Clinical Syndromes Associated with Cardiovascular Diseases: A Review

Xing Sheng Yang, MD, PhD, FACC, FAHA, Jing Ping Sun, MD and Bryan Yan, MD

Division of Cardiology, Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, N.T. Hong Kong, China

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Abstract
In clinical practice, a variety of syndromes are associated with cardiovascular disease and have characteristic findings. Most of them are an autosomal dominant genetic disorder and have different types of cardiovascular abnormalities, including electrocardiographic conduction defects, arrhythmias, cardiomyopathy, vascular and valvular diseases, cardiac septal defects, and pulmonary problems. There is a growing need for physicians to pay more attention to these syndromes.

Keywords: Clinical syndrome; Marfan syndrome; Down syndrome; Ehlers-Danlos syndrome; Fabry disease; LEOPARD syndrome; Loeys-Dietz syndrome; Noonan syndrome; Turner syndrome

Down Syndrome

In every cell of the human body there is a nucleus that contains 23 pairs of chromosomes. When an individual has a full or partial extra copy of chromosome 21, Down syndrome occurs [1]. This is characterized by an upward slant of the eyes, oblique fissures, epicanthic skin folds on the inner corner, and white spots on the iris. The individual has low muscle tone, small stature and a short neck, a flat nasal bridge, single, deep creases across the center of the palm, a protruding tongue, large space between the large toe and the second toe, and a single flexion furrow of the fifth finger [2]. The cause of the extra full or partial chromosome is still unknown, but the extra partial or full copy of chromosome 21 can originate from either the father or the mother. Approximately 5% of cases have been traced to the father [1].

Down syndrome has three different types: trisomy 21 (nondisjunction), which affects around 1 in every 800 babies born in the United States [3]; translocation, which accounts for about 4% of the total number of cases; and mosaicism, which accounts for only about 1% of all cases [1].

In patients with Down syndrome, abnormalities of the cardiovascular system are common [4]. About half of all infants born with Down syndrome have a heart defect, the most frequent being atrioventricular septal defect (formally called endocardial Cushion defect) or atrioventricular canal defect (45%), ventricular septal defect (35%), secundum atrial septal defect (8%), persistent ductus arteriosus (7%), and tetralogy of Fallot (4%), or any combination of multiple defects [2, 5]. Hypertrophic cardiomyopathy can occur in individuals with Down syndrome, and in adult patients, although it
is rare, the apical form is frequent [6]. Down syndrome is associated with pulmonary hypertension, but there are many causes, requiring a multidisciplinary approach to the problem. Extra problems include pulmonary hypoplasia, structural lung disease, and gastroesophageal reflux [7].

**Ehlers-Danlos Syndrome**

Ehlers-Danlos syndrome (EDS) consists of a heterogeneous group of diseases, characterized by fragility of the soft connective tissues and manifested in skin, ligaments, joints, blood vessels, and internal organs. The clinical manifestation ranges from mild skin and joint hyperlaxity to severe physical disability and life-threatening vascular complications. The current Villefranche classification recognizes six subtypes. (1) classic, which is the most frequent form; (2) hypermobility; (3) kyphoscoliosis; (4) arthrochalasia; (5) dermatosparaxis; and (6) vascular, which is the most dramatic form [8]. Mutations in type V and type III collagen cause classic and vascular EDS respectively [9].

EDS hypermobility type is a very common subtype of EDS and the least severe one; EDS hypermobility type is same as joint hypermobility syndrome and manifests itself as musculoskeletal problems, joint instability, and soft tissue overuse injury. Extra manifestations include cardiovascular disorder [10].

EDS vascular type is a rare inherited autosomal dominant connective tissue disorder caused by a mutation in the COL3A1 gene encoding pro-\(\alpha_1\) chain of type III collagen, with an estimated prevalence of 1 in 150,000, and has four main characteristics: (1) rupture of blood vessels or internal organs such as the uterus and intestines, (2) an unusual facial appearance, (3) easy bruising, and (4) translucent skin with visible veins [11]. An important clinical event in EDS vascular type is that of systemic arteries, which may undergo dissection, aneurysm, or rupture. These dramatic events may also occur spontaneously [12]. There have been reports of some cases of EDS associated with hypertrophic obstructive cardiomyopathy [13], and with a ruptured celiac artery and a strong family history of EDS [14]. Mitral valve prolapse is a manifestation in patients affected by the vascular type of EDS [15].

