

SOME EPIDEMIOLOGICAL AND GENETIC ASPECTS OF CONGENITAL HEART DISEASES *

N. FREIRE-MAIA

Department of Genetics, Federal University of Paraná, Brazil

This paper presents a general view on congenital malformations and a summary of some anatomic, clinical, epidemiological and genetic aspects of congenital heart diseases. Some "recommendations" for research are also briefly mentioned.

INTRODUCTION: CONGENITAL MALFORMATIONS

Congenital malformations (CM) form a large and heterogeneous array of defects as regards form, size, position, number, etc., of one or more parts. They are capable of being ascertained macroscopically at birth or are derived from some congenital morphological deviation that, because of being discrete, could not be verified at that time. Therefore, excluded from CM are metabolic disturbances, microscopic anomalies, genetic diseases with morphological signs secondary to them, etc. On the other hand, "congenital" heart diseases (CHD), which are only diagnosed later or during the patient's life, may be included among CM. Ductus arteriosus (present in every newborn child and naturally "repaired" with time) and ectopic testicles should not be incorporated, for obvious reasons, into CM, unless their natural correction does not occur. Pyloric stenosis may, however, be considered a CM in spite of not being generally diagnosed strictly at birth.

The incidence figures of CM vary largely according to a number of factors: definition of CM, time in which examinations are made, competence and interest of the physicians in charge of the examinations, etc. Figures as low as 0.3% and as high as 13% are mentioned in the literature, for livebirths. Among stillborn children, even 23% of CM have already been found. Generally, CM have been detected with frequencies between 1% and 5% among livebirths, all depending on the above-mentioned concomitant variables. With regard to the most severe CM, the range may be approximately 1-2%.

The total frequency of CM is about the same in different countries, ethnic groups, social levels, etc., but individual CM may vary from one place to another. For instance, polydactyly is more prevalent among Negroid, palatolabial defects are rare among Mongoloid, spina bifida and anencephaly seem to be more frequent among Caucasoid people, etc.

* This paper includes "The epidemiology of congenital cardiovascular malformations", *Human Hered.*, 21: 209-215, by N. Freire-Maia and B. Arce-Gomez (1971). Its present form has been written mostly at the World Health Organization, where the author stayed as a consultant during a few months, in 1972. Our Department of Genetics receives grants from the *Conselho Nacional de Pesquisas*, the World Health Organization, CAPES, the Bamerindus Foundation and the *Conselho de Ensino e Pesquisas da UFPr*.

Etiological heterogeneity and nosological complexity are the rule among CM. Different CM may be produced by the same etiological factor, as well as different etiological factors may produce the same CM. A certain proportion of CM is clearly due to "simple" genetic mechanism; others derive from exogenous factors (maternal rubella, maternal diabetes, drugs, etc.); while still others seem to be due to polygenic inheritance. A large proportion of CM presents, however, a totally unknown etiology. This latter group is particularly interesting as regards genetic counselling: we do not know what produces them, but we know that they have extremely low recurrence risks.

CM are generally classified as *minor* and *major*. They may be found as *isolated*, *multiple* or *associated* (dysmorphic syndromes). The known syndromes are increasing in number each year and pose much more profound problems as regards etiology and clinical delineation than simple CM.

While CM are not a "high priority" group of conditions, as regards public health, in developing countries, they are certainly of concern to public health in the developed countries. Since developing countries will reach, sooner or later, the level of the developed ones, investigations on CM are of increasing importance for the whole of mankind.

CONGENITAL HEART DISEASES

Congenital heart diseases (CHD) form a large and heterogeneous group of congenital malformations. The most common are ventricular septal defect, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, coarctation of aorta, pulmonary stenosis, transposition of the great vessels and aortic stenosis. Ventricular septal defect alone may account for as high as one third of all cases; the others generally one tenth or less each.

CHD may be found isolated or associated with each other (tetralogy and pentalogy of Fallot, for instance), as well as with malformations of other organs (gastrointestinal tract, urogenital system, limbs, etc.), and mental retardation. About 5% of CHD were found, for instance, among 195 children with cleft lip and palate. CHD is present in a number of syndromes with different etiological mechanisms, such as Down's (21 trisomy), Patau's (13 trisomy), Edwards's (18 trisomy), Turner's (XO), Marfan's, Ellis-van Creveld's, Meckel's, lissencephaly, Smith-Lemly-Opitz's, thalidomide, rubella, etc.

