Intrinsic and Extrinsic Factors of Congenital Heart Disease

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Intrinsic factors which cause congenital heart disease (CHD) are genetic in origin. In other words, they are spontaneous alterations in D.N.A. (Deoxyribonucleic Acid), and may be classified as either Quantitative or Qualitative. Quantitative may be defined as an abnormal quantity of genetic material or, as noted below, chromosomal aberrations. Qualitative is an abnormal quality of genetic encoding as it pertains to a particular gene.

CHROMOSOMAL ABERRATIONS

Chromosomal aberrations, which cause from 2–6% of all congenital heart disease, appear as an aberrant gene either of the autosomes or of the sex chromosomes.

In 1956, Tijo and Levan determined the normal human chromosome number as 46. In this number each single set of 23 chromosomes are maternal or fraternal in origin. Thus one set of 23 genes is contributed by the mother along with another set of 23 genes from the father. The resulting 23 pairs of genes are referred to as Haploid pairs. A trisomy syndrome is the presence of an additional (third) chromosome of one type in an otherwise diploid cell. Speculation of how many malformed offsprings could survive the 9 month gestation is difficult to imagine since fetal imperfections are usually aborted, and only a relatively small percentage of trisomy syndromes are seen.

There are three known trisomy syndromes: trisomy 13-15, 18, 21. Trisomy 13-15 which occupies the D group of chromosomes has a low perinatal and postnatal survival rate. A mortality rate exceeding 88% for the first year of life is primarily due to various complex malformations involving cardiac, intestinal, and nervous systems. Abnormalities of cardiac development include transpositions, dextrocardia, V.S.D., pulmonic stenosis, and bicuspid aortic valve.

Trisomy 18, first described by Edwards in 1960, has a higher mortality rate than trisomy 13-15; a one year mortality of 96% was reported in one series. Again, complexity of systemic and cardiac malformations are the cause(s). Cardiac malformations include V.S.D., dextroposition, malformed pulmonic and aortic valves, and patent ductus arteriosus.

Trisomy 21 or Down's syndrome has the greatest chance of long term survival, primarily due to the decrease in systemic malformations. Death in the first decade of life is usually due to cardiac malformations of which Atrioventricularis Communis seems to be the most lethal. A-V canal is an endocardial cushion defect which is manifested by an ostium primum A.S.D., cleft mitral and tricuspid valve and a high V.S.D.
INTRINSIC FACTORS

Quantitative:
Trisomy Syndromes
13,15
18 Edwards Syndrome
21 Downs Syndrome
Chromosomal Deletions
4-5 "Cri du Chat"
(XY) Turner's Phenotype
Turner's Mosaics

Qualitative:
Recessive and Dominant (Mendelian)
Inheritance

Figure 1. This table shows relationship between the quantitative and qualitative factors of the intrinsic mechanism of congenital heart disease.

Down’s syndrome has also been noted as a byproduct of a partial chromosomal trisomy.\textsuperscript{14} Autosomal translocation of the long arm of a G group autosome onto a D group autosome results in defects having characteristics of Down’s syndrome. Other translocations of genes from one group of autosomes to another group of autosomes seem to mimic the Down’s syndrome profile. Only Karyotyping of the surviving child’s chromosomes can distinguish the trisomy syndromes from the translocation syndromes.\textsuperscript{14}

Chromosomal deletions can be defined as complete elimination of an arm of an autosome. “Cri du chat” or cry of the cat syndrome is an example of a deletion of the short arm of the B group (4-5) autosomes. This syndrome is characterized by a cat-like cry and physical and mental subnormalities. In a series of studies by McCraken,\textsuperscript{17} seven patients were studied with 2 having cardiac malformations.

Turner’s syndrome or deletion of one sex chromosome is usually associated with gonadal dysgenesis, webbing of the neck, and short stature. Since the X chromosome is present, the child will be a female usually without the ability to achieve secondary sexual maturity due to ovarian dysgenesis. A male Turner phenotype is also known although normal XY sex chromosome pairs are present. This syndrome is due to a recessive sex-linked mutant gene similar to the traits of a missing Y chromosome. Bonnevie-Ullrich syndrome is interpreted as a Turner phenotype with normal sexual chromosome pairing and normal gonadal function but with secondary Turner syndrome characteristics. These are said to be Turner mosaics (XY/XX) syndromes.\textsuperscript{18} Cardiac anomalies in the deletion group include a predominance of coarctation and cardiac hypertrophic myopathies.\textsuperscript{19}
SINGLE GENE MUTATIONS

Single gene mutation is the term given to inherited traits and are accomplished through Mendelian recessive and dominant inheritance. A substantial number of inherited syndromes are attributed to these mutations but are still classified in the percentage of 2–6% of all CHD cited earlier. To simplify the categories of inherited syndromes, the diseases are classified according to area of pathogenic cause, after Doyle and Rutowski.

