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Congenital heart disease and the role of genetic factors in cardiac morphogenesis

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Abstract

Cardiovascular malformations are the most common types of birth malformations, causing a significant increase in mortality worldwide. The etiology of most of these abnormalities remains unknown, but the genetic factors involved are considered to have an increasingly important role. Advances in understanding normal molecular cardiac development have led to the identification of numerous genes required in cardiac morphogenesis and drove to the discovery of a growing number of monogenic causes of human cardiac malformations. Sequencing of the human genome and advances in molecular techniques have led to an increase in proving the crucial role of the genetic factors.
Keywords: *congenital malformations, genetic factors, newborn*

Introduction

Cardiac malformations are structural or functional diseases of the fetal heart which manifest immediately after birth or later. These anomalies affect the heart and the intrathoracic great vessels and determine poor functioning or predisposition to malfunctioning[1-3]. The clinical signs are:

- cianosis;
- cardiac murmurs;
- tachypnea;
- respiratory distress syndromes;
- heart failure;
- low pulse, petechiae, hypotension, metabolic acidosis, circulatory failure;
- abnormal heart rhythm (i.e. tachycardia/bradycardia, atrio-ventricular block);
- abnormal location, size and shape[4].

History and general presentation

When a newborn baby presents with cianosis, repiratory distress syndrome and/or shock, the clinician must choose the right diagnosis, taking into consideration a pulmonary disease, a cardiac disease, a neurological disease or an infection.

Family history and pregnancy medication

a) the existence of a brother or a sister with congenital heart disease triples the risk of recurrence. If the mother suffers from a congenital heart disease, the risk for the child to be affected is higher;

b) alcohol and drugs (i.e. amphetamines, anticonvulsants, lythium, progesterone, estrogen) intake during the first trimester of pregnancy increases the risk of heart malformations. Viral infections (like rubella, enterovirus, coxsakie B), diabetes, systemic lupus erythematosus, maternal age of over 40, phenylketonuria, may be maternal conditions that predispose to heart malformations;

c) Pregnancy, labour and birth complications, may be considered risk factors for congenital heart diseases. For example, intrauterine and perinatal hypoxia is a risk factor for developing myocardial dysfunctioning and persistent pulmonary hypertension;

d) Assisted Reproductive Technologies: the risk of cardiac malformations in babies conceived by *in vitro* fertilization appears to be a little higher than naturally conceived babies. The most frequent congenital heart diseases are atrial and ventricular septal defects. There is no proven relation between *in vitro* fertilization and the incidence of cardiac malformations.

Neonatal history: gestational age, onset signs and severity[4,5,6]. If, during the first week of life, the newborn baby presents with general cyanosis, murmurs, heart failure and/or vasculary collapse, the possibility of a congenital heart disease must be evaluated. Clinical history and detection of onset clinical signs are very important[3].

Prognostical classification of the fetal cardiac diseases

- associated pathology:
  - ✓ isolated 50-60%;
  - ✓ associated extracardiac malformation 10-20%;
  - ✓ genetic syndromes 30%.
- survival:
  - ✓ malformations incompatible with life;
  - ✓ malformations that can benefit from palliative treatment;
  - ✓ malformations that can be entirely treated[7].

On the basis of the prognosis and the possible, genetic or structural, associated pregnancy pathologies may be continued or aborted. Heart defects detected during intrauterine life may be more severe than those detected after birth[8,9].

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During the last decades a multitude of studies on the genetic factors and molecular pathways that interfere with the development of the cardiac system have been made. Various structural genes, critical in normal cardiac morphogenesis, have been discovered as the result of these studies and helped the identification of the genetical ethiology of congenital heart diseases[10,11].

In most of the children born with a congenital heart malformation, their condition is not associated with other inborn errors, but in 25-40% of the cases, heart malformation is associated with another anomaly or is a part of a genetic syndrome[12]. In approximately 30% of the affected children, a cromosomial defect is associated with a heart malformation[13].