Different forms of CHD may be present in the same syndrome. In Down's syndrome, for instance, 20 different defects have been found. The most frequent of them are ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricularis communis and ostium primum. Different syndromes show, however, different constellations of CHD, but the same CHD is found in a number of different syndromes. Coarctation of aorta and pulmonary stenosis are, for instance, particularly common in Turner's syndrome, a situation completely different from that found in Down's syndrome. Patent ductus arteriosus and atrial septal defects are, however, common components of both Down's and rubella syndromes. Patients with Bonnevie-Ullrich-Noonan syndrome (clinically similar to Turner's syndrome) generally have lesions of the right side of the heart (valvular pulmonic stenosis being the most frequent), whereas those with Turner's syndrome present more frequently defects of the left side (coarctation of the aorta or aortic stenosis). In spite of being quite similar, to the point that they were thought, some years ago, to form only one nosologic entity, these two syndromes are now known to have distinct etiologies (one is a chromosome disease, the

other seems to be due either to an X-linked or to an autosomal dominant gene). They also show some distinct clinical features.

The frequency of other (noncardiac) CM in patients with CHD varies from 6 to 54% in the different reports. There is no constant association between a specific noncardiac CM and a specific CHD. In Holt-Oram's syndrome, for instance, CHD is generally (but not always) atrial septal defect and the limb malformation involves mostly (but not always) only the thumb. Since cases of ventricular septal defect and much more extensive limb malformation (including phocomelia, with multiple ectrodactyly) have been described with this syndrome, the designations of *atriodigital*, *atrioextremal* and *heart and hand*, suggested for it, are misleading and must be discouraged. *Heart and upper limb* syndrome would be a more accurate term.

EPIDEMIOLOGY

The epidemiological approach is widely accepted as providing an important clue for the understanding of the etiology of congenital malformations. Descriptive epidemiology is, however, only the first step in the direction of the analytical aspect, that may point to the etiological factor or factors in operation. Investigations in this area are generally retrospective, but there is now an increasing tendency to use the prospective approach, which, at least in some areas, is expected to lead to more reliable conclusions.

Incidence and Prevalence

Incidence at birth is generally mentioned as 2-6 per thousand. Incidences as low as 0.2 and as high as 12.0 per thousand live births are, however, reported in the literature, but difficulties in diagnosis may be responsible for at least some of the reported variations. The highest figures have been found through intensive studies where cohorts of children have been followed during some years.

Only about 30-50% of the cases may be diagnosed in the neonatal period. A ductus arteriosus, for instance, is not a defect at birth (being not, therefore, a congenital malformation *sensu strictu*), but only if it remains patent a few weeks after birth. As will be mentioned later, the fate of the ductus depends, in part, on the oxygen pressure in the atmosphere. On the other hand, a certain proportion of affected neonates presents small ventricular septal defects that close spontaneously in the first few years of life. Incidences of CHD tend to be higher among stillbirths and children dying soon after birth. Prevalence among schoolchildren is roughly 2 per thousand.

Due to all the uncertainties of the estimates of incidence of CHD, it is hazardous to compare data from different countries and ethnic groups. A few studies show, however, some differences in this respect, but they may have been produced by extraneous concomitant variables. CHD has been reported, for instance, to be more frequent among Ashkenazi Jews than among non-Ashkenazi Jews in Israel. Caucasians also seem to present higher incidences than Black Americans.

Reports from different countries and races generally suggest that the distribution of the different types of CHD is roughly the same in tropical, subtropical and temperate zones, the small differences verified probably being due to sampling accidents and to differences

in diagnostic standards. Some of the reported variations may, however, be real. Among 555 consecutive cases of CHD studied in Ceylon, for instance, atrial septal defect was much more common (32%) than ventricular septal defect (18%), truncus arteriosus was present in excess (6%), coarctation of aorta was very rare (1%) and aortic stenosis was absent.

Data from autopsy examinations reveal from less than 1 to 8% of cases of CHD. Two reasons for this wide range are the age composition of the samples and the criterium used to define CHD.

There does not seem to be a close relationship of CHD with social class. Mortality due to CHD is, however, higher in the lowest socioeconomic levels, as with all other major CM.

Prematurity

Premature children show a higher incidence of cardiovascular defects. This incidence is particularly high among the children with very low (< 1500 g) birth weight as well as among those between 1501 and 2500 g, but whose gestational age was "normal". This last group of children have been *in utero* for a relatively long period for their low birth weight.

