46 Connective-Tissue Disorders

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TCH conducts a comprehensive Cardiovascular Genetics Clinic to evaluate, diagnose, and manage children with connective tissue disorders that affect the heart as well as other conditions associated with significant aortic or arterial disease. Initial evaluation of a patient in this clinic includes:

- A thorough medical history, including a detailed family history and creation of a 3-generation genetic pedigree
- Review of any prior imaging, interventions, and genetic testing
- A complete physical examination, including:
  - A standard cardiovascular and pulmonary assessment
  - An evaluation for dysmorphic features
  - A Marfan syndrome systemic score (see below)
  - A Beighton score for joint hypermobility

If appropriate genetic testing has not been performed, it will be ordered as indicated. Due to the phenotypic similarity and genetic heterogeneity observed in many of these syndromes, the most often ordered test is an aortopathy panel, which typically includes sequencing and deletion/duplication analysis for genes causing Marfan syndrome, the Loeys-Dietz syndromes, classical and vascular Ehlers-Danlos syndromes, *ACTA2* and *FLNA* smooth muscle diseases, and arterial tortuosity syndrome, among others. For ease for the family, a saliva sample is obtained in the office for this testing. Knowing that children may not meet clinical criteria for genetic testing and that some connective tissues disorders are not well-characterized in children, the threshold for testing is often low. Testing is performed if one of the conditions below is suspected, or if there is significant aortic dilation in the presence of at least one of the following: skeletal features consistent with connective tissue disorder, a Beighton score >4, a family history of a similar condition, or significant mitral valve prolapse. Results are discussed with the family by the genetic counselor and/or the cardiologist once resulted. If genetic testing identifies a pathogenic variant, genetic counseling and cascade testing are recommended for all appropriate first-degree relatives to evaluate the need for cardiovascular screening and surveillance.

Marfan Syndrome

Marfan syndrome is the most prevalent connective tissue disorder. It is a multisystem genetic disorder caused most commonly by autosomal dominant missense, premature termination, or splice-variant pathogenic mutations in the *FBN1* gene, although *FBN1* exon deletions may also cause the condition. Individuals with Marfan syndrome exhibit significant variability in features and severity, even among relatives who share the same pathogenic variant, and there is minimal genotype-phenotype correlation. The hallmark features include tall stature with disproportionately long limbs, long fingers and toes, pectus excavatum or carinatum, progressive scoliosis, myopia, ectopia lentis, aortic root dilation, and mitral valve prolapse. The cardiovascular manifestations

Table 46-1. Calculation of systemic score for Marfan syndrome by Revised 2010 Ghent Nosology. A score ≥7 is a positive systemic score (Loeys et al. 2010).

Feature	Point Value
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum deformity	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Pes planus	1
Spontaneous pneumothorax	2
Dural ectasia	2
Protucio acetabulae	2
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
3 of 5 facial features: malar hypoplasia, downward slanting palpebral fissures, retrognathia, enophthalmos, and dolichocephaly	1
Skin striae	1
Severe myopia	1
Mitral valve prolapse	1
Reduced upper segment/lower segment ration and increased arm span/height ratio	1

are the leading driver of early mortality in Marfan syndrome, but recent advances in management are mitigating the excess risk to approach that of the general population.

When evaluating for Marfan syndrome in the pediatric population, it is important to remember that the features of this syndrome are often more subtle in children, and additional clinical findings may evolve over time. A diagnosis of Marfan syndrome can be established in a proband with 1) a confirmed pathogenic variant in *FBN1* in addition to aortic root dilation (z-score ≥2.0) or ectopia lentis; or 2) aortic root dilation in addition to ectopia lentis or a systemic score ≥7 (Table 46-1). It is also crucial to assess the family history for signs of additional affected relatives, as Marfan syndrome is inherited in approximately 75% of cases.

