Review

Genetic syndromes and congenital heart defects: how is surgical management affected?

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Summary

The population of neonates and children with congenital heart defects presents about a 30% prevalence of associated genetic syndrome or additional extracardiac anomalies and may show an increased risk of death or major complication at cardiac surgery. Since a well-defined pattern of combined cardiac and extracardiac anomalies may be found in relation to specific genetic defects, correct understanding of the genetic issues may help improving diagnosis, surgical approach and final outcome of these patients. Hereby we review the medical and surgical issues correlated to the genetic asset in patients with congenital heart defects and genetic syndromes, including trisomy 21, deletion 22q11, Noonan/LEOPARD, Turner, Marfan and Williams syndromes. Recognition of specific surgical risk factors can lead to the preparation of specific diagnostic and perioperative protocols in order to reduce operative mortality and morbidity.

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1. Introduction

Recent epidemiological studies showed that about 30% of patients with congenital heart disease (CHD) present a genetic syndrome or an association of cardiac and extracardiac anomalies [1—3].

Despite the impressive improvements in surgical repair of even the most challenging CHD, patients featuring genetic syndromes or extracardiac anomalies may show an increased risk for death or major complications, requiring dedicated care in the postoperative period [2—4], and representing the 'last challenge' in pediatric cardiac surgery.

During the last decades, the study of the inherent causes of CHD has been one of the most stimulating fields of cardiovascular research and recent advances allowed to better outline the etiology, the pathogenesis and the link between genetics and morphology of cardiac defects.

Although a non-specific homeostasis damage [5] cannot be ruled out in some chromosomal defects, congenital malformations associated with genetic syndromes are explained in the majority of cases on the basis of the specific genetic defect. The genotype—phenotype correlation is founded on the study of several well-known syndromes [6], including Down syndrome [7], DiGeorge velocardiofacial syndrome with chromosome 22q11 deletion [8], Williams syndrome [9] Holt—Oram syndrome [10], Ellis—Van Creveld syndrome [11], Marfan syndrome [12], Noonan syndrome [13] and Turner syndrome [14]. Patients with these genetic syndromes show not only specific types of CHD but frequently present specific additional cardiovascular defects that, in association with their extracardiac anomalies, may represent peculiar prognostic pictures. The increasing experience of pediatric cardiac surgery suggests that in this field, the genotype—phenotype correlation, time has come for a genotype-prognosis correlation.

2. Specific genetic syndromes

2.1. Trisomy 21

Trisomy 21 (Down syndrome) is the most common identifiable cause of mental retardation with a prevalence of 1:700 live births. Clinical characteristics include facial anomalies, short hands with a high frequency of single palmar
crease, neonatal hypotonia, gastrointestinal malformations, and cardiovascular defects in about 50% of patients [1]. Down syndrome is caused by trisomy of chromosome 21. Molecular studies performed on chromosome 21 have identified a ‘critical region’ for CHD. Several genes mapping inside this region have been suspected to be implicated. These genes, including DSCAM, the gene for collagen type VI [15] have been demonstrated to be involved in mechanisms of cellular adhesion and fusion of endocardial cushions. Cardiac defects are frequent in this syndrome including atrioventricular canal, atrial and ventricular septal defects and tetralogy of Fallot [1,16]. In 1986 our group first reported a low prevalence of left-sided obstruction in patients with Down syndrome and atrioventricular canal [7]. This observation was confirmed by subsequent epidemiological studies in a high number of patients [1,16—18]. In concert with these observations, results of surgical repair of both the partial [19,20], and the complete type [21—24] of atrioventricular canal did not show an increased risk for surgical mortality and morbidity in Down patients, despite the known tendency to develop pulmonary hypertension [25—28]. The finding of this ‘protective’ effect of the syndrome has considerably challenged the frequent skepticism about offering cardiac surgery to persons with Down syndrome [29]. Even the vexing need for reintervention on the left atrioventricular valve has proven less common in Down patients [30—32]. Other cardiac conditions associated with Down syndrome should also be considered at no increased risk for corrective surgery. This is the case of isolated ventricular septal defect [33], despite the prevalence of ‘inlet type’ defect in this syndrome [34]. The same applies to the case of tetralogy of Fallot [35—37]. On the contrary, although the knowledge on this argument is limited, Down syndrome still seems to represent a relative contraindication to Fontan operation in relation to pulmonary hypertension [38,39]. The prevalence of immediate or late postoperative atrioventricular block in children with Down syndrome has been reported [40,41]. In particular, after surgical closure of a perimembranous ventricular septal defect, the most significant risk factor for atrioventricular block identified was Down syndrome [41]. This finding should be explained on the basis of the specific anatomy in this syndrome including the prevalence of inlet extension of the defect [34]. Moreover, a higher mortality was reported among black children with CHD and Down syndrome [42] probably in relation to a more difficult access to cardiac care in these patients [29].

