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GENETIC CLUES IN CONGENITAL HEART DISEASES

Review Article

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Abstract

The frequency of genetic diseases is estimated at approximately 1 in 40 live newborns, including both minor and major disorders. The medico-psycho-social impact of diseases with genetic determinism is important. Although taken individually, genetic diseases are considered rare, cumulatively, they represent such a frequent pathology, that one can rightfully consider genetic anomalies the basis of the majority of currently diagnosable and treatable conditions. This is the hypothesis that underlies the orientation of contemporary medicine towards individualized therapy. Congenital heart malformations associate a high morbidity and mortality potential even as an isolated disease, even more so if they appear in the context of a genetic syndrome. For these reasons, it is particularly important for today's practitioner to know the small clues that should raise a reasonable suspicion for the presence of a genetic syndrome in a patient diagnosed with a congenital heart disease. Dysmorphology is the youngest genetic branch, studying the structural anomalies commonly reffered to as birth defects. It has proven to be an important tool for the modern practitioner when dealing with complex congenital anomalies.

GENERAL GENETIC CONSIDERATIONS

Depending on the nature of the morphogenesis errors, congenital anomalies are classified into: malformations, disruptions, deformations and congenital dysplasias.
A reasonable suspicion of a genetic anomaly should arise when at least one of the following criteria is met (Smith):

- One major anomaly or at least two minor anomalies.
- Intrauterine growth restriction or postnatal growth retardation
- Developmental regression or delayed development
- The ambiguity of the external sexual organs
- Craniofacial dysmorphism

Craniofacial dysmorphism, neurodevelopmental delay, and congenital heart anomalies have been linked in the setting of a genetic disorder. As a general guideline principle genetic testing is required in a child with CHD and an extracardiac lesion that falls within any of the above mentioned categories. In this review, we aim at characterizing phenotype-genotype correlations found in children with congenital heart anomalies, with an emphasis on facial dysmorphic cues. We will approach the matter by classifying genetic diseases according to the main mechanism - structural or numerical chromosomal anomalies, and monogenic anomalies. For the purpose of our article, we will exemplify each genetic category through the diseases which have distinct facial features and comment upon the associated cardiac anomalies.

MONOGENIC DISORDERS WITH CARDIOVASCULAR INVOLVEMENT

Noonan, LEOPARD, Costello, and cardiofaciocutaneous syndromes are united under the general name of RASopathies, because they involve mutations in genes of the RAS-MAPKinase pathway. In theory, each syndrome has its own phenotypic and genotypic characteristics, but their overlap makes diagnosis often difficult from a clinical point of view (Cassidy and Allanson, 2010).
Noonan syndrome (NS) occurs in 1: 1000 live births. The disease has an autosomal dominant (AD) transmission, but the high mutation rate in the *PTPN11* gene causes numerous sporadic cases.75 Clinically, the disease is manifested by short stature, dysmorphic features such as hypertelorism, low insertion of the ears with posterior rotation, ophthalmological disorders, auditory disorders going as far as deafness, pectus excavatum, cardiac and genitourinary anomalies (Ware and Jefferies, 2012).
80% of individuals with NS have cardiac abnormalities. Valvular pulmonary stenosis is the most common along with atrial septal defect (ASD), followed by ventricular septal defect (VSD), tetralogy of Fallot (TOF), pulmonary artery stenosis, coarctation of the aorta, and polyvalvulopathies (Cassidy and Allanson, 2010).
Costello syndrome has common characteristics with Noonan, but its manifestations are markedly more severe, being caused by mutations of the HRAS gene, transmitted through the paternal line. The skin damage translates into hyperpigmentation, papillomas, hyperelastic skin with a tendency to premature aging. Mental retardation is moderate, and the risk of developing a malignancy, especially rhabdomyosarcoma, is estimated at 15%. The most frequently reported cardiac lesions are pulmonary stenosis, hypertrophic cardiomyopathy, heart rhythm disorders, especially multifocal atrial tachycardia (Cassidy and Allanson, 2010).
As in NS, individuals with cardiofaciocutaneous syndrome (CFCS) show facial dysmorphism, but with more severe skin changes. Mental retardation is pronounced. Cardiopathies that are part of the NS spectrum are present in 75% of patients, with a significant share of hypertrophic cardiomyopathy, compared to various heart defects, such as ASD VSD, aortic bicuspidy tricuspid or mitral dysplasia. Valvular pulmonary stenosis is found in approximately one third of patients. The cause of these multiple malformations is mutations of the BRAF, MEK1, MEK2 genes, CFC syndrome showing a genetic heterogeneity similar to Noonan syndrome (Jones, Jones and del Campo, 2021).
Kabuki syndrome is a consequence of the MLL2 gene mutation, that manifests itself through characteristic facial features, reminiscent of the masks used by Japanese actors, with long palpebral slits, ectropion of the lower eyelids, hyperarched eyebrows with diminished pilosity in the outer third.12 In addition, fetal finger pads in the upper and lower limbs, growth retardation, renal anomalies, immunological disorders, intellectual disabilities. ASD, VSD have been identified in Kabuki syndrome, as well as left heart hypoplasia and Shone complex (Muenke, Kruszka, Sable, Belmont, 2015)
Other monogenic syndromes with distinct facial features are summarized in Table 1.