Management of patients with Marfan syndrome at TCH includes:

- Cardiology follow-up and imaging.
  - Lifelong cardiology follow-up with at least annual cardiovascular evaluation and echocardiography.
  - For patients with severe dilation or an absolute root measurement ≥4 cm, we will often perform a cardiac MRI with angiography (MRA) to best assess the aorta. We will also assess the vertebral-artery tortuosity index to assist in risk stratification.
- Initiation of medical management with beta-blocker and/or angiotensin-receptor

blocker (ARB, typically losartan) in the setting of aortic root dilation; consideration should be given to initiation of prophylactic medical management at the time of diagnosis even with a normal root dimension.
  - For beta-blockers, propranolol will be prescribed to infants and toddlers, atenolol will be prescribed to grade-school children and adolescents, and metoprolol XL will be prescribed to adolescents and adults.
  - For most patients with severe dilation, or more rapid growth than is expected, dual therapy with both a beta-blocker and ARB will be recommended, if tolerated.
  - During follow-up, medication doses will gradually be increased to achieve adequate beta-blockade (heart rate drop of at least 20% from baseline or 70s bpm in younger children, 60s bpm in older children/adolescents), and maximum-dose ARB (goal 1-1.5 mg/kg losartan in most patients), as tolerated, until minimum aortic growth is noted. We define optimum treatment in growing children as an unchanging aortic dimension and a declining z-score.
- First-degree relatives should undergo known familial mutation testing whenever possible as they have a 50% chance to be affected. If genetic testing cannot be performed, we will order an echocardiogram in potentially affected relatives, although those affected can be missed by echocardiography alone.
- Encourage routine aerobic exercise with strong counseling about avoidance of competitive and contact sports and high-strain activities depending upon severity of cardiovascular manifestations.
- The indication for surgical intervention in aortic root dilation is an absolute aortic dimension >5.0 cm. In the pediatric population, this may not be applicable and the rate of change of aortic root dimension is an important consideration. Counseling is given to families regarding valve-sparing aortic root replacement versus valve-replacing root replacement (Bentall procedure). Most families of young patients will opt for valve-sparing surgery to avoid bleeding complications and lifetime anticoagulation. Intervention may be indicated at >4.0 cm in any of the following situations:
  - A woman planning a pregnancy
  - Another cardiac surgery is planned
  - A family history of dissection at an aortic root dimension <5.0 cm is noted
  - Severe vertebral-artery tortuosity is present, defined as vertebral artery tortuosity index ≥50).
  - The patient reaches 4.0 cm at a very young age (i.e., <5 years old)

Ehlers-Danlos Syndromes

The Ehlers-Danlos syndromes (EDS) are a group of genetically and phenotypically heterogeneous connective tissue disorders primarily characterized by joint hypermobility and skin hyperextensibility. There are now more than 10 recognized subtypes of EDS, which are distinguished by genotype and the presence of specific additional phenotypic features. There are 3 subtypes of EDS that most commonly present to the cardiology clinic: classical, vascular, and hypermobile EDS.

Classical EDS (cEDS)

cEDS is an autosomal dominant condition caused by pathogenic variants in *COL5A1* (and less commonly in *COL5A2* and *COL1A1*). The clinical features of cEDS include hyperelastic, fragile skin that is soft and doughy to the touch, poor wound healing with atrophic scarring, significant joint hypermobility (and complication of joint hypermobility including sprains, subluxations, etc.), easy bruising, hernias, and fatigue. While cardiovascular manifestations are uncommon, aortic root dilation and mitral valve prolapse have been reported. These patients are only typically followed in the Cardiovascular Genetics Clinic if cardiovascular manifestations are present.

Management of patients with cEDS includes:

- Cardiology follow-up and imaging.
  - If no cardiovascular features noted on initial echocardiography, either no follow-up or intermittent echocardiographic follow-up (every 5 years with echocardiography) is performed.
  - If aortic dilation or significant mitral valve prolapse is present, annual evaluation with echocardiography is performed.
  - With severe dilation or an absolute root measurement ≥4 cm, we may perform cardiac MRA to best assess the aorta.
- Medical therapy
  - Patients are not typically treated with medical therapy unless aortic dilation is moderate, as aortic dissection is exquisitely rare in cEDS.
  - If moderate-to-severe dilation is present, monotherapy with a beta-blocker or ARB may be started, with same goals as in treatment for Marfan syndrome.
- First-degree relatives should undergo known familial mutation testing whenever possible as they have a 50% chance to be affected.
- Activity limitations are usually not prescribed from a cardiac perspective, although contact sports and weightlifting are sometime advised against to protect again subluxations, hernias, and skin injury in more severely affected patients.
- Aortic surgery is rarely indicated in cEDS. If aortic dilation is present nearing surgical consideration, additional/alternative diagnoses should be considered.