The idea that Down syndrome has a detrimental effect on cardiac outcome [29] was clearly dismantled by clinical experience showing a rather repetitive cardiac pattern in these patients [6,7,18]. Therefore, a strategy of early diagnosis and surgical repair without cardiac catheterization [43] was endorsed by many centers. Moreover cardiac surgery for children with Down syndrome does not result in an additional hospital charge since there is no difference between Down and non-Down children who underwent cardiac surgery in terms of the burden that is placed on the health care system [44,45]. Nevertheless, the associated non-cardiac issues in Down patients, e.g. the occurrence of respiratory obstructive disease, immune system disorders and infections need always to be addressed in the perioperative period [21—28,46—51,52].

### 2.2. Deletion 22q11

During the last 10 years, this condition has become the second most important genetic syndrome after Down syndrome, with an estimated prevalence of approximately 1:2—4000 live births [53,54]. Advances in molecular/cytogenetic techniques have led to the identification of microdeletion of chromosome 22q11 as the cause of DiGeorge/velocardiofacial syndrome. Clinical characteristics of deletion 22q11 include facial dysmorphism, CHD, palatal anomalies, neonatal hypocalcemia, immune deficit, speech and learning disabilities [55]. The typical 3-megabase deletion found in patients with deletion 22q11 contains just over 30 genes. It is still unknown if all clinical features are caused by different genes or whether the majority of phenotypical signs are caused by a single gene in the chromosomal region. TBX1 gene is mapping in the del22 ‘critical deleted region’ of the chromosome 22, and is likely to be responsible for many heart and vascular anomalies in this syndrome [56]. The prevalence of cardiac defects (in particular conotruncal defects) is about 75%, and deletion 22q11 is associated with peculiar aspects of cardiac anatomy, which should be known to any pediatric cardiologist and cardiac surgeon.

In children with tetralogy of Fallot and deletion 22q11, 50% of the cases present associated cardiac anomalies, e.g. absent or hypoplastic infundibular septum, absent pulmonary valve, hypoplastic or nonconfluent pulmonary arteries, multiple pulmonary blood supply in the form of major aorto-pulmonary collaterals and aortic arch anomalies including right aortic arch or cervical aortic arch [57—60]. These anatomical entities usually require some adaptation of routine surgical techniques. However recent data show that, if appropriate treatment is provided, these additional cardiac defects do not worsen surgical prognosis and deletion 22q11 do not represent a surgical risk factor in children with tetralogy of Fallot in spite of the presence of the additional cardiovascular malformations [36,37].

The prevalence of del22q11 in pulmonary atresia and ventricular septal defect is higher than in patients with tetralogy of Fallot [61]. The complex pulmonary arterial anatomy [62—64] usually associated with the syndrome may entail an additional surgical risk. Moreover, the prevalence of major systemic-to-pulmonary collaterals may be responsible for bronchomalacia and persistent airway hyperresponsiveness with bronchospasm in the pre- and postoperative periods [65]. Deletion 22q11 syndrome certainly affected surgical results in early experience, probably not only because of the unfavorable anatomy, but also for the concomitant reduction of the immune competence and tendency to postoperative airway bleeding [67,68]. Improved experience with unifocalization techniques [69], strict application of irradiated blood transfusions and modified perioperative antimicrobial prophylaxis probably may reduce the operative risk of patients with pulmonary atresia with ventricular septal defect and deletion 22q11 and make it comparable to that of non-deleted patients [70].