Mitral regurgitation and mitral valve prolapse are reported in EDS kyphoscoliosis type [16]. Recently a study indicated that EDS vascular type is associated with platelet dysfunction and low vitamin D serum concentration in more than half of patients and the importance of detailed laboratory screening methods for these patients to allow targeted application of platelet-interacting substances that might be of decisive benefit in the emergency setting [17].

EDS arthrochalasia type is very rare [18], and is due to a defective processing of type I collagen synthesis and characterized by joint hypermobility, skin hyperextensibility and tissue fragility. There are two forms: types A and B. Type A is due to the disruption of procollagen chain \(\alpha_1(I)\), encoded by COL1A1; type B is due to abnormality of \(\alpha_2(I)\), a procollagen chain encoded by COL1A2 [19]. A girl with EDS arthrochalasia type B developed mitral valve regurgitation, and aortic and tricuspid insufficiency confirmed by echocardiography at 7 years of age [19].

**Fabry Disease**

Fabry disease is a rare genetic lysosomal storage disease, inherited in an X-linked manner, and can cause a wide range of systemic symptoms [20].

When glycolipids build up in different heart cells, complications occur; heart-related effects worsen with age and may increase the risk of heart disease. High blood pressure and restrictive cardiomyopathy are commonly observed [21]. Patients with a cardiac variant are mainly characterized by myocardial hypertrophy. Therefore the cardiac variant of Fabry disease may be defined as a cardiomyocytic storage disorder, thus mimicking the clinical features of hypertrophic obstructive cardiomyopathy and especially hypertrophic nonobstructive cardiomyopathy [22]. In clinical practice if the patient shows unexplained left ventricular hypertrophy, especially after 40 years of age [23], the diagnosis of a cardiac variant of Fabry disease should be considered, and examination is performed by light and electron microscopy evaluation of endomyocardial catheter biopsy specimens and/or serologic studies (decreased activity of \(\alpha\)-galactosidase A in plasma or leukocytes). Several studies showed that between 4 and 8% of unselected patients with the clinical
features of hypertrophic nonobstructive cardiomyopathy have a cardiac variant of Fabry disease [24].

In patients with Fabry disease, palpitations and arrhythmias are common features. The most frequent rhythm abnormalities include supraventricular tachycardia, atrial fibrillation, and flutter. Non-sustained ventricular tachycardias and fatal malignant arrhythmias have been reported [25, 26]. Valvular disease is partly due to infiltrative changes within valvular fibroblasts. Valvular changes are almost exclusively in the left heart valves, and may be due to the higher hemodynamic stresses in the left side of the heart [24], although pulmonary valvular involvement has been reported [27]. Valvular regurgitant lesions are usually mild to moderate and only rarely require surgical intervention. Some cases associated with aortic root dilatation at the valve level have been reported, particularly in advanced stages of the disease [22, 28].

Data from the Fabry Outcome Survey database indicated a low incidence of ischemic events and myocardial infarctions. Angina and chest pain are reported by almost 23% of females and 22% of males [29, 30]. In some cases, vasospasms may contribute to the anginal symptoms [31]. Anginal pain and electrocardiographic changes including ST-segment depressions and T-wave inversions are more frequent in patients with left ventricular hypertrophy, and might be the cause of misdiagnosis of acute or subacute myocardial infarction, Epicardial coronary arteries are only rarely occluded [32]. On the basis of a case report [33], the risk of death from coronary artery disease should not be underestimated.

**LEOPARD Syndrome**

LEOPARD syndrome is an autosomal dominant genetic disorder, consisting of lentigines, electrocardiographic conduction defects, ocular hypertelorism/obstructive cardiomyopathy, pulmonary stenosis, abnormalities of the genitals, retarded growth resulting in short stature, and deafness or hearing loss [34]. Facial dysmorphisms are characteristic features and change with age, and can occur or may be only mildly expressed in newborns as well as infants and become evident during childhood. Almost all patients have hypertelorism, and about 87% of the patients have a flat nasal bridge and dysmorphic ears [35]. Adult patients usually manifest hypertelorism, palpebral ptosis, low-set ears, deep nasolabial folds, and premature skin wrinkling [36].

