

THE IMPORTANCE OF EPIDEMIOLOGICAL EVALUATION OF RISK FACTORS IN CONGENITAL HEART DEFECTS

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Keywords: congenital heart defects, risk factors, epidemiological evaluation

Abstract: Congenital heart defects (CHD) are an important cause of infant mortality, which is why epidemiological studies can help monitoring the health of newborn babies, which are both a paediatric cardiology and a public health priority. Epidemiological evaluation of risk factors and of their influence on the development of CHD must be conducted before birth by means of prenatal prevention programmes, especially in the first trimester of pregnancy, and also by means of screening programmes. Epidemiological studies concerning the effects of risk factors are very important because the life expectancy of children suffering from CHD has increased and also because of the huge impact that this disease has on the lives of the children and of their families.

Cuvinte cheie: malformații congenitale de cord, factori de risc, evaluare epidemiologică

Rezumat: Malformațiile congenitale de cord (MCC) reprezintă o importantă cauză de mortalitate infantilă, motiv pentru care studiile epidemiologice pot contribui la monitorizarea stării de sănătate a nou-născutului, o prioritate în cardiologia pediatrică, dar și pentru sănătatea publică. Evaluarea epidemiologică a factorilor de risc și a influenței acestora în apariția MCC trebuie făcută înainte de nașterea copilului, prin introducerea de programe de prevenție antenatală și în special în primul trimestru de sarcină, și de programe de supraveghere. Studiile epidemiologice asupra influențelor factorilor de risc au o importanță crescută datorită creșterii duratei de viață a copiilor cu MCC, iar impactul acestor boli asupra calității vieții lor și a familiilor acestora este semnificativ.

Congenital heart defects are structural and functional defects of the heart and of the great vessels, present at birth.(1) Congenital heart defects are among the most common birth defects and are an important cause of infant morbidity and mortality especially within the first year of life.(2) This is where the serious problems regarding the medical approach stem from: the fragility of the underlying area. Patients who survive childhood have a higher rate of both cardiac and extracardiac comorbidities. This is significant because, according to recent studies, the total number of adults suffering from CHD surpasses the number of children suffering from the same disease.(3) In Romania, the true incidence of this disease is not estimated accurately because of the number of unreported cases.

According to WHO figures concerning the death rate of children younger than one year of age, in our country, the neonatal mortality is at least two times higher than in developed countries, even four times higher when it comes to infants, whereas child mortality rate is two times higher than in the same developed states. The same figures showed that life expectancy is 8 years shorter than in the developed countries.(1) In this respect, ever since 2010, the WHO adopted a resolution meant to promote primary prevention and the health of children with congenital defects. Moreover, WHO recommends the development of a health surveillance and registration system, the reinforcement of etiological studies, diagnosis, prevention and international cooperation.(4) Infancy is the most important period given the fact that approximately 70% of congenital heart defects can be diagnosed by one month of age and 90% of cases can be diagnosed under age one. According to estimates, 1 in 10

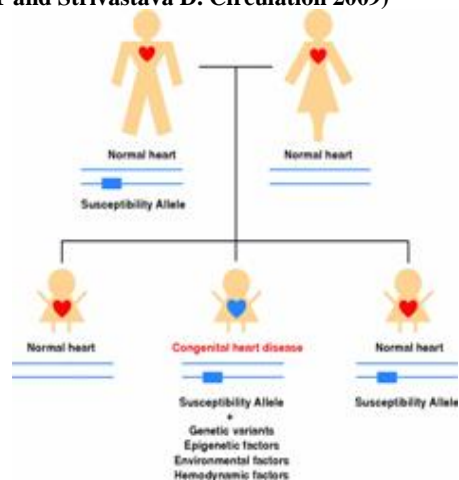
babies die within the first year of life (5) because they were not diagnosed. Hence, these defects are a public health priority. That is why epidemiological studies can help to determine the true value of the incidence of CHD and to establish the risk factors involved. In order to establish the risk factors, there are certain useful steps that can be taken: preconception screening, preconception counselling to help identify persons who might be at risk (family medical history, consanguinity), prenatal screening to determine the mother's gestational age, haematological and echographic screening to detect genetic disorders and newborn screening to detect isolated congenital heart defects or associated malformations.(6) Early detection allows quick treatment and prevents other complications.(7,14) In many studies, around 75-80% of the reviewed cases of CHD presented an isolated defect, without any extracardiac anomalies. In general, the extracardiac anomalies more commonly associated with heart defects include urinary, central nervous system, alimentary tract, and skeletal defects.(6)

The etiology of congenital heart disease results from the interactions of the genetic and environmental factors. Many studies tried to show that there is a link between congenital heart defects (CHD) in offspring and maternal exposure to several factors, which is also known as multifactorial etiology.(8) Only a small proportion of the total number of cases of congenital heart disease is attributed to the genetic factors, the interaction of genetic and environmental factors (9), being the cause in the majority of cases.(10) Genetic polymorphisms can disrupt normal development.(11)

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Article received on 03.04.2013 and accepted for publication on 20.06.2013
ACTA MEDICA TRANSILVANICA September 2013;2(3):214-216

Figure no. 1. CHD multifactorial etiology (adaptation after Shieh JT and Strivastava D. Circulation 2009)