In the case of common arterial trunk, patients with deletion 22q11 may present pulmonary discontinuity with a dysplastic and stenotic truncal valve [71,72], but with no
evidence of increased risk for surgery [36,73,74], even at long-term follow-up.

In patients with interrupted aortic arch, clinical investigations have provided evidence that type B interruption (between left carotid artery and left subclavian artery) is most frequently associated with deletion 22q11, in up to 80% of cases [75]. A hypoplastic and posteriorly deviated infundibular septum with additional aortic arch anomalies are also frequent in deleted patients with interrupted arch [75]. The aortic valve can be bicuspid and/or associated with hypoplastic aortic annulus. While it is still unclear, yet, whether deletion 22q11 should be considered as a risk factor for short-term surgical mortality, recent observations seems to indicate the possibility of an higher surgical risk [36,76—78], probably due to the specific anatomy of the left ventricular outflow tract.

Cardiologists and surgeons should be alerted by the presence of this syndrome as an indicator of complex cardiac and vascular anatomy and the preoperative assessment should include cardiac catheterization and angiography for a better definition of the systemic and pulmonary vascular morphology. Magnetic resonance imaging can improve the visualization of the thoraco-vascular anomalies. Perioperative care should be focused on prevention of hypocalcemia and infections, including: (1) analysis of lymphocyte populations prior to transfusion, (2) administration of irradiate blood products, and (3) aggressive treatment of perioperative infections with antimicrobial and antifungal prophylaxis [79]. Vasomotor instability should also be taken into account [80], as well as possible bronchospasm [65,66], laryngeal web [81,82] and airway bleeding [67]. Moreover recent studies showed in these patients a worse post-operative neurodevelopmental outcome [83,84], as the result of the syndrome itself or from an interaction between the syndrome and the surgical treatment [85,86].

2.3. Noonan and LEOPARD syndromes

Noonan syndrome is characterized by CHD, short stature, pterygium colli, thoracic anomalies, bleeding diathesis and facial anomalies. PTNP11, a gene encoding the protein tyrosine phosphatase SHP-2 located at chromosome12q22-2qter, is the first gene identified for Noonan syndrome, found to be mutated in 40—50% of the patients [87]. Different mutations in the same gene cause LEOPARD syndrome, a genetic condition with clinical features overlapping those of Noonan syndrome but presenting also multiple lentigines and deafness [88]. In both syndromes cardiac defects are frequent (50—60% of cases) including pulmonary valve stenosis and hypertrophic cardiomyopathy [13,87—89].

Noonan syndrome is more often associated with pulmonary valve stenosis with typically thickened semilunar leaflets usually unsuitable for interventional balloon dilation, thus requiring surgical intervention. If an atroventricular canal is present, it is prevalently of the partial type, possibly associated with left ventricular outflow obstruction due to anomalous insertion of the mitral valve [13], a demanding associated malformation for the surgeon. When cardiac surgery or other invasive procedures are needed, possible bleeding disorders including thrombocytopenia and platelet dysfunction should be taken in account [90]. These complications were reported only in patients with PTNP11 mutations [91]. Hypertrophic cardiomyopathy is less common in patients with Noonan syndrome and PTNP11 gene mutations, while it is the prevalent cardiac defect in LEOPARD syndrome [88,89]. PTNP11 mutations associated with Noonan syndrome cluster mainly in exons 3 and 8, while those associated with LEOPARD syndrome cluster in exons 7 and 12 [89]. Severe left ventricular hypertrophy carries a risk of fatal event during the follow-up and coronary and myocardial anomalies may also occur in LEOPARD syndrome [92]. A recent study showed that hypertrophic cardiomyopathy associated with malformation syndromes (represented by Noonan syndrome in 78% of cases) has a worse clinical outcome [93]. More recently, three additional genes have been identified to be related to Noonan syndrome, all belonging to the same pathway as PTNP11. KRAS (causing a severe phenotype with pulmonary stenosis or hypertrophic cardiomyopathy), SOS1 (related to a distinctive phenotype characterized by pulmonary valve stenosis with/without atrial septal defect and ectodermal anomalies) [94], and RAI1 (detected in patients with Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy) [95].