Recessive and dominant inheritance, simplified for discussion, states that traits whether normal or abnormal, are passed via genetic encoding on the chromosomes. Recessive inheritance is a passive condition that can only manifest its traits if another gene carries the same trait. As an antithesis to recessive inheritance, dominant inheritance can manifest itself without another gene present. This is a simplified definition of recessive-dominant inheritance. As may be seen most inherited syndromes are recessive in nature although sex-linked recessive syndromes may be dominant in one sex and not in the other.

Disorders of metabolism or derangements that occur as metabolic syndromes are inherited mostly as a recessive trait. The determinants are usually the absence or low concentration of a specific enzyme. This deficiency increases the accumulation of a specific metabolite which eventually leads to abnormal organ function to some degree. There are five disorders of metabolism that cause cardiac malformations: (a) Carbohydrate metabolism, (b) Protein metabolism, (c) Amino acid metabolism, (d) Lipid metabolism, and (e) Purine metabolism.

Carbohydrate metabolism is a glycogen storage disease of which there are five principle diseases: Pompe’s, Coni’s, Anderson’s, McAndle’s, and Her’s. Of the five listed, only Her’s is autosomal dominant. Pompe’s disease is the most well known of the glycogen storage diseases since it affects the heart directly, and is usually immediately recognized by its cardiac manifestations. Cardiomyopathy is the common symptom for glycogen storage diseases, but muscle deposition of glycogen in the extremities is also very common.

Polysaccharide storage disease is a relatively seldom identified disease since it mimics glycogen storage disease in that it allows abnormal deposits of polysaccharide to accumulate in cardiac tissue. This disease can be autosomal recessive or dominant.

Mucopolysaccharidoses is usually detected by abnormal urinary excretion of mucopolysaccharides. Of the reported diseases in this category, Hurler’s and Hunter’s syndromes are the most well known since they have similar clinical manifestations. Although they are autosomal recessive, Hunter’s is X-linked recessive which incurs selective importance hereditarily. The most common cardiac manifestations are depositions of material into the myocardium and the intimal areas of vessels. Myocardial myopathy and diffuse arterial aneurysms are the most frequent cause of death.

Protein metabolism, a condition that has two sub-groups: Amyloidosis and primary hyperoxaluria, both have autosomal recessive inheritance. Cardiac amyloidosis accounts for 5 to 10% of non-coronary cardiomyopathy, whereas primary hyperoxaluria is uncommon but is the cause of calcium oxalate crystals in the urine and tissues. Primary hyperoxaluria causes disorders of electrical conduction in the heart.
Amino acid metabolism of which alkaptonuria and homocystinuria are autosomal recessive. Dark urine is featured in alkaptonuria and involvement of mitral and aortic valve is common; left ventricular aneurysms have also been reported. Homocystinuria simulates Marfan's syndrome in clinical manifestations, but its cause is due to increased amounts of homocystine in the urine.

Lipid metabolism is a complex entity caused by abnormal metabolism of Spingolipids or beta lipoproteins. These lipid abnormalities are numerous and are thought to be autosomal recessive. The major clinical manifestations seem to be due to abnormal lipoprotein depositions in major vessels and cardiac valves; severe atheromatous plaques can result due, primarily, to excessive amounts of serum lipoproteins.

Purine metabolism, otherwise known as hyperuricemia (gout), causes urate deposits in coronary arteries and pericardium. Usually symptoms will be due to uric arthritis and will sometimes occur in conjunction with atherosclerosis. Genetically hyperuricemia is a recessive autosomal trait.

Connective tissue disorders that are not caused by mucopolysaccharidosis, but nevertheless are common autosomal traits in man include Marfan's, Pseudoxanthoma elasticum, and Ehler's Danlos syndromes which manifest their symptoms usually at the vascular level. Marfan's which is autosomal dominant is characterized by media hypoplasia causing aneurysm of the aorta and aortic valvular insufficiency. Pseudoxanthoma elasticum is an elastic fiber defect and usually causes medial thickening and, ultimately, hypertensive cardiovascular disease. Pseudoxanthoma elasticum is a recessive autosomal genetic trait. Ehler's Danlos syndrome is a collagen fiber defect, causes aortic aneurysm, and is a dominant autosomal disease.

CONDUCTIVE DEFECTS

Inherited rhythm disturbances such as Wolff-Parkinson-White syndrome and those caused by neuromuscular diseases are important when the affliction is a primary or secondary symptom of the existing disease state. Neuromuscular syndromes in which ECG disturbances are noticed are manifested usually secondary to the general neuropathies that are present.

The muscular dystrophies, of which Duchenne's disease is the most familiar, causes general muscle weakness of the skeletal myofibrils. This dominant X-linked trait will have manifestations of cardiac muscular atrophy and fibrosis of the myocardium. These are usually latent symptoms of the disease.

Friedreich's ataxia produces in the afflicted patient a lack of muscular coordination and can be autosomal dominant or recessive. Again, conduction disturbances are manifested late in the disease and are secondary to the general neuropathy.

Myotonia dystrophica is an autosomal dominant trait that appears relatively late in life. The conduction defect that occurs is usually a first degree A-V block.