In patients with LEOPARD syndrome, about 70% display heart anomalies, and electrocardiographic abnormalities occur in about 75% of them, including left or biventricular hypertrophy in 46% and often in association with q waves (19%), corrected QT prolongation (23%), and repolarization abnormalities (42%). Progressive conduction anomalies occur in 23% of patients, and p-wave abnormalities occur in 19% of patients [37]. Current data indicate that pulmonary valve stenosis is not a common defect [37, 38]. Hypertrophic cardiomyopathy is generally asymmetric and involves the left ventricle, and is found in up to 80% of patients with cardiac anomalies, which may be associated with significant left ventricular outflow tract obstruction in up to 40% of cases [34, 37, 38]. Fatal events and sudden death have been reported in patients with hypertrophic cardiomyopathy [35, 37, 39, 40]. Mitral valve prolapse, clefting, or other morphological abnormalities are found in up to 42% of cases [37]. Less frequent heart defects include atrial and atrioventricular septal defects, multiple ventricular septal defects, apical aneurysm and noncompaction of the left ventricle, isolated left ventricular enlargement, endocardial fibroelastosis, and coronary artery abnormalities [37, 41].

**Marfan Syndrome**

Marfan syndrome is an autosomal dominant disorder of the connective tissue. The incidence is around 2–3 per 10,000 individuals; there is no family history in about 25% of patients [42]. People with Marfan syndrome tend to be tall and thin, with long arms, legs, fingers and toes, and have flexible joints and scoliosis [43].

Virtually all adults with Marfan syndrome have an abnormal cardiovascular system [42]. Aortic root dilatation has an incidence of 60–80% of individuals with Marfan syndrome but is rare in children younger than 10 years, and the complication is dissection [44]. For pulmonary artery dilatation, the incidence is 76%, diagnostic features displace
in those younger than 40 years [45]. Mitral regurgitation/prolapse/annular calcification occurred in 52–68% of patients with Marfan syndrome, and regurgitation may be intermittent [46]. Tricuspid valve prolapse occurs in 4% of cases, and may progress, requiring repair, and severe diseases are uncommon except in the infantile type [47]. Four percent of cases have atrial septal defect, which is more frequent than in the normal population and may need surgical repair [48]. Children with valvular complications are at increased risk of infective endocarditis [42]. Left ventricular dysfunction occurs in almost all patients, even those with normal valves [42]. Endothelial dysfunction/abnormal aorta elasticity occurs in 80–100% of patients with Marfan syndrome, and increased vascular stiffness may contribute to dissection risk [49, 50]. In patients with Marfan syndrome, left ventricular contractility and ventricular-vascular coupling are abnormal, and the impaired function appears to be intrinsic to the Marfan syndrome ventricle and is independent of aortic stiffness. The ventricular-vascular index may serve as an identifier of Marfan syndrome patients at higher risk of heart failure and sudden death, whereas β-blockers may partially reverse abnormal ventricular-vascular coupling for them [51]. Patients with Marfan syndrome have a higher prevalence of cardiac dysrhythmias (up to 20–30% higher). They have prolonged atrioventricular conduction time, have longer QT intervals (disturbed depolarization) and more commonly have ST-segment depression [52].

