included in this study.

**Exclusion criteria**

1. Age more than 5 years is excluded.

2. If there is no data on history of mother it will be excluded.

**Investigations:** Echocardiogram, Electrocardiogram, Chest X-ray and BMI
Blood investigations: GTT

Genetic findings: Molecular NKX2-5 Gene studies in Congenital Heart Diseases by Conventional PCR.

What are some of the future directions which research could heavily influence? In many surgical repairs, from the newborn period to adulthood, somatic growth of the heart and vessels parallel to that of the patient must be taken into consideration. Prosthetic materials and implants are willingly avoided, with preference given to biological ones. While autologous tissue from the patient itself is the ideal material, having the advantages of being living tissue, thereby allowing for somatic growth, resisting infection, not requiring anticoagulation, and not inducing any rejection phenomenon, it is not always available in the appropriate amount or shape. The extant research and results of tissue engineering, using various combinations of biological scaffolds seeded with autologous stem or mature cells are most promising, but still have a ways to go. Although various living bio-engineered tissues have been produced and shown to function in vitro and in vivo, either in the myocardium, as valve substitutes, or as patch material, they have to date failed to endure the mechanical wear and tear of time, and therefore still need to stand the ultimate test of acceptable longevity. Furthermore, time constraints pertinent to harvesting cells from a given patient, treating and culturing them in vitro and seeding onto a scaffold which will eventually result in a functioning tissue ready for implantation back into the patient itself, make the current bio-engineered tissues unpractical, or definitely not a “real time” alternative. Ideally, such autologous bio-materials should instantly be “ready to use” in an off-the-shelf, custom-made, tailored-to-the-patient’s-size manner, which will hopefully be achieved through technological advances in the near future.

As the various intricate and delicate stages of embryogenesis of the heart are better defined and understood, so also has advanced the bold strategy to intervene and hopefully influence certain critical key structures and blood flow patterns in the developing heart. Intrauterine intervention, either by percutaneous/trans-uterinal catheter balloon dilatation or by open surgical technique, has been successfully performed, most notably on the aortic valve, in fetuses with aortic valve stenosis, hypoplasia or atresia and variants of hypoplastic left heart syndrome. The risk-benefit ratio should take into consideration treating two patients, the mother and the fetus, since both of
the patients could potentially suffer, and only one (the fetus) benefits. Whether in-utero treatment techniques can reliably result in favour of both mother and fetus remains to be demonstrated, which is why only a few highly specialized centers are undertaking it with promising results.

Accurately tracking congenital heart defects (CHDs) is the first step in preventing them and reducing their effect. Information from tracking systems provides a basis for research. Below is a summary of CDC’s CHD tracking and research work.

In conclusion, the field of care for congenital heart defects has made tremendous strides in its young infancy. In no other field of science or medicine has so much been accomplished in so little time, with heart defects that were an unconditional death sentence 60 years ago, to the current operative survival rates of more than 96% for all defects considered together. We must give tribute to bold pioneers in the early days of the 1940’s and 1950’s for taking the biggest steps, with further refinements in the 1970’s and 1980’s to reach the point where we are today. However, for certain defects, we are only scratching the surface, and short-term as well as long-term outcomes are still unsatisfactory. Owing to huge advances in perinatal care, increasingly premature babies with complex syndromes involving multiple organs are no longer subject to “natural selection” and are surviving, bringing with them an array of cardiac and associated non-cardiac malformations that confound not only cardio-pulmonary physiology, but require a more holistic approach to patient care. Furthermore, although surviving an operation or intervention for a congenital heart condition is now expected for the vast majority of patients as neonates and infants, the focus is shifting towards quality of life, long-term issues, and treatment/care algorithms for adults having survived their initial hurdles, who now represent the majority of patients with CHD, a new fast-growing population. Much collaboration, vision and innovation is still needed to tackle and understand congenital heart defects, giving providers who are privileged to be involved in the care of these patients and families challenges for many decades to come.

Key words: CHD, Prevalence, NKX2-5 Gene,