Aneuploidy, abnormal chromosomial number, represents an important proportion of the congenital cardiac malformation (Table 1), so, the most frequent syndromes associated with heart defects are as follows: 50% of the children born with 21 trisomy have a heart defect, 80% of the children with 13 trisomy, and almost all the children born with 18 trisomy have a heart defect, usually the defect being a septal one[14].

Most cases of cardiac malformations are present in the Down syndrome, their severity influencing the

Table 1 Aneuploidies and microdeletions associated with common syndromes[19]

Syndrome	Cardiac malformations	% with MCC	Other clinical signs
13 trisomy Patau syndrome	DSA, DSV, PCA, SVSH, dextrocardia	80%	microcephaly holoprosencephaly, scalp defects, severe mental retard, polidactilia, cleft palate, urinary and genital malformations, omphalocele, microphtalmia
18 trisomy Edwards syndrome	ASD, VSD, PAC, FT, DORV, ACo, BAV	90-100%	Polyhydramnios, rocker-bottom foot, hypertonia, biliary atresia, severe mental retard, diaphragmatic hernia, omphalocele
21 trisomy(Down syndrome)	ASD,VSD,SVSD,PAC,FT, HLVS	40-50%	Hypotonia, development retard, characteric facial appearance
Turner syndrome	ACo, BAV, AS, HLVS	25-35%	Short stature, primary amenorrhea, flat chest with spaced nipples, short throat, lymphedema
Klinefelter syndrome	PAC, ASD, mitral valve prolaps	50%	High stature, hypoplastic testicle, delayed puberty
22q11.2 deletion (DiGeorge syndrome)	AAI Type B, aortic arch annomaly, arterial trunc, FT	75%	Hypoplastic thymus and parathyroid, imunodeficiences, low implanted ears, hypocalcemia, mental retard, renal annomalies
7q11.23 deletion (Williams-Beuren syndrome)	Supravalvular AS, SPS	50-85%	hypercalcemia, characteristic appearance, development retard, deafness

ASD= atrial septal defect; VSD= ventricular septal defect; PAC= persistent arterial canal; HLVS= hypoplastiv left ventrical syndrome; FT= Fallot tetrallogy; DORV= double outlet right ventricle; ACo= aortic coartation; BAV= bicuspid aortic valve; IAB= interrupt aortic branch; AS= aortic stenosis; PS= pulmonary stenosis; AVSD= atrioventricular septal defect

Table 2 Genetical syndromes associated with congenital heart malformations[19]

Syndrome	Cardiac anomaly	Other associated signs	Genes
Noonan syndrome	PS, AVSD, HCM, ACo	Short stature, short throat, flat chest, delayed development, cryptorchidism, abnormal facial appearance	PTPN11, KRAS, RAF1, SOS1
Costello syndrome	PS, HCM	Short stature, delayed development, characteristc facies, high risk of carcinoma	HRAS
LEOPARD syndrome	PS, cardiac conduction abnormalities	hypertelorism, genital anomalies, growth retardation, sensory deafness	PTPN11, RAF1
Alagille syndrome	PS, FT, DSA,PS	cholestasis, characteristic facies, butterfly vertebra, ocular anomalies, delayed growth,deafness, horseshoe kidney	JAG1, NOTCH2
Marfan syndrome	Mitral valve prolaps	High stature, finger anomalies,scoliosis, skeletal anomalies, spontaneous pneumothorax	FBLN, TGFBR1, TGFBR2
Holt-Oram syndrome	ASD, VSD,AVSD	Limb defects, hematological anomalies	TBX5
Heterotaxic syndrome	DILV, DORV, TMV, AVSD	Intestinal malrotation	ZIC3, CFC1
Char syndrome	PCA	Dismorfic figures and digital anomalies	TFAP2b
CHARGE syndrome	ASD, VSD, valve defects	Coloboma, coan atresia, delayed development, genitourinary anomalies	CHD7, SEMA3E