Loeys-Dietz Syndrome

Loeys-Dietz syndrome (LDS) is characterized by vascular findings including cerebral, thoracic, and abdominal arterial aneurysms and/or dissections, and skeletal manifestations such as pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus [53]. There are four types of LDS: classic, hypermobility, vascular, and kyphoscoliosis types, respectively [54]. Classic type (LDS type I) and hypermobility type (LDS type II) show aortic root enlargement [55]. Aortic dissection was found in early childhood (age 26 months) and/or at aortic dimensions that do not confer risk in other connective tissue disorders such as Marfan syndrome [53]. Arterial aneurysms have been found in almost all side branches of the aorta, including the subclavian, renal, superior mesenteric, hepatic, and coronary arteries [56]. Approximately 50% of an aneurysm is distant from the aortic root and would not be detected by echocardiography [53]. Vascular type (EDS type IV) is characterized by thin, translucent skin, easy bruising, characteristic facial appearance, and arterial, intestinal, and/or uterine fragility [57]. Vascular rupture or dissection and gastrointestinal perforation or organ rupture are the presenting signs in 70% of adults. Arterial rupture may be preceded by aneurysm, arteriovenous fistulae, or dissection, or it may occur spontaneously. The median age at death is 48 years [53]. Although mitral valve prolapse with mitral regurgitation has been observed in patients with LDS, it occurs less frequently than in Marfan syndrome [53].

Noonan Syndrome

Noonan syndrome is a relatively common autosomal dominant congenital disorder [58]. The estimated prevalence of Noonan syndrome is approximately 1 in 1000 to 1 in 2500 live births worldwide [59]. The principal features include congenital heart defect, short stature, a broad or webbed neck, chest deformity with pectus carinatum superiorly and pectus excavatum inferiorly [60], and a characteristic configuration of facial features, including a webbed neck and a flat nose bridge. In patients with Noonan syndrome, oral findings include a high arched palate (55–100%) [61], dental malocclusion (50–67%) [62], articulation difficulties (72%) and micrognathia (33–43%) [63], developmental delay of variable degree, and cryptorchidism in up to 80% of boys [64]. Various coagulation defects and lymphatic dysplasias are frequently observed [65, 66]. Congenital heart disease occurs in 50–80% of individuals with Noonan syndrome. Pulmonary valve stenosis, often with dysplasia, is the most frequent heart defect, and is found in 20–50% of individuals with Noonan syndrome [58]. Hypertrophic cardiomyopathy is found in 20–30% of patients, and may be present at birth or may appear in infancy or childhood. Other structural defects frequently observed include atrial and ventricular septal defects, branch
pulmonary artery stenosis, and tetralogy of Fallot. Aortic aneurysms are rare [65]. Mild intellectual disability is seen in up to one-third of affected individuals. Ocular abnormalities, including strabismus, refractive errors, amblyopia, and nystagmus, occur in up to 95% of affected individuals [67].

**Turner Syndrome**

Turner syndrome is a genetic disorder that only affects females, wherein there is only has one normal X sex chromosome rather than the usual two (XX). The prevalence is approximately 1 in 2500 live births of girls [68]. The most important phenotypic features are short stature, gonadal dysgenesis, neck webbing [69], and an increased incidence of renal and cardiovascular abnormalities. In a study of 244 patients with Turner syndrome, 136 (56%) had cardiovascular abnormalities, 96 (71%) were structural and 40 (29%) were functional, including hypertension, mitral valve prolapse, and conduction defects. Coarctation of the aorta and bicuspid aortic valve, alone or in combination, accounted for more than 50% of the cardiac malformations [70]. Fifty-one patients with Turner syndrome were evaluated with cardiac MRI: 16 patients (31.4%) had elongation of the transverse aortic arch, 8 patients (15.7%) had coarctation of the aorta, 20 patients (39.2%) had bicuspid aortic valve, and 8 patients (15.7%) had partial anomalous pulmonary venous return. The presence of partial anomalous pulmonary venous return can be hemodynamically significant [71]. Elongation of the transverse aortic arch was significantly associated with bicuspid aortic valve, coarctation of the aorta, and aortic sinus dilatation. This association between elongation of the transverse aortic arch and well-known risk factors for aortic dissection may reflect the significance of elongation of the transverse aortic arch as another independent risk factor for aortic dissection [71]. Aortic dilatation is less frequent than some other cardiovascular malformations, but dilatation of the aortic sinus has been postulated to be an independent risk factor for aortic dissection in Turner syndrome [68, 72, 73]. Current health surveillance recommendations for Turner syndrome include echocardiography or MRI for evaluation of the diameter of the aortic root and ascending aorta at least every 5 years.

**REFERENCES**