CHROMOSOMAL ABNORMALITIES

Down syndrome (DS) has an incidence assessed at 1:1000 in England and 1:800 in the USA (Qian, Mo, Da, Peng, Hu, & Mo, 2014), with a strong correlation between advanced maternal age at the time of conception and the risk of the syndrome in offspring. It is considered that most cases of trisomy 21 result from maternal chromosomal

nondisjunction during meiosis. In about 6% of cases a Robertsonian translocation is identified, the most frequent being rob (14;21) or rob (21;21) translocations, and in about 3% of cases there is a chromosomal mosaicism: 47,XX(XY),+21/46,XX(XY) (Shaddy, Penny, Feltes, Cetta, & Mital, 2021)

The clinical diagnosis is generally easy, thanks to the specific physical and behavioral features of the individuals. Diagnostic difficulties may arise only in the case of premature newborns, adults of advanced age or belonging to certain ethnic or racial groups, or in cases where a mosaicism or partial duplication is present, a fact that significantly changes the phenotypic expression (Cassidy and Allanson, 2010). Patients with Down syndrome characteristically have a short neck with excess skin on the back of the neck, brachycephaly, epicanthus, small nose with a flattened root, protruding tongue, small ears, small hands, clinodactyly, the presence of a single transverse palmar fold, skeletal abnormalities, visual, auditory and balance disturbances, generalized hypotonia and moderate intellectual deficiency. Cardiac malformations are present in approximately 56% of cases 50, the most common being the atrioventricular canal defect, the ventricular septal defect and the persistence of the arterial canal (Turnpenny, Ellard, & Cleaver, 2022).

On chromosome 21, a so-called „critical area" for DS was identified, with dimensions of 1.77Mb (Muenke et al., 2015), including the DSCAM gene, expressed during cardiac development, which encodes cell adhesion molecules. Studies in individuals with partial trisomy have established a 2.42 Mb region between the DSCAM and CBS genes sufficient to determine the cardiac phenotype in DS, while others have identified a gene located outside this region, in a telomeric positioning, COL61A, which encodes the α1 chain of type VI collagen, with a significantly higher degree of expression in DS patients compared to the euploid control group (Lana-Elola, Watson-Scales, Fisher, & Tybulewicz, 2011).

Susceptibility to heart disease is not only due to genes on chromosome 21, but also to genes located on other chromosomes, such as MTHRF, located on chromosome 1, or CRELD1, on chromosome 3. (Lana-Elola et al., 2011).

Trisomy 18, known as Edwards syndrome, is in most cases due to the complete trisomy of chromosome 18, but there are also cases of unbalanced translocations or cellular mosaicism (Cassidy and Allanson, 2010). Investigation of the mechanisms leading to this chromosomal abnormality revealed that, when the trisomy is complete, most often it is due to a chromosomal nondisjunction, which, in half of the cases, occurs in meiosis II of oogenesis, unlike most other trisomies, in which this phenomenon occurs in meiosis I (Cereda and Carey, 2012). The attempt to determine the nondisjunction mechanism led the researchers to the conclusion that the polymorphism of the MTHFR gene, found in 44 cases of trisomy 18 analyzed and absent in many other cases of chromosomal abnormalities studied, could be involved in this phenomenon and deserves an in-depth study (Turnpenny et al., 2022).

Clinically, patients with Edwards syndrome present with micrognathia, prominent occiput, hypertelorism with short palpebral fissures, hands with crossed fingers, short sternum, congenital anomalies of most organ systems, and growth retardation. Cardiac abnormalities that occur in this context are perimembranous VSD, TOF, double outlet right ventricle and polyvalvular dysplasias (Shaddy et al., 2021).