Maternal Diseases

The association between certain maternal diseases in the first months of pregnancy and specific embryopathies has been reported several times. Maternal diabetes and rubella have been shown to produce CHD in the offspring.

Altitude Effect

CHD (particularly patent ductus arteriosus and, to a lesser extent, ventricular and atrial septal defects) seem to be more prevalent in high altitudes as compared with the situation at sea level. At altitudes around 4500 m, for instance, patent ductus arteriosus has been verified to occur from 18 to 30 times more frequently than at sea level. The pathology of high altitudes as regards cardiovascular diseases is, however, more complex than this simple increased occurrence. It is known, for instance, that pulmonary hypertension is also much more common and severe in these defects as found in patients from populations situated at high altitudes than from those at sea level. A series of observations clearly shows that hypoxia (either experimentally or chronic hypoxia of high altitudes) leads to pulmonary hypertension, and that administration of oxygen decreases appreciably the pulmonary pressure. Combined hypoxia and hypercapnia may have a higher teratogenic action than hypoxia alone.

Parental Age and Parity

There is a positive maternal age effect which is particularly impressive in the cardiopathy associated with Down's syndrome, as is well known, and little or dubious, if any, in other CHD. No paternal age effect seems to exist. Parity effect is small, if any.

Inbreeding Effect

Parental consanguinity shows a slight association with congenital heart diseases in general. This relationship seems to be somewhat larger for some forms, such as pulmonary valvular

stenosis and atrial septal defect. Dextrocardia with transposition of the viscera is, however, the form which shows the largest association with inbreeding.

Sex Ratio

Sex ratio among affected individuals is generally reported as slightly higher than among normals (more clearly for aortic defects), but low sex ratio characterizes some forms such as patent ductus arteriosus and atrial septal defect. The association of CHD with other defects as well as the occurrence of multiple CHD seem also to be more frequent among males than among females.

Seasonal Variation

Seasonal incidence seems to vary at least for some of the forms. Cases with multiple CHD as well as with single ones associated with other defects have also been reported as showing a seasonal effect.

Dermatoglyphics

Dermatoglyphic patterns have been claimed to be somewhat different among patients with CHD as compared with controls. These differences are, however, rather small and may be spurious. Anyway — as with many other “associations” so far found (such as those between blood groups and diseases) — they do not have any diagnostic value.

GENETIC ASPECTS

It is well known that the frequency of CHD among sibs of propositi is roughly five to seven times larger than in the general population and that different forms of CHD may be found in the same family. A given type of CHD may occur sporadically in many families as well as being verified several times in the same sibship and in different sibships of the same family. The last two instances suggest an inheritance mechanism. Situations are known, for instance, in which patent ductus arteriosus has been verified in several members of two or even three generations of the same family, including parents and children. Apparent cases of autosomal dominant and recessive inheritance, as well as sporadic cases with unknown etiology, have been investigated. Families with high concentration of other forms of CHD (pulmonary stenosis, tetralogy of Fallot, atrial septal defect, etc.) are also known. These data should be noted and acted upon by the genetic counsellor.

In spite of the fact that the *average* recurrence risk of CHD *in general*, diagnosed at birth, for sibs, is about 2%¹, the *average* for specific forms of CHD may be a little higher or a little lower. The same form of CHD may, however, have a low recurrence risk in some families and a high one in others. Therefore, no genetic counselling is to be done without a good knowledge of the family as a whole, not only of the sibship and their parents. This basic rule in genetic counselling is specially important in the field of CHD.

¹ According to a recent review (Neill 1973), the risk of recurrence for first degree relatives of a patient with CHD “can be confidently predicted to be less than 5%”; “the presence of another affected first-degree relative probably increases the risk of recurrence to between 15 and 20%”.

CONCLUSIONS

What general conclusions may we draw from this entire information? The following seem to be particularly important.

(1) CHD may be produced either by genetic or by environmental causes. The genetic factors may be seen both at the gene and chromosome levels. At the gene level, not only oligogenes but also polygenes may be important. The environmental factors are reflected in the investigations showing seasonal effect, altitude effect, maternal disease effect, drug effect, etc. Interactions between genetic (polygenes?) and environmental factors seem to exist.

(2) Different congenital heart diseases, associated or not with different malformations of other systems, may be associated with the same basic genetic or environmental mechanism.

(3) Different mechanisms may produce the same CHD.

(4) There is a tremendous amount of combinations of CHD among themselves as well as with malformations of other systems, thus leading to the occurrence of complex and highly heterogeneous syndromes.