Vascular-type EDS (vEDS)

vEDS encompasses a more severe spectrum of cardiovascular features, including a substantial risk for arterial aneurysm, dissection, and rupture. It is a rare, autosomal dominant disorder caused by pathogenic variants in the *COL3A1* gene. The significant fragility of the vasculature in vEDS can lead to rupture even in the absence of dilation/aneurysm or trauma. Other common features include thin, translucent skin with a propensity for easy bruising, joint hypermobility, chronic joint subluxation and dislocation, congenital hip dislocation, and pneumothorax, as well as fragility and rupture of the GI tract, uterus, and other organs. The average lifespan for individuals with vEDS is 48 years.

Management of patients with vEDS includes:

- Cardiology follow-up and imaging.
  - Lifelong cardiology follow-up is necessary. In our clinic, we perform at least annual cardiovascular evaluation. Most years include either MRA from head

to pelvis or echocardiography, although for some very stable patients with no apparent cardiovascular events or aneurysm, intermittent evaluations may only include a physical examination and BP monitoring.
  - For patients with known dilation/aneurysms, or who have had a vascular event, at least annual MRA or CTA from head to pelvis is performed.
  - BP should be monitored regularly, and hypertension should be treated promptly.
- Initiation of medical management with beta-blocker is recommended for all patients with vEDS, given a European trial that showed reduced events after celiprolol, a beta-blocker, was given. Celiprolol, a third-generation beta-blocker, is not available in the US. Therefore, we recommend similar beta-blockers, including labetalol and carvedilol, even in the absence of aortic/arterial dilation or hypertension.
- First-degree relatives should undergo known familial mutation testing whenever possible as they have a 50% chance to be affected.
- All patients are counseled extensively about risks in vEDS, and to have emergency medical provider contact information and emergency plans. Patients are provided with written material to carry with them to inform emergency personnel about vEDS.
- Encourage routine aerobic exercise with strong counseling about avoidance of competitive and contact sports and high strain activities.
- Vascular interventions and surgery are avoided as much as possible, as many reported deaths in vEDS are a result of diagnostic and prophylactic interventions, including cardiac catheterization. Surgery and arterial intervention should only be considered in collaboration/communication with a team familiar with complications of vEDS or in an absolute life-threatening emergency. Colonoscopy should also be avoided for risk of colonic rupture.
- Affected women should be counseled extensively regarding pregnancy, as pregnancy confers at least a 5.3% risk for death as a result of uterine or arterial rupture.

Hypermobile EDS (hEDS)

In contrast to vEDS, the features of hEDS occur on the milder end of the phenotypic spectrum in terms of cardiovascular features. The genetic etiology of hEDS is unknown and genetic testing is therefore *not indicated* for this condition, except in circumstances where vEDS or cEDS need to be ruled out. In hEDS, the joints are hypermobile and while the skin may still be soft and doughy, it is often less hyperextensible than other EDS subtypes. Affected individuals may also exhibit spontaneous subluxations and dislocations, easy bruising, and bowel disorders, as well as cardiovascular autonomic dysfunction with frequent episodes of syncope or near syncope. Postural orthostatic tachycardia syndrome is common and may need to be treated. Chronic pain secondary to degenerative joint disease is also a common manifestation and can be debilitating. Approximately 11-33% of individuals have mild aortic root dilation, but the risk for dissection is very low and the size typically remains stable. Therefore, mild root dilation is rarely treated with medical therapy in patients with hEDS.