Individuals with Wolf-Hirschorn syndrome have a deletion at the level of the 4p16.3 region, the phenotypic consequences of which are intellectual disability, multiple congenital anomalies, and a „Greek warrior's helmet" skull appearance (prominent brow arches, hypertelorism, prominent broad-rooted nose, micrognathia, mouth with drooping corners). Atrial septal defects are the most common, but individuals may also present with DSV, patent ductus arteriosus, or TOF. The FGFRL1 gene is a candidate for cardiac pathogenesis, with experiments done on mice null for the homologous Fgfrl1 gene showing skeletal and cardiac septal and valvular abnormalities (Muenke et al., 2015).

22q11.2 deletion syndrome is the most common syndrome with chromosomal microdeletions, affecting 1/4,000 – 1/6,000 live newborns (Jones et al., 2021).

The chromosomal abnormality translates phenotypically into renal, endocrinologic, cardiac, and immunologic malformations and malfunctions. Behavioral disorders, psychiatric illnesses, difficulties in learning and oral expression (hoarse voice) and typical facial features affecting the hard and soft palate are other features of the microdeletion (Cassidy and Allanson, 2010).

Cardiopathies are present in 76% of cases12, the most frequently encountered being tetralogy of Fallot, interrupted aortic arch type B, persistent arterial trunk, perimembranous VSD, and, less commonly, pulmonary valvular stenosis, ASD, heterotaxy and hypoplastic left heart syndrome HLHS (Shaddy et al., 2021). The anomaly of the aortic arch is pathognomonic for this disease, therefore current cardiology guidelines recommend testing the 22q11.2 deletion in all patients presenting the association between the intracardiac malformations mentioned above and aortic arch interruption.

Other chromosomal abnormalities and their specific facial and cardiac features are detailed in Table 2.

DISCUSSIONS

With regard to isolated heart diseases, it was possible to establish their genetic but only in broad terms, still lacking sufficient evidence or a rigorously constructed case history to allow detailed knowledge of all the genes involved in their pathogenesis. The available genetic tests for the diagnosis of DNA mutations, such as next generation-sequencing, whole genome sequencing and whole exome sequencing have a cost/effectiveness ratio that does not justify their large-scale application. The curative therapy of non-syndromic cardiac malformations remains based on interventional or surgical methods, while stem cell infusion or tissue bioengineering remain in the trial stage. Prenatal ultrasonographic screening is a valuable tool for the early detection of cases of congenital heart malformations, providing the time window needed to detect possibly associated abnormalities and to counsel the future parental couple.

Syndromic heart diseases represent a significant cause of mortality and morbidity not only in the case of children, but also among the adult population. The association of multisystemic manifestations allows the faster detection of these anomalies, but it is also the cause of difficulties in their management. The treatment of a chromosomal syndrome or a monogenic syndrome is mostly palliative, with the cardiac component still benefiting from the same therapeutic measures applicable to isolated malformations. Cytogenetic diagnostic techniques are more accessible than those required in nonsyndromic heart diseases. Moreover, there are clear indications for prenatal or preconception investigation in carefully selected cases. Prenatal screening methods are not only imagistic. Biochemical and invasive maneuvers for harvesting fetal genetic material are also possible in order to carry out the necessary tests for the positive diagnosis of a certain syndrome.

The clinical diagnosis of a genetic disease in a pediatric patient with CHD might be facilitated by the early recognition of tell-tale signs such as facial dysmorphism and intellectual disability.

We propose that the dysmorphologic approach for medical practitioners other than the geneticist should follow 8 criteria:

- skull shape anomalies
- abnormal lateral distance between the orbits
- anomalies of the palpebral fissures
- ear abnormalities
- maxillary or mandibular defects
- neck anomalies (short neck, webbed neck, etc)
- limb abnormalities (brachydactyly, clynodactyly, simian crease, etc).

In syndromes with distinct facial features, one or more of the above mentioned aspects will be modified, prompting the suspicion of a genetic disease. If a cardiac murmur or a developmental delay is associated, it becomes paramount to request the geneticist's evaluation.

In patients with CHD, uncovering the underlying genetic condition is an essential step prior to surgical repairmen. Genetic diseases associate different intra- and postoperative risks depending on the specifics of each anomaly. For example, trisomy 21 predisposes to malignant rhythm disorders immediately postoperatively and monosomy X is associated with a significant risk of renal failure in patients undergoing surgery (Peterson, Setty, Knight, Thomas, Moller, & Kochilas, 2019).