In summary, these facts show that: (1) congenital cardiovascular defects are not only anatomically, but also etiologically, a very heterogeneous group of malformations; (2) their etiologies are, however, better known than those of other groups of CM, such as limb reductions; and (3) some prevention is possible through the application of a few simple rules related to some overlapping areas such as cytogenetics, empirical risks, maternal age, maternal diseases, consanguinity, seasons of the year, etc.

Congenital heart diseases remain an important cause of infantile morbidity in developed countries, with an incidence near 1% of live births, as mentioned. They are also one of the most important causes of infantile mortality, in spite of all the improvements introduced in infant care, since they may account for roughly 50% of all deaths due to CM in general.

RECOMMENDATIONS

Long range investigations at the interdisciplinary level are needed to speed up knowledge in this area. Because of being internal CM, whose precise diagnosis requires a much higher group of refined techniques and raise a much large array of problems, investigations on CHD need a highly qualified team of specialists working with well equipped facilities. CHD constitute, however, a sector in the field of CM in general, and share, together with other sectors, some particularities that deserve to be mentioned here:

(1) high clinical heterogeneity;

(2) high etiological heterogeneity: "simple" genetic mechanisms and exogenous factors may be seen together with sporadic cases with a totally unknown etiology as well as with cases suggesting a polygenic inheritance;

(3) nonrelationship between clearly defined "clinical forms" and etiological "factors"; i.e., the same "form" can be produced by different "factors" and the same "factor" can produce different "forms";

(4) the frequency of CHD shows geographical and ethnic variations. Besides altitude, other factors (both genetic and exogenous) with a less clear-cut effect may be operating.

Since, on the one hand, CHD are in many instances associated with CM of other systems, any comprehensive research project for CHD should be part of a larger project for CM in general. Naturally, this recommendation poses an immense burden (maybe impossible to

solve) on small groups of specialists planning investigations exclusively on CHD. In such cases, cardiologists should at least have the assistance of specialists from other medical areas *always when it is needed*. Since CHD are seen many times, either as components of complex syndromes or together with one or another malformation of other systems, it would be *impossible* to separate CHD from other CM for investigation purposes.

Areas or ethnic groups supposed to have "high" concentrations of CHD should be extensively and intensively investigated for comparisons with those showing "low" or "normal" incidences. This recommendation is also to be applied to situations in which the distribution of the different forms of CHD seems to differ from that commonly found.

Four problems also deserving special investigation are those of the seasonal, maternal diseases, parental age, and inbreeding effects. The first three are important as regards exogenous factors, and the fourth as regards genetic factors. Data showing seasonal effects on incidence of CHD are, however, purely descriptive epidemiological ones and should be further investigated to the field of analytical epidemiology in order to disclose the actual teratogenic factors.

Since only a small fraction of CHD can be diagnosed at birth, and probably less than 50% at the neonatal period, any diagnostic improvement for obtaining better results at earlier ages is highly desirable.

SELECTED BIBLIOGRAPHY

Since this paper is not a review but only a summary of some epidemiological and genetic findings in CM and CHD, reference is made here to only a small fraction of the papers dealing with the subjects and which have been used in its preparation.

