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Recommended Citation
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol17/iss2/5

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Etiology of Congenital Heart Disease

Jami G. Shakibi, M.D.

Research on the etiology of congenital heart disease (CHD) has a direct bearing on its prevention and treatment. To appreciate the importance of this, consider that the incidence of CHD in the U.S. and U.K. is around 0.5% of all births (varying from 3 to 9/1000 according to different authors). According to these statistics each year in the U.S. more than 20,000 babies are born with CHD. In the North American continent over 50% of all heart disease in children is due to CHD. Congenital malformations of the circulatory system account for roughly half of the mortality from all congenital malformations.

In discussing the etiological factors in the genesis of CHD, the possible causative factors may be divided into two major groups: One consisting of CHD occurring in the genetically distinct syndromes, and the other group consisting of poorly understood but probably hereditary types. As yet, no chromosomal defect has been convincingly identified as producing isolated cardiac defect. In most instances the cause remains unknown.

The first group consists of such well-known chromosomal aberrations as Down’s syndrome, Turner’s syndrome, cri-du-chat syndrome and others.

In a discussion of the etiology of congenital heart disease, Rainier-Pope stated that although Down (who first described the syndrome named after him) did not mention the presence of CHD in his patient, we know that this syndrome is frequently associated with CHD. No specific anomaly is associated with Down’s syndrome, though endocardial cushion defect, ostium primum, atrial septal defect (ASD) and abnormalities of the tricuspid valves are frequent. Transposition of the great vessels, infantile coarctation of the aorta and dextrocardia apparently are very rare.
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Trisomy 13-15 as well as trisomy 18 are frequently associated with CHD. Warkany et al reported that the major and the most common cardiac defect in these trisomies are ventricular septal defect (VSD) and patent ductus arteriosus (PDA). Trisomy 13-15 is more frequently associated with ASD, whereas it is comparatively rare in trisomy 18. Trisomy 18 is more frequently associated with VSD and some degree of aortic dextroposition, coarctation of the aorta and hypoplastic left ventricle.

The cri-du-chat syndrome, which is due to a deletion of the short arm of chromosome 5, is frequently associated with CHD. Defects have been noticed in nine of 33 cases.

Turner's syndrome is frequently associated with CHD, the most frequent varieties being coarctation of the aorta, pulmonic stenosis, VSD, ASD and PDA. In large series it has been shown to be associated with CHD in 44% of cases.

The majority of patients with Noonan's syndrome have CHD involving the right side of the heart, particularly pulmonary arterial stenosis or peripheral pulmonary arterial stenosis. This is in contradistinction to the Turner's syndrome which is more frequently associated with the lesions of the left side of the heart, e.g. coarctation of the aorta or aortic stenosis of valvular and subaortic type.

If the classical aberrations of chromosomes are included, chromosomal abnormalities as a cause of CHD may be estimated at between 3 to 5%.

A number of chromosomal abnormalities, such as Klinefelter's and the triple X syndrome, are not associated with heart abnormalities.

2. Hereditary conditions without obvious chromosomal abnormalities.

Marfan's syndrome, Hurler’s and Kartagener's syndromes are associated with CHD; however, there are no obvious chromosomal abnormalities, at least with the present methods, in these conditions.

3. Congenital heart disease with hereditary tendency.

In a review of literature on this subject Higgins concluded that familial aggregation of cases of CHD seems to be established, with frequency higher in siblings of those afflicted than in the general population. Also, it appears to vary with the type of malformation.

One example of a heart disease which shows a pattern of hereditary transmission is ASD which may follow an autosomal dominant type of transmission. There are also cases of isolated families with conduction defects and arrhythmias. A syndrome of conduction defect as well as generalized lentigo has been described recently.

Although the sex ratio in CHD does not differ from expectation, certain malformations such as aortic stenosis, coarctation and tetralogy of Fallot are more common in males, and others like PDA and ASD are more common in females.

Consanguinity does not seem to be an important factor, although there are suggestions that the incidence of consanguinity is highest in pulmonary valvular stenosis and ASD.

Environmental Factors in the Genesis of CHD

1. Viruses as etiological factor.

Except for rubella and Coxsackie viruses, investigators have failed to es-
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establish any cause and effect relationship between viral infections and CHD.

There is a 15% incidence of major defects after rubella in the first trimester of pregnancy; however, the figures on congenital anomalies in offspring of these mothers have ranged from 12 to 90%. Campbell found a distribution of lesions as follows: PDA—58%; VSD—17%; tetralogy of Fallot—7%; ASD—6%; pulmonic valvular stenosis—6%; and miscellaneous—4%. Peripheral pulmonary artery stenosis due to maternal rubella syndrome is a well-known entity.

Campbell concluded that maternal rubella is responsible for less than 2% of cases of CHD. Myocardial damage as evidenced by the presence of ECG abnormalities, congestive heart failure, myocardial necrosis and fragmentation of myocardial fibers has also been reported in cases of maternal rubella syndrome, as has pulmonary valvular insufficiency secondary to rubella embryopathy.