Loeys-Dietz Syndromes

The Loeys-Dietz syndromes (LDS) are another group of multisystem connective tissue disorders with demonstrating similar skeletal, craniofacial, cutaneous, and cardiovascular features. All known LDS subtypes are autosomal dominant and inherited from an affected parent approximately 25% of the time. Several genes have been implicated, but pathogenic variants in *TGFBR2* (causing LDS2) and *TGFBR1* (LDS1) have been observed in 55% and 20% of cases, respectively. Less frequently, pathogenic variants in *SMAD3* (LDS3), *SMAD2* (LDS5), *TGFB2* (LDS4), and *TGFB3* (LDS5) have also been reported, but the cardiac phenotype in these patients appears milder than in LDS1 and LDS2. Given this genetic heterogeneity, panel testing is most appropriate when a diagnosis of LDS is suspected.

Similar to other disorders, LDS occurs on a phenotypic spectrum from mild to severe, and variable expressivity is observed even among relatives with the same pathogenic variant. The physical findings of LDS include pectus excavatum or carinatum, joint hypermobility, scoliosis, widely spaced and prominent eyes, bifid uvula, cleft palate, craniosynostosis, easy bruising, and translucent, velvety skin with occasional dystrophic scarring. Severe cardiovascular manifestations may be observed, including widespread abdominal, thoracic, and cerebral arterial aneurysms with significant risk for dissection and rupture. More than 95% of affected individuals have some degree of aortic root dilation. There is also frequent tortuosity of the head and neck vessels. Inflammatory disease is another common symptom, including manifestations such as eczema, asthma, inflammatory bowel disease, and increased allergic reactions to dietary and environmental allergens. Spontaneous pneumothorax, recurrent hernias, and myopia can also occur.

Arterial aneurysms in LDS may be more aggressive than those observed in Marfan syndrome. In particular, the aorta has a higher risk to dissect at smaller diameters, and dissections typically have a younger age of onset, at least in the LDS1 and LDS2 subtypes.

- Cardiology follow-up and imaging.
  - Lifelong cardiology follow-up with at least annual cardiovascular evaluation.
  - Head to pelvis MRA (or occasional CTA) is recommended every 1-3 years. In years without MRA/CTA, echocardiography is performed. We will also assess the vertebral artery tortuosity index on MRA/CTA to assist in risk stratification.
- Patients should be treated with beta-blockers and/or ARBs to decrease stress to the arterial walls and reduce the risk for dissection. Commonly, patients in our clinic are placed on dual therapy.
- First-degree relatives should undergo known familial mutation testing whenever possible.
- Encourage routine aerobic exercise. Competitive and contact sports as well as isometric exercise, including lifting weights above 30 pounds, should be strictly avoided.
- Aortic root surgery is indicated when the aortic dimensions reach 4.0-4.4 cm in patients with LDS1/2. Less is known about other LDS syndromes; we assess case by case, and recommend surgery between 4.0 and 5.0 cm.
- Pregnancy may be dangerous in women with LDS, as there is risk for aortic dissection or rupture as well as uterine rupture and death, although many women tolerate

pregnancy without a problem. Comprehensive counseling should be performed prior to pregnancy planning, and should depend on each patient's individual risks. Affected individuals who become pregnant should follow closely with a high-risk obstetrician and receive frequent aortic imaging both during and after the pregnancy.

Arterial Tortuosity Syndrome

Arterial tortuosity syndrome (ATS) is a rare connective tissue disorder. Unlike most connective tissue disorders, ATS exhibits an autosomal recessive inheritance pattern, and requires a pathogenic change to both copies of the *SLC2A10* gene. As such, both parents of the affected patient are likely to be unaffected carriers, and each of their offspring has a 25% chance of having ATS, a 50% chance of being an unaffected carrier, and a 25% chance of being an unaffected noncarrier.

As its name suggests, it causes severe vascular arterial tortuosity. In addition to significant cardiovascular findings, ATS is also characterized by skeletal, craniofacial, and generalized connective tissue features. The cardiovascular features include severe elongation and tortuosity of the aorta and other mid-sized arteries, significant risk for aneurysm and dissection, and stenosis of the aorta and pulmonary arteries. There is also an increased risk for mitral valve prolapse, valvar regurgitation, dilation of the large veins, and ischemic events affecting cerebrovascular and abdominal circulation. As with most connective tissue disorders, the cardiovascular features are the primary cause of morbidity and mortality in ATS. The extracardiac manifestations of ATS include scoliosis, joint laxity and/or contractures, arachnodactyly, camptodactyly, pectus carinatum or excavatum, high-arched palate, dental crowding, myopia, hypotonia, as well as abdominal, inguinal, and/or diaphragmatic hernia.