PS= pulmonary stenosis; AVSD= atrioventricular septal defect; HCM= hypertrophic cardiomyopathy; CoA= aortic coartation; TF= Fallot tetrallogy; DSA= atrial septal defect; DSV= ventricular septal defect; DILV= double inlet left ventricle; DORV= double outlet right ventricle; TMV= transposition of great vassels; PAC= persistent arterial canal

Table 3 Non-syndromic cardiac anomalies[19]

Cardiac anomalies	Genes
ASD, FT, tricuspid valve anomalies, conduction anomalies	NKX2.5
ASD, VSD	GATA4
ASD, HCM	MYH6
Cardiac anomalies associated with pulmonary hypertension	BMPR2
BAV	NOTCH1
TGV	PROSIT-240

ASD= atrial septal defect; VSD= ventricular septal defect; FT= Fallot tetrallogy; TGV= transposition of great vassels; BAV= bicuspid aortic valve; HCM= hypertrophic cardiomyopathy

prognosis of these children. These heart defects vary from simple to complex ones, determining various signs and symptoms. The most common malformations are: atroventricular canal defect, ventricular and atrial septal defects, persistent arterial canal or cyanogenic cardiac malformation such as Fallot tetralogy or the hypoplastic left ventricle[13].

Edwards syndrome or 18 trisomy is characterized by low birth weight, intrauterine growth retardation, mental retardation. About 80% of the pacients are female. The incidence is 1/3500-8000 births. Life expectancy is of approximately 2-4 months, as these pacients present with severe heart malformations, central nervous system defects and other anomalies that lead to premature death. The karyotype features chromosome 18 in triple dose, commonly citogenetic, as it is homogenous. Only 10% of the cases have mosaicism. It has been observed that in 10% of the babies born with Edward syndrome, this is associated with 13 or 21 trisomy. Affected females survive longer. The most frequent cardiac malformations are: septal defects, persistent arterial canal, and complex defects as double outlet right ventricle, Fallot tetrallogy, aortic coarctation[13].

Patau syndrome or 13 trisomy, is characterized by a plurimalformative syndrome with neurological anomalies (mental retardation, apnea, seizures etc.), cranio-facial defects (ear malformations, microcephaly, cleft palate, micrognatia etc.), oculoorbital defects (microphthalmia, coloboma etc.), cervical, cardio-vasculary, gastro-intestinal, urinary and genital defects, skeletal anomalies (polidactilia)[13]. Multiple and severe malformations associated with this syndrome cause death during the first month of life in 50% of the cases. Only 3% of the patients survive over a year with severe mental retardation. Commonly, the condition of these patients is associated with septal defects, persistent arterial canal, dextrocardia, hypoplastic left ventricle[15].

One third of the females with Turner syndrome or X monosomy have a congenital heart malformation (most frequent are bicuspid aortic valve, aortic stenosis, hypoplastic left ventricle, aortic coarctation), 50% of the males with Klinefelter syndrome or 47XXY associate a heart defect (persistent arterial canal, septal defects)[13]. Furthermore, there are many other, less frequent, chromosomial defects detected in patients with a congenital cardiac malformation.

The development of fluorescence *in situ* hybridization technique (FISH), a procedure in which marked flourescent probes are hybridized to metaphase chromosomes, detecting small submicroscopic chromosomal deletions, various syndromes caused by chromosomial defects have been elucidated (Table 1), such as 22q11deletion known as DiGeorge syndrome and Williams-beuren syndrome. DiGeorge syndrome is caused by the microscopic deletion on chromosome 22q11.2 and leads to defects of the heart, thymus and parathyroid glands, dysmorphic facies due to the abnormal development of the pharyngeal arch[14]. The most frequent cardiac malformations are common arterial trunk and Fallot tetrallogy. Genetic tests are required in patients with cardiac defects[15]. William-Beuren syndrome caused by the microdeletions on the 7p11.23 chromosome, is characterized by cardiac defects, associates typical elf facial appearance, hypercalcemia, renal impairment and cognitive disability[16]. Loss of elastin is thought to be the cause of cardiac defects in this syndrome[17,18].