- Abramovici A., Liban E. 1964. The incidence of congenital malformations of the heart among Jews in Jerusalem. *Cardiologia*, 45: 347-355.
- Berendes H.W., Weiss W. 1970. The NIH collaborative study. A progress report. Proc. 3rd Int. Conf. Congen. Malf. (pp. 293-298), Amsterdam: Excerpta Medica Foundation.
- Böök J.A., Fraccaro M. 1956. Research on congenital malformations. *Etud. Neo-natal.*, 5: 39-54.
- Böök J.A. 1960. Heredity and heart disease. *Am. J. Public Health*, 50: 1-4.
- Campbell M., Polani P.E. 1961. Factors in the aetiology of atrial septal defect. *Br. Heart J.*, 23: 477-493.
- Carlgen L.-E. 1969. The incidence of congenital heart disease in Gothenburg. *Proc. Ass. Europ. Paediat. Cardiol.*, 5: 2-8.
- Edwards J.H. 1961. Seasonal incidence of congenital disease in Birmingham. *Ann. Hum. Genet.*, 25: 89-93.
- Espino-Vela J. 1967. Congenital cardiac malformations in high altitude populations. (Manuscript).
- Kaplan S. 1968. Cardiac malformations associated with craniofacial anomalies. In Longacre (ed.): *Craniofacial Anomalies: Pathogenesis and Repair* (pp. 119-120). Philadelphia: Lippincott.
- Menashe V.D., Osterud H.T., Griswold H.E. 1967. Mortality from congenital cardiovascular disease in Oregon. *Pediatrics*, 40: 334-344.
- Murdoch J.L. 1969. Holt-Oram syndrome. Digital and heart anomalies in three generations. 1st Conf. Clin. Delin. Birth Defects. *Birth Defects*, 3: 187-188.
- Mustacchi P., Sherins R.S., Miller M.J. 1963. Congenital malformations of the heart and the great vessels; prevalence, incidence and life expectancy in San Francisco. *JAMA*, 183: 241-244.
- Nadas A.S. 1963. *Pediatric Cardiology* (2nd ed.). Philadelphia: Saunders.
- Neel J.V. 1958. A study of major congenital defects in Japanese infants. *Am. J. Hum. Genet.*, 10: 398-445.
- Neill C.A. 1973. *Genetics of congenital heart disease*. (Reprint).
- Pitt. D.B. 1962. A study of congenital malformations. I. *Aust. N.Z. J. Obstet. Gynaecol.*, 2: 23-30.
- Polani P.E., Campbell M. 1955. An etiological study of congenital heart disease. *Ann. Hum. Genet.*, 19: 209-230.
- Polani P.E., Campbell M. 1960. Factors in the causation of persistent ductus arteriosus. *Ann. Hum. Genet.*, 24: 343-354.
- Preus M., Fraser F.C., Levy E.P. 1970. Dermatoglyphics in congenital heart malformations. *Hum. Hered.*, 20: 388-402.
- Pruzanski W. 1964. Familial congenital malformations of the heart and upper limbs. A syndrome of Holt-Oran. *Cardiologia*, 45: 21-38.

- Saldanha P.H. 1964. Frequency of congenital malformations in mixed populations of southern Brazil. In Fishbein (ed.): Proc. 2nd Int. Conf. Congen. Malf., New York 1963 (pp. 323-333). New York: International Medical Congress.
- Shakibi J.G. 1969. Etiology of congenital heart disease. Henry Ford Hosp. Med. J., 17: 101-106.
- Walloppillai N.J., Jayasinghe M.S. 1970. Congenital heart disease in Ceylon. Br. Heart J., 32: 304-306.
- Yerushalmy J. 1970. The California child health and development studies. Study design and some illustrative findings in congenital heart disease. Proc. 3rd Int. Conf. Congen. Malf. (pp. 299-306). Amsterdam: Excerpta Medica Foundation.
- Zoethout H.E., Carter R.E.B., Carter C.O. 1964. A family study of aortic stenosis. J. Med. Genet., 1: 2-9.

For analyses of the etiologic aspects of limb reductions and of the clinical delineation of malformation syndromes (two problems mentioned in the text), see the following:

- Freire-Maia N. 1969. Congenital skeletal limb deficiencies: a general view. Birth Defects, 5: 7-13.
- Freire-Maia N. 1975. Nosologic groups with special reference to ectodermal dysplasias. J. Med. Genet. (in press).

RIASSUNTO

Alcuni Aspetti Epidemiologici e Genetici dei Vizi Cardiaci Congeniti

Viene presentata una rassegna generale delle malattie congenite ed un riassunto di alcuni aspetti anatomici, clinici, epidemiologici e genetici dei vizi cardiaci congeniti. Vengono anche rapidamente avanzate alcune «raccomandazioni» per la ricerca.

RÉSUMÉ

Quelques Aspects Épidémiologiques et Génétiques des Maladies Cardiaques Congénitales

L'on présente un inventaire général des maladies congénitales ainsi qu'un résumé de certains aspects anatomiques, cliniques, épidémiologiques et génétiques des maladies cardiaques congénitales. Quelques «recommandations» pour la recherche sont ensuite brièvement suggérées.

ZUSAMMENFASSUNG

Einige epidemiologische und genetische Aspekte der angeborenen Herzfehler

Allgemeiner Ueberblick über die angeborenen Krankheiten und Zusammenfassung einiger anatomischer, klinischer, epidemiologischer und genetischer Aspekte der angeborenen Herzfehler. Es folgen einige kurze Hinweise für die diesbezüglichen Forschungen.

Prof. N. Freire-Maia, Department of Genetics, Federal University, Caixa Postal AA, 80000 Curitiba, Pr, Brazil.