2.4. Turner syndrome

Turner syndrome is a genetic disorder with absence or structural anomalies of the second sex chromosomes. Clinical features include short stature, gonadal dysgenesis, CHD, renal malformation, facial anomalies, and pterygium colli [14]. The presence of cardiac defect varies in this syndrome between 20% and 40% including partial anomalous pulmonary vein connection, bicuspid aortic valve, aortic coarctation and other types of left-sided obstruction, up to a full hypoplastic left heart syndrome [14]. CHD, in particular aortic valve abnormalities and aortic coarctation, seems to be prevalent in children with 45,X karyotype versus patients with 45,X/46,XY karyotype [96]. In children with Turner syndrome and aortic coarctation, friability of the aortic wall with higher risk of hemorrhages has been reported at surgery [97,98] and after stent implantation [99]. Furthermore the presence of Turner syndrome was reported as a risk factor for Norwood stage I repair of hypoplastic left heart syndrome [100,101]. However a recent study suggests that extracardiac anomalies and genetic syndromes did not increase the operative mortality for this cardiac defect but were predictors of a poor mid-term outcome [102]. Finally, in patients with this syndrome aortic dilation, dissection and even rupture have been described early in life with a prevalence of 36/100000 Turner syndrome per year [103,104]. The majority of these patients have additional risk factors including bicuspid aortic valve, aortic coarctation or systemic hypertension and deserve accurate cardiological assessment [103] in particular during pregnancy [105,106]. However aortic dissection in persons with Turner syndrome can occur also in absence of CHD or systemic hypertension suggesting that the presence of the syndrome alone is an independent risk factor [107]. Ascending aortic diameter should be normalized in these patients to body surface area and an aortic size index ≥2.5 cm/m² is a higher risk factor for aortic dissection [108]. Moreover, recent papers [109,110] identified in patients with Turner syndrome a vasculopathy involving intimal and medial
thickening of large arteries and these findings can represent the substratum for the development of dilation and dissection of the aorta. In order to prevent this complication, patients with Turner syndrome should be offered a protocol with accurate clinical and echocardiographic follow-up [111], including monitoring of blood pressure [112].

2.5. Marfan syndrome

Marfan syndrome is an autosomal dominant disorder of the connective tissue characterized by musculoskeletal, ocular, and cardiovascular complications, caused by mutations in fibrillin 1 gene on chromosome 15 [113]. Fibrillin is the principal structural component of the elastin associated connective tissue microfibrils. Cardiovascular involvement is present in the 70–80% of cases including aortic dilatation with the risk of aortic dissection and mitral valve prolapse with or without mitral regurgitation. Also the main pulmonary artery is enlarged in this syndrome but this feature rarely leads to clinical consequences. The aortic stiffness is reported to be increased in patients with Marfan syndrome compared to patients with juvenile forms of ascending aortic dilatation without Marfan syndrome [12].

Beta-blockers have been considered the therapy of choice in order to delay aortic aneurysm and dissection. However a recent meta-analysis suggests that there is no evidence of significant clinical benefit of this drug [114], and ACE inhibitors seem to provide a better aortic distensibility and reduced aortic stiffness index [115]. It is interesting to note that in a mouse model of Marfan syndrome the angiotensin-receptor antagonist losartan reduced the aortic grow rate and prevented elastic fiber degeneration [116]. Large randomized control trials may help to define which is the better therapy for the long-term management of these patients [117–120]. Ventricular arrhythmias in relation to increased left ventricular size and mitral valve prolapse can represent a further risk factor for sudden death in these patients [121].