Mentioned earlier, Wolff-Parkinson-White syndrome is a primary electrical conduction defect in which late studies seem to indicate an extra muscle bundle (Bundle of Kent) between the atria and the ventricle causing little or no delay across the A-V node. This pre-excitation syndrome is either recessive or dominant inherited.
EXTRINSIC FACTORS

Physical
Inadequate response of tissues in development to septate, rotate, etc., due to malnutrition Anemia, or other Maternal “host” diseases

Chemical

<table>
<thead>
<tr>
<th>teratogenic agents</th>
<th>Fall into criteria for Multifactorial Inheritance theory as teratogens</th>
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<tr>
<td>thalidomide</td>
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<tr>
<td>trypan blue</td>
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<tr>
<td>dextroamphetamine</td>
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<td>ethyl alcohol</td>
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<td>cigarettes</td>
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Biological
Rubella
Herpes Virus
enteroviruses (Coxsackie)

Figure 2. This table indicates the three important factors that can cause congenital heart disease through the extrinsic method and lists the possible teratogenic agents.

EXTRINSIC CAUSES OF CONGENITAL HEART DISEASE

Extrinsic factors that cause maldevelopment can be classified according to their natural occurring modality. These factors are physical, chemical and biological, and affect cells which are in the process of differentiation, either as a direct cause or indirectly, using the model of multifactorial inheritance.

Multifactorial inheritance can be defined as a “genetic predisposition caused by many genes, and there is usually an important interaction with an environmental influence—a genetic environmental interaction.” A correlation between intrinsic (single gene mutations) and extrinsic causes (physical, chemical, biological) are interrelated when the multifactorial hypothesis is applied. For example, if a genetic encoding of an Atrial Septal Defect is apparent in a family’s genetic structure, but the defect is not passed with great frequency to offspring, the family is said to be predisposed to congenital heart disease. If by chance the mother is exposed to a teratogen in a vulnerable period of fetal development, to either delay or make deficiencies of material, the threshold of malformation is reached and a defect can result. In Nora’s theory, his example uses dextroamphetamine as the teratogen (environmental trigger) to cause the malformation to occur.

Teratogens that cause congenital heart disease have only recently been investigated prompted somewhat by the thalidomide controversy a decade ago. The discovery of this chemical teratogen stimulated research into other drugs and biological agents and their possible effect on cardiovascular malformations.

Viral agents such as Rubella, Herpes virus, and enteroviruses of Coxsackie virus are reported to cause congenital heart disease if the mother contracts them within
the first trimester. The mode of infection is, of course, in utero, usually passing across
the placenta or, in the case of Herpes, it can be contracted in the vagina at birth or in
utero.\textsuperscript{34} The most common cardiovascular anomalies that occur are patent ductus arte-
riosus\textsuperscript{34} and atrial septal defects.\textsuperscript{35,36}

Chemical agents. As mentioned earlier, thalidomide is a chemical teratogen and
has been indicated as a cause for cardiac maldevelopment. Other chemical agents are
trypan blue,\textsuperscript{31} dextroamphetamine,\textsuperscript{4,29} ethyl alcohol,\textsuperscript{37} and cigarettes.\textsuperscript{38-40} Trypan blue,
cited in the late 1940's,\textsuperscript{31} can cause cardiac maldevelopment. This would seem to be
consistent with multifactorial inheritance theory. Ethyl alcohol has been identified as
a teratogen that in one study caused cardiac anomalies in 50% of the offspring.\textsuperscript{37} Most
anomalies are patent ductus arteriosus and simple A.S.D.'s.

Teratogenicity of cigarettes in three studies\textsuperscript{38-40} elicited the theory that they possibly
cause congenital heart disease. But further epidemiological studies need to be undertaken
before conclusions can be established. This would be consistent with multifactorial in-
heritance hypothesis unless a specific chemical could be the direct causative factor.

MISCELLANEOUS FACTORS

Radiation and cancer chemotherapeutic agents have been identified as possible
causes of congenital cardiac malformations.\textsuperscript{41,42} In one study, an exhaustive survey of
861 mothers and their offspring showed a slight increase in the general population. These
patients were subjected to routine radiological procedures. But conclusive testing of ra-
diation causing increased congenital morbidity cannot be realized since other possible
teratogens could not be eliminated. In another study, a woman who had Hodgkins disease
was started on a regimen of cyclophosphamide and later, radiation therapy. The fetus
was still born at 6 months gestational age with a single coronary artery. Although the
radiation therapy, in itself, cannot be cited as a direct cause of CHD, it is suspected as
being a teratogen when compared to other studies.\textsuperscript{43}

SUMMARY

Congenital heart disease has two distinct pathways: intrinsic, which includes
chromosomal aberrations, recessive and dominant (Mendelian) inheritance, and extrinsic,
physical, chemical and biological environmental factors. The theory of multifactorial
inheritance can show a correlation of the two pathways via the genetic environmental
interaction.

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