Coxsackie viruses have been suggested as possible causative agents in the development of CHD. Brown et al reported that Coxsackie virus B type 3 and 4 were most frequently associated with malformed infants. Most infections had occurred during the first trimester of pregnancy and the congenital anomalies observed were PDA, VSD, ASD, aortic stenosis and atresia. Mumps virus infection during pregnancy has been claimed to be important in the etiology of endocardial fibroelastosis. This has not been confirmed by other workers. Higgins states that despite the predominantly negative results, further studies would seem indicated on the relation of virus infections to the development of CHD.

2. Teratogenic agents in the etiology of CHD.

In addition to viruses, innumerable agents can cause congenital abnormalities if administered under special circumstances. Some essential points in teratology have recently been discussed by Brent. Among the teratogenic agents one should mention ionizing radiations, vitamin A deficiency and excess, vitamin D excess, endocrine preparations such as steroids and antithyroid drugs, cytotoxic drugs, thalidomide, antibiotics, sulphonamides, and other drugs like dexamethasone, and salicylates. The present discussion will center on those drugs or agents which have been proven to cause CHD under controlled conditions.

1) X-ray as an etiological agent in CHD.

Wilson produced situs inversus and common atrioventricular canal in rats who had been subjected to irradiation on the ninth day of pregnancy.

2) Hypoxia and hypercapnia as etiological agents in CHD.

This was first reported by Alzamora who demonstrated that the incidence of PDA is 18 times more common in the infants born in regions 4500-5000 meters above the sea level than in those born at the sea level. This study was done in Peru.

However, this finding has not been confirmed. Despite this, the teratogenic effect of hypoxia and its relation with CHD in animals seems to be more convincing. Baird studied by microdissection the hearts of rats conceived and reared at high altitude and found cases of PDA and VSD in his animals. Later Haring studied the effect of hypoxia on pregnant rats and produced 5.4% CHD in the experimental ani-
mals vs 3.2% in the normal control group. Another study by Clemmer et al confirms this result. Combined hypoxia and hypercapnia seems to be far more important in the genesis of CHD than hypoxia alone. Haring's experiment on rats subjected to these agents produced 28.1% CHD, compared with 4.5% in the normal control animals. Thus it seems that, in animals at least, hypercapnia can produce CHD when applied at the proper time during pregnancy.

3) Steroids as etiological agent in CHD.

Cortisone is a well-established teratogenic agent in animals and also probably in man. Investigations of its effect on the development of CHD are few. Clavert et al produced ASD, VSD and other abnormalities by injection of dexamethasone phosphate in rabbits during pregnancy.

4) Thalidomide as an etiologic agent in CHD.

Besides other abnormalities in man, thalidomide has produced CHD such as hypoplasia of aorta, ASD and VSD, transposition of the great vessels, tetralogy of Fallot and pulmonary stenosis. A syndrome of anotia or microtia, facial palsy and CHD (but without phocomelia) has also been reported—due to thalidomide ingestion during pregnancy.

5) Anticonvulsants as etiologic agents in CHD.

Anticonvulsant drugs such as primidone, phenytoin, toxidone and phenobarbital are among possible teratogenic agents. This effect is suspected to be secondary to folic acid deficiency produced by these drugs. Hydantoin and phenobarbital have been held responsible for the production of the sporadic cases of Holt-Oram (digitocardiac) syndrome.

6) Azo dyes as etiologic agents in CHD.

Azo dyes (Trypan blue) have been extensively studied because of their teratogenic effects. The varied CHD thus produced are out of the scope of this article. It is of interest, however, that trypan blue exerts its effects both by systemic and local application.

7) Miscellaneous factors.

Isolated reports in the literature allude to the possible effect of pesticides in the genesis of CHD. Dexamphetamine sulfate, a drug usually taken during pregnancy to suppress appetite, has been incriminated. Experimental production of CHD in mice has been very successful by intraperitoneal injection of this drug. However, the dose administered to the mice was far beyond the usual therapeutic dose. Investigating the effect of high temperature on the development of CHD in chick embryos, De la Cruz thought that the teratogenic effects of viral infections was secondary to fever. Their investigation showed, however, that high temperature does not produce CHD in chicks—but incubation of eggs at low temperature produced a 21.8% incidence of CHD, mostly high membranous VSD.

The study of teratogenic agents in relation to CHD is extremely important if one considers that maternal exposure to potential teratogens is very common. Nora et al reported that in their survey of 240 mothers, each mother had been exposed to 3.7 teratogenic agents.
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(3.1 drugs per mother) during the first trimester of pregnancy. Comparative studies of CHD in animals can elucidate the pathogenesis of CHD in man. Although extrapolation of the results is not easy, it has important bearing on our understanding of the pathogenesis of the disease.

ACKNOWLEDGMENT

The author wishes to thank Dr. R. F. Ziegler and Dr. Lester Weiss for their advice.

REFERENCES