Along with the progress în genetic technology and the discovery of the human genome, singular genetic defects that lead to syndromes associated with congenital cardiac malformations have been elucidated (Table 2).

Most recent studies have made possible the discovery of the mutation of fibrillin 1, the cause of Marfan syndrome characterized by the progressive dilatation of the aortic root with a high risk of dissection, pathology of the lens and skeletal anomalies[20]. Holt-Oram syndrome characterized by atrial and ventricular septal defects, a progressive disease of the atrioventricular conduction system and limb anomalies, is associated with mutations of the transcription factor Tbx5[21]. Alagille syndrom, that encodes a ligand in signaling pathway Notch is characterized by intrahepatic billiary atresia and cardiac malformations (pulmonary stenosis, mpulmonary valve stenosis and Fallot tetrallogy)[22,23]. In Noonan syndrome phenotip that includes cardiac defects, pulmonary stenosis and hypertrophic cardiomiopathy as well as mental retardation, characteristic figure, hemorrhagic disorders, mutations of protein tyrosine phosphatase non-receptor type 11 are involved in 50% of the cases[24]. Heterotaxic syndrome that associates cardiac, pulmonary and gastrointestinal positional defects is commonly complicated with congenital heart diseases (atrioventricular septal defects, great vassels transposition)[25].

Singular genic defects associated with isolated/non-syndromic congenital heart malformations (Table 3) have also been discovered.

The progress in this field also proves that singular genic defects can lead to congenital heart diseases and reveal more information about the molecular pathways in cardiac morphogenesis.

In spite of the ultimate discoveries, the great majority of patients with mutated in colorectal cancers do not have singular genic defects[26-30]. Along with the sequencing of the human genome, new information about the genetic variety has been reported.

One type of genetic variation, changes in children number, leads to a change in the gene dose and affects aproximatly 12% of the human genome[31]. These variations are considered to be polymorphisms when present in more than 1% of population and are more susceptible in presenting associated diseases when present in less than 1% of the patients.

The variation in the number of copies is associated with cardiac malformations.

CHARGE syndrome, a constellation of anomalies that includes coloboma, cardiac defects, coan atresia, growth retard and anomalies of the ear, has been re-

cently associated with a microdeletion on the 8p21 chromosome[32]. Later sequencing of the critical region showed heterozygous mutations in chromodomain helicase deoxyribonucleic acid (DNA)-binding 7 (CHD7), a gene that encodes a binding protein in DNA[32]. Further studies have identified pathogenic mutations in CHD7 in over 50% of the pacients with CHARGE syndrome[33]. Array and contributors helped with detecting the gene responsible for the great majority of cases of this syndrome, proving the importance of this method in discivering the gene, especially when studying rare diseases[33].

Thien other authors studied patients with congenital heart malformations and other inborn anomalies and detected a variation in the number of copies in 30%[34]. The relation cause-effect was supported when variation în number of copies include important genes in cardiac development when they appeared by novo.

Variations in the number of copies were also identified in pacients with isolated congenital heart malformations. They appear also in parents with no proof of congenital heart malformation, thus showing probably the fact that variation in number of copies increases the sensitivity in developing heart anomalies, also needing another factors.

The decrease in sequencing DNA price, the rate of discovering the gene in cardiac malformations may be higher.

At the same time with the discovery of new genetic anomalies associated with heart malformations, the development of a phenotipic information international database, one can study clinical results and prognosis on the basis of a genetic average[34].