Prophylactic cardiovascular surgery can avoid aortic dissection and substantially prolong survival by aortic root replacement with appropriate technical modifications [122–124]. Patients with Marfan syndrome have typically a younger presentation of aortic dissection [122] and the gender differences suggest considering a reduction of threshold limits for elective aortic root replacement in women [125]. Surgical indications in adults include a dilated aortic root reaching 5 cm, rapid aortic dilation exceeding 1.5 mm per year (or 5% per year) and a family history of aortic dissection [123–126]. Moreover severe aortic valve regurgitation and progressive left ventricular dilatation and/or dysfunction indicate early surgery also at an aortic dimension <5 cm [110]. A very early clinical presentation necessitating operation in neonatal age and infancy obviously represents a significant risk factor [127,128]. Moreover cardiac transplantation should be considered after ineffective surgery and in the presence of refractory heart failure [129,130].

2.6. Williams syndrome

Williams syndrome is characterized by typical facial anomalies, mental retardation, CHD, short stature, and connective tissue abnormalities, caused by a submicroscopic deletion of chromosome 7q11.23 [131]. More than 20 genes have been mapped inside the commonly deleted region, spanning approximately 1.5 megabases. Many of the clinical features of Williams syndrome, including cardiac defect, are caused by the deletion of the elastin gene [131]. In fact, the abnormal elastin protein product causes proliferation of arterial smooth muscle and intimal hyperplasia resulting in arterial stenoses in particular at supravalvar aortic and pulmonary artery levels but also at mesenteric and renal artery levels with a tendency to arterial hypertension [9,132].

Cardiac defects occur in about 75% of cases and present a specific anatomy, natural history, and treatment [9]. Supravalvular aortic stenosis is a progressive lesion [9], which can occur both in the form of localized hourglass narrowing of the supravalvar area or diffuse narrowing extending into the aortic arch and into the origin of brachiocephalic arteries. Good surgical outcome can be achieved especially in the localized variety by appropriate surgical treatment, with particular care for complexity and specificity of featured left ventricular outflow tract obstruction [133,134]. On the contrary, stenoses of pulmonary arteries are likely to spontaneously improve in patients with this syndrome [9]. However in the most severe cases a staged approach with dilation of distal segments followed by surgical reconstruction of proximal segments of the pulmonary arteries may be advisable [135]. Moreover characteristics of peripheral vascularity, coronary arteries, and cerebral vessels of these patients may specifically complicate both history or treatment procedures, such as cardiac catheterization, anesthesia, and surgery [132–137]. Due to the frequent association with coronary artery stenosis, the preoperative assessment must include coronary angiography [133,134,136,137]. Moreover specific perioperative procedures are needed in order to minimize the risk factors associated with this syndrome including difficult intubation and/or ventilation and/or intubation and atypical reaction to drugs, and temperature regulation [136,137].

Children and adolescents with Williams syndrome are at high risk for systemic hypertension [138] probably in relation to structural arterial anomalies [139]. Moreover anomalies of left ventricular myocardial mechanics are also described in children with Williams syndrome even in the absence of supravalvular aortic stenosis or hypertension [140].

Sudden death is rare in this syndrome [141] being prevalently related to cardiac defects with biventricular obstruction and/or to coronary artery stenosis. Finally coronary artery stenosis can occur in this syndrome also in patients without supravalvar aortic obstruction [142,143].

3. Other syndromes

Trisomy 13 and trisomy 18 carry quite an unfavorable short-to-mid-term prognosis per se and are usually considered unsuitable for repair of associated cardiac malformations such as ventricular septal defects, tetralogy of Fallot, atrioventricular canal defects and aortic coarctation. Interestingly, however, recent data show an improvement of the overall surgical results [144].
With respect to the other less frequent types of genetic syndromes associated with CHD, a few data are available on their impact on surgical prognosis. In our recent experiences, in the overall population of patients with conotruncal defects [36,37,78], Down syndrome and 22q11 deletion do not represent surgical risk factors but VACTERL, Alagille1 and Cantrell syndromes do. On the other hand at present no surgical data are available on specific operative prognosis for patients with CHD and Holt–Oram [10] or Ellis–van Creveld [11] syndromes.