Patients with confirmed ATS should be monitored closely by a cardiologist. Treatment depends on specific cardiovascular findings. For those with aortic dilation, medical therapy is typically limited to a beta-blocker, as the risk of renal artery stenosis may limit the use of ARBs. They should have regular echocardiograms as well as head-to-pelvis MRAs or CTAs with 3D reconstruction to evaluate aortic dimensions and stenoses.

Heritable Thoracic Aortic Disease (HTAD) caused by *ACTA2*

HTAD is a group of disorders characterized by genetically-mediated predisposition to thoracic aortic aneurysms and dissections. While there are several genes implicated in HTAD, this section will discuss features specific to HTAD caused by autosomal dominant pathogenic variants in *ACTA2,* the most frequent cause of nonsyndromic familial HTAD. Individuals with this type of HTAD typically have fusiform aortic aneurysms that involve the aortic root, ascending aorta, and aortic arch. Arch hypoplasia and coarctation are common, as is PDA. While descending and abdominal aortic aneurysms are also possible with *ACTA2* pathogenic variants, these are less common. Syndromic forms of HTAD have also been observed in association with *ACTA2*, with some pathogenic variants conferring increased risk for early-onset stroke, coronary artery disease, and/or cerebrovascular disease. A recurrent pathogenic variant disrupting the arginine 179 (R179) residue in *ACTA2* has syndromic anomalies that include aortic coarctation,

pulmonary hypertension, large PDA, gut malrotation, hypotonic bladder, congenital mydriasis, and Moyamoya-like cerebrovascular disease.

Treatment is challenging for aneurysms caused by *ACTA2*. Treatment efficacy has not yet been studied to data, but we traditionally will use ARBs or beta-blockers. However, patients are prone to baseline low diastolic pressure and high risk of stroke, especially if they have the R179 pathogenic variant. For them, hypotension can be quite risky, and often antihypertensive medications are strictly avoided. Anesthesia that is necessary for cardiac surgery may also introduce significant risk. Therefore, treatment is individualized and based on coexisting risks and morbidities.

FLNA-Related Periventricular Nodular Heterotopia (PVNH)

While *FLNA*-related PVNH is characterized as a seizure disorder caused by abnormal neuronal migration, there are associated connective tissue and cardiovascular manifestations. As its name suggests, *FLNA*-related PVNH is caused by pathogenic variants in the *FLNA* gene. In addition to seizures which are not typically observed in other connective tissue disorders, another distinguishing feature of *FLNA*-related PNVH is its inheritance pattern. This is an X-linked condition that most often exhibits prenatal or neonatal lethality in males. As such, a majority of affected individuals are female. A family history of cardiac anomalies and/or seizures primarily affecting females in an X-linked manner should indicate the need for *FNLA* or panel testing.

The cardiovascular manifestations of this condition include thoracic aortic aneurysm and dissection, coarctation of the aorta, PDA, ventricular and atrial septal defects, as well as mitral and aortic valve insufficiency. Pulmonary hypertension is also common. The unique combination of pulmonary hypertension and ascending aortic dilation should trigger suspicion for *FLNA* disease. The extracardiac features in this disorder include seizures, congenital strabismus, joint laxity, short digits, and dyslexia. The phenotype may range from mild to severe. While seizures have historically been considered the presenting feature of *FLNA*-related PVNH, recent data suggests that these patients may present to a cardiologist well before receiving a diagnosis from neurology. This indicates a need for earlier recognition and diagnosis of this disorder, which can be aided by recognizing key features in the family history in conjunction with the above cardiac manifestations.

Treatments for *FLNA*-associated aortopathy and arteriopathy have not been studied, and guidelines have not been established. For most patients, given the often severe dilation, we use a combination of ARBs and beta-blockers in affected girls. As many patients may have undergone lung transplant for the sometimes severe pulmonary manifestations, renal function must be monitored when on posttransplant medications and ARBs. There are no surgical guidelines for *FLNA* aneurysms at this time.

Suggested Readings

Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476–485.