Yet, the high cost of these genetic tests and the impossiblity of performing them in many countries, makes evaluation of children with congenital heart malformations syndromic or non-syndromic almost impossible.

When a new patient is diagnosed with heart pathology, the examination of the relatives to exclude genetic involvement is recommended as well as detailed evaluation of the newborn.

The clinical examination must search for dismorphic appearance, eye and ear anomalies, skeletal and limb anomalies, gastrointestinal and genitourinary pathology, a change in the neurologic status.

Multidisciplinary consults (neurological, ophtalmological, orthopedical, ORL, genetical, imagistic) and adjuvant tests (cardiac ultrasound, abdominal ultrasound, brain imaging) in establishing the diagnosis are recommended when necessary.

Genetic tests should be performed in the following situations:

- every newborn/child with suggestive phenotype
- every newborn with dysmorphic features, multiple anomalies, growth retard without a clear cause
- children with a family history of genetic anomaly
- when anomalies are discovered in fetal ultrasound examination

In case of a normal cariotype, when the child presents with sugestive clinical features for a genetic disorder, detailed genetic tests (i.e. FISH) are recommended for detecting a singular inborn anomaly[32].

Discovering a genetic anomaly in a child with congenital heart malformation is beneficial for the patient and his/her familly, alerting the specialist on the possible associated asymptomatic anomalies, on one hand, and conducting a family investigation which can detect genetic defects in other members, on the other hand, offering important data for genetic counselling of the familly[33].

The most important congenital defects

Congenital heart malformations are the most important congenital defects in a newborn[34]:

1. In Romania there is no efficient functional network for approaching this pathology, there is no national screening program for congenital heart defects to ensure the diagnosis, treatment and follow-up of these children. In our country the number of cardiovascular surgery centers is insufficient to treat all the newborns with cardiac malformations.

2. The obstetrician has an important role in detecting cardiac malformation by fetal 3-dimensional ultrasound. The neonatologist should be informed if there is a high suspicion of a cardiac malformation, as there are many that represent an immediate medical and surgical postnatal emergency.

3. If the diagnosis is made before birth, the pregnant woman can be sent to a high level of neonatal unit or to a specialized local cardio-vascular surgery center or abroad. Thus, mortality decreases and also neurological sequelae and the quality of life increases.

4. The family has an important role in detecting the patients with congenital heart malformations in time, through periodic antenatal and postnatal consults by the paediatrician or familly practitioner when discovering certain abnormalities in the infant's state (growth retardation, central or peripheric cyanosis, feeding difficulties, pale skin, respiratory effort, hypotonia).

5. The newborn should be examined in detail by the neonatologist and if there is suspicion of a heart disease he/she should be monitored in order to establish a rapid diagnosis. Many of the newborn babies with a congenital heart disease may have a real chance if diagnosis is quickly established and treatment is started immediately.

6. Neonatologists should be familiar with cardiac ultrasound as they are the main factor in the precocious detection of congenital heart diseases, thus contributing to a decrease in neonatal mortality and morbidity. If the newborn is in a critical state, neonatal transport to another unit for cardiac ultrasound is made with difficulty and agravates the state.

7. Unless immediately treated, congenital heart malformations lead to existus or irreversible and severe complications such as persistent pulmonary hypertension, systemic arterial hypertension, hyper-

tophic cardiomiopathy, cardiac failure. All of these create a physical and psychological impairment for the patient. Patients diagnosed at a later time need a more laborious surgical technique or the surgery can not be performed anymore, leading to a decrease of the quality of life.

8. We also need to mention here long and short term cardiac complications of prematurity: persistent arterial canal and later right ventricular hypertrophy.

Conclusions

Genetic factors have a much greater influence on determining various types of cardiac malformations than it was established previous to the multitude of studies in this area. All accomplished knowledge regarding genetic influence over heart malformations can develop early detecting or preventing strategies, of great importance for future generations of affected children with isolated forms or genetic syndromes. ■

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