4. Conclusions

Nearly one third of all patients with heart defects show an association with extracardiac malformations or with a genetic syndrome, which prompts further clinical and molecular investigations [1–6]. These patients may not only represent a surgical challenge but also suffer from a specific impairment of their clinical conditions. Moreover since the final goal of our inquiry is the comprehensive outcome of patients, we cannot feel satisfied by the surgical result only but we must pursue the general well-being of children with cardiac defects. Nowadays, a comprehensive medical approach must include a genetic assessment, in particular in cases with extracardiac anomalies [6]. For an accurate ‘case management’ an early and accurate multispecialistic approach together with a strict follow-up are essential for the care and for the prevention of complications.

Risk stratification based on genotyping is a very interesting perspective in cardiology [146,147] as brilliantly showed by the experience with hypertrophic cardiomyopathy [148] or with the long-QT syndrome [149]. This process of ‘reversal medicine’ should provide clinicians the ability to further test the accuracy of the anatomic and clinical criteria used for phenotyping, and search for new sensitive and specific diagnostic criteria based on the genetic status also in order to improve the classification of congenital defects [146–150].

The shift from a genotype–phenotype correlation [6] towards a genotype-prognosis paradigm in pediatric cardiology is finally on the way, making the ‘predictive medicine’ [146–149] a reality of the near future also in this field. A careful assessment of the specific risk factors obtained by large multicentric studies on patients with and without genetic syndromes could significantly reduce the operative mortality and morbidity, providing the opportunity to prepare genetic-specific treatment protocols. Under such circumstances, our perioperative policy adopted in patients with pulmonary atresia with ventricular septal defect and deletion 22q11 might confirm the value of this approach in order to improve surgical results [67,70]. In this regard genetic counseling and laboratory tests should be performed in all children with syndromic clinical aspects and surgical papers should always report in their series the actual presence of patients with genetic syndrome. More precise data on specific surgical prognosis may also increase our ability to counsel families after prenatal diagnosis of CHD and genetic syndrome.

1 Alagille syndrome is due to a mutation of JAG1 gene. It is frequently associated with peripheral pulmonary arterial stenoses. This may have a negative impact on survival in children with pulmonary atresia [145].

In the past, treatment of CHDs associated with genetic syndromes has always been a debated issue [29]. The most striking example is the case of Down patients, who often had difficult access to cardiac care [151], including delay of the diagnosis, controversies about medical versus surgical treatment [29] and discrimination in accessing life insurances [152]. The results of cardiac surgery and the scientific evidence that Down syndrome does not have a negative prognostic value [19–24], have made the arguments for denying cardiac care to these patients very tenuous. The medical and surgical care for Down patients which are currently standard practice in many modern countries greatly enhanced survival and postoperative clinical conditions of these patients [153,154]. We think that the experience with Down syndrome should act as a raw model of unbiased treatment policy for every other genetic syndrome.

Survival in the early era of cardiac surgery was a challenge even in simple cases and society was somewhat biased towards considering syndromic patients eligible for a cardiac repair [155]. The greatly improved ability to repair the heart has changed the perspective and nowadays the surgical results for many patients with a genetic syndrome are much better than in the past [156].

While waiting for the bench scientists to make gene therapy become a plausible expectation, the primary role of the bedside physicians is to continue their efforts towards repairing the phenotype even in the most complex cases. Moreover, in order to reduce the ‘social charge’ of congenital defects and the handicap of these patients, doctors could expand their role to reach a friendlier environment for all persons with congenital malformations obtaining for them a quality of life as close to normal as possible.

References