Genetic factors – genetic disorders are associated with abnormal heart development. Consanguinity plays an important part in the prevalence of congenital heart defects. In this case, the risk of CHD is higher than in the general population. This high risk in related parents suggests CHD is influenced by genes.(12) As more patients with congenital heart defects (CHD) survive adult life, with or without surgery, the problem of the defect being transmitted to offspring comes to light. If one or both parents have CHD, the risk of recurrence of a heart problem is three times higher.(7,13) Single gene defects, which account for less than 1% of the total cases of CHD, are the least likely cause of CHD.(14) The next in line are chromosome abnormalities, which account for less than 5% of the total cases of CHD, a relevant example being the Down syndrome (trisomy 21). The other trisomies (trisomy 18, or Edwards syndrome, and trisomy 13, or Patau syndrome) and the Turner syndrome are also associated with CHD, along with extracardiac anomalies. Routine screening for trisomy 21 can reduce the prevalence of CHD.(7) The third cause, that accounts for 90% of cases, is multifactorial etiology and is a result of the genetic-environmental interaction.(14)

Environmental factors - Most studies showed that CHDs are the result of the interaction of environmental factors and genetic disorders. Many factors can influence fetal development. Identifying these factors will help preventing CHD. Prevalence studies and studies concerning environmental factors reviewed by the American Heart Association have shown a link between maternal exposure, maternal diseases and CHD.(7) Pregestational diabetes increases the risk of CHD in the fetus and is also associated with extracardiac malformations. Gestational diabetes is also a risk factor but the proportion is not known at this point.(6,7) Obesity is a public health issue and some studies suggested that the association of a BMI > 29 with undiagnosed diabetes or other factors can be seen as a relative risk factor. Rubella's teratogenic effects have been known since 1941. Rubella is linked to severe CHD. 45% of children who suffer from Congenital Rubella Syndrome can develop CHD.(16) Influenza and fever, especially in the first trimester of pregnancy, have been linked with an increased risk of CHD. Phenylketonuria, or a high level of phenylalanine in the blood, not only affects mental development but can also cause cardiac defects. According to studies, approximately 12% of children whose mothers have uncontrolled levels of phenylalanine in the blood, are at a high risk for developing CHD.(17) Seizures and seizure medication, especially phenytoin, hydantoin, carbamazepine, phenobarbital and valproic acid are linked to an

increased risk of CHD.(18) A small number of CHDs were associated with maternal thyroid disease, toxicosis or hydramnios.(8) Thalidomide is currently prohibited to pregnant women or to fertile aged women because it has proven teratogenic effects, which can cause complex and severe heart anomalies. Some studies associated high doses of vitamin A and its precursors with an increased risk of CHD, especially the transposition of the great vessels.(19,20) Maternal exposure to other drugs (antibiotics, oral contraceptive pills or intrauterine devices, corticosteroids, nonsteroidal anti-inflammatory drugs, lithium therapy) were associated with a low/medium risk of CHD. Prenatal exposure to angiotensin-converting enzyme inhibitor is associated with a high risk of CHD.(7) In what concerns the mother's lifestyle, it is known that high caffeine intake, increased cigarette smoking or alcohol consumption, all have an impact on fetal development. Excessive alcohol consumption, whose teratogenic effect has been proven, is a public health concern especially for pregnant women. It is well-known that smoking can cause low birth weight, premature birth or perinatal death. Maternal occupational exposures, one year before conception or in the first 8 weeks of pregnancy, or paternal exposure to organic solvents, to coatings, to dyes used in the textile industry, in metallurgy or printing houses, or to herbicides or pesticides in agriculture were linked to CHD etiology.(12) Maternal exposure to air pollution (CO, NO) was linked to CHD.(21) Father's age (over 40) was linked to ventricular septal defect, atrial septal defect and pulmonary stenosis.(22)

Prevention is a public health concern as many environmental factors are variably linked to congenital heart defects. The concept of preconception health refers to the trimester before pregnancy and involves diagnosis and treatment of chronic diseases, acute disease prevention, education and healthy eating promotion. Moreover, according to this concept, strict diets, particularly the ones lacking in folate, smoking, medication and exposure to harmful substances should be banned. The risk of CHD can be significantly lowered for the babies of women with diabetes who keep their sugar levels in check before conception.(6,11) The risk associated with maternal phenylketonuria can be lowered if the disease is diagnosed and treated before conception.(6) Women who suffer from epilepsy should get pre-conception counseling in order to properly evaluate the benefits of anticonvulsants.

WHO recommendations concerning vaccinations have proved efficient, both in the case of seasonal flu vaccination campaigns and particularly in the case of national rubella vaccination programmes. Nevertheless, rubella and congenital rubella syndrome will continue to be public health issues until they are eradicated.(4,6) Vitamin intake decreases the risk of certain congenital heart defects if they are administered before conception or in the first month of pregnancy. Vitamin and folic acid intake may reduce the risk of CHD by 52%.(6,23)

Conclusions:

Epidemiological studies can help identifying and evaluating the risk factors involved in CHD. Knowing and establishing the risk factors that can influence cardiovascular development, especially between the 14th and 60th day of pregnancy, which is seen as the period most strongly marked by vulnerability, is extremely important as CHD continues to be a pressing issue in the medical world. This is due to the difficulties encountered by the pediatricians and the problems of patient management during the neonatal period and then in infancy, when external factors (complications) must be avoided, since it is well-known that the odds of survival are influenced by an early and accurate diagnosis and also by a timely treatment.

Moreover, an anamnestic identification of the factors that influence embryonic development can lead to an active, prenatal diagnosis. This means that surgical reconstructions can be performed as soon as possible. Among the immediate and long-term results are: the decrease of infant mortality, the ease of psychosocial impact and the improvement of the quality of life of the children and of their families. Unlike the developed countries, where there are active screening, a national paediatric cardiology network and accessible treatments, in Romania CHD incidence is rising. That is why it is important to identify the risk factors which bear negative effects.

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