CONCLUSIONS

In a patient with suspected or diagnosed CHD, the presence of dysmorphic features should be an indicator of an underlying genetic condition that needs to be diagnosed before surgical management of the cardiac defect. Despite the multitude of monogenic and chromosomal abnormalities associated with congenital heart anomalies, there are a few classic tell-tale signs that any medical practitioner should be able to recognize. In this paper, we proposed a simple dysmorphologic algorithmic evaluation that should be performed during every clinical examination.

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LIST OF TABLES

Table 1
Monogenic disorders: facial dysmorphism, cardiac and genetic testing considerations[5,8]

MONOGENIC DISORDER	DYSMORPHIC FEATURES	CARDIAC ANOMALIES	GENETIC TESTING
RASopathies	Hypertelorism, Low insertion of the ears with posterior rotation Short palpebral fisures Micrognathia	VSD, ASD, TOF Pulmonary stenosis	Gene sequencing
Treacher Collins	Important microretrognathia Coloboma Low insertion of the ears with posterior rotation	Atrioventricular canal Atrial septal aneurysm	Gene sequencing PCR, MLPA
Cornelia de Lange	Microcephaly Hypertelorism, Small nose with a flattened root Microstomia Limb anomalies	VSD, ASD, patent foramen ovale	Clinical diagnosis
Rubinstein	Hypertelorism Small nose with a flattened root Low insertion of the ears with posterior rotation Micrognathia Broad thumbs and first toes	VSD, ASD, PDA, HLHS	Clinical diagnosis FISH
Seckel	Microcephaly Short neck	PDA, VSD	Gene sequencing Array-CGH
Klippel-Feil	Hemifacial microsomia Retrognathia	Coarctation of the aorta ASD	Gene sequencing

Table 2. **Chromosomal anomalies: facial dysmorphism, cardiac and genetic testing considerations**[5,8]

GENETIC SYNDROME	DYSMORPHIC FEATURES	CARDIAC ANOMALIES	GENETIC TESTING
Chromosomal Aneuploidies			
Down	Short neck Loose nuchal skin Brachycephaly Epicanthus Upslanting palpebral fissures Brushfiled spots Small nose with a flattened root Low nasal bridge with upturned nares Protruding tongue Small ears Brachydactyly Clinodactyly, Single transverse palmar fold Small hands	ASD, VSD, Atrioventricular canal, Great Arteries Transposition, PDA	Karyotyping
Edwards (Trisomy 18)	Prominent occiput Narrow bifrontal diameter Low-set, malformed auricles Short palpebral fissures Micrognathia	ASD, VSD, TOF, DORV	Karyotyping
Patau (Trisomy 13)	Microcephaly Sloping forehead Microphathalmia Colobomata of the iris Cleft lip or palat Skeletal anomalies	ASD, VSD, Great Arteries Transposition, Coarctation of the aorta, PDA	Karyotyping
Turner (Monosomy X)	Short neck Webbed posterior neck Ear anomalies	Aortic bicuspidy, Coarctation of the Aorta, HLHS, ASD, VSD	Karyotyping
Chromosomal deletions			
DiGeorge		TOF, PTA, VSD, ASD, HLHS	FISH, MLPA
7q11 deletion (Williams syndrome)	Broad forehead Short palpebral fissures Depressed nasal ridge Bitemporal narrowing, Stellate iris pattern, Short upturned nose with bulbous tip Long philtrum Wide mouth, full lips and mild micrognathia.	Valvular, coronary and systemic stenosis	FISH Array-CGH
11q23 deletion (Jacobsen syndrome)	High prominent forehead Facial asymmetry Broad nasal bridge and short nose; Thin upper lip Down-turned mouth Micrognathia Low-set and malformed ears.	VSD, mitral and aortic valvular anomalies	Array-CGH
4p16.3 deletion (Wolf-Hirschhorn	Prominent brow arches Hypertelorism	ASD, VSD, TOF, PDA	FISH Array-CGH

syndrome)	Prominent broad-rooted nose Micrognathia, Down-turned mouth		
17p11.2 deletion (Smith-Magenis syndrome)	Brachycephaly Flat midface Broad nasal bridge Synophrys Prognathia Ear anomalies	ASD, VSD, Aortic bicuspidy, PDA,	FISH MLPA
17q21.31 deletion (Koolen-de Vries syndrome)	Macrocephaly Long face Upslanting palpebral fissures Epicanthal folds Tubular nose Long columella	VSD, ASD, bicuspid aortic valve	Chromosomal microarray (CMA), Multigene panel, Genomic testing