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A Phenotypic Review of Connective Tissue and Related Disorders

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Introduction

The 21st century has been a time of change in the landscape of connective tissue disorders. Nowadays, multigene panels can analyze 20+ genes associated Marfan syndrome and related disorders. However, clinical diagnosis can still be challenging due to phenotypic overlap and variability within these conditions. It remains important for clinicians to be aware of distinguishing characteristics of connective tissue disorders including cardiac phenotype, systemic issues, and neurologic involvement, which can aid in clinical diagnosis. Diligent management of these conditions are improving lifespans, while early diagnosis and therapeutic intervention by the Newborn Screen programs are helping to prevent devastating neurologic complications seen in conditions like homocystinuria. In this article, we will review common connective tissue and related disorders including Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Shprintzen-Goldberg syndrome and homocystinuria.

Clinical Presentation

1. Marfan Syndrome

Marfan syndrome (MFS) is a complex autosomal dominant genetic disorder with an incidence of 2-3 people in 10,000. MFS is caused by genetic alterations of the fibrillin-1 (*FBN1*) gene at 15q21. The *FBN1* gene is necessary to create microfibrils (a very fine strand), which plays a significant role in providing flexibility and strength to connective tissue, as well as, activation of transforming growth factor β (TGF-β) signaling that controls growth and repair of tissues.

Key features of MFS include involvement of the cardiac, ocular, and skeletal systems. The most common ocular issue is myopia (nearsightedness), but lens dislocation (ectopia lentis) is a hallmark feature of this condition. Individuals with MFS are at risk for retinal detachment, glaucoma, and cataract formation. Skeletal features consist of specific facial features, joint laxity, greater arm span to height ratio, long fingers (arachnodactyly), chest anomalies (pectus excavatum/carinatum), and scoliosis.

Basic cardiac anatomy and flow of blood through the heart can be seen in Figure 1. The cardiovascular manifestations include:

- Dilatation of the aorta (ascending aortic aneurysm or aortic root aneurysm). The onset and progression of aortic dilation is variable. There is a significant risk for aortic dissection (tear of the aortic wall) in adults when the maximal dimensions approach 5.0 cm. Aortic dissections are rare in childhood. For these reasons, the aorta should be routinely monitored.
- Valvular dysfunction (mitral valve prolapse (MVP) with/without regurgitation or tricuspid valve prolapse), heart rhythm disorders, congestive heart failure
- Enlargement of the proximal pulmonary artery

MVP with congestive heart failure is the leading cause of cardiovascular morbidity and mortality.

Researchers have examined the possible association of hyperactivity and learning disabilities in Marfan syndrome. However, there is no conclusive evidence to suggest that learning disabilities observed in individuals with Marfan syndrome occur at a higher frequency that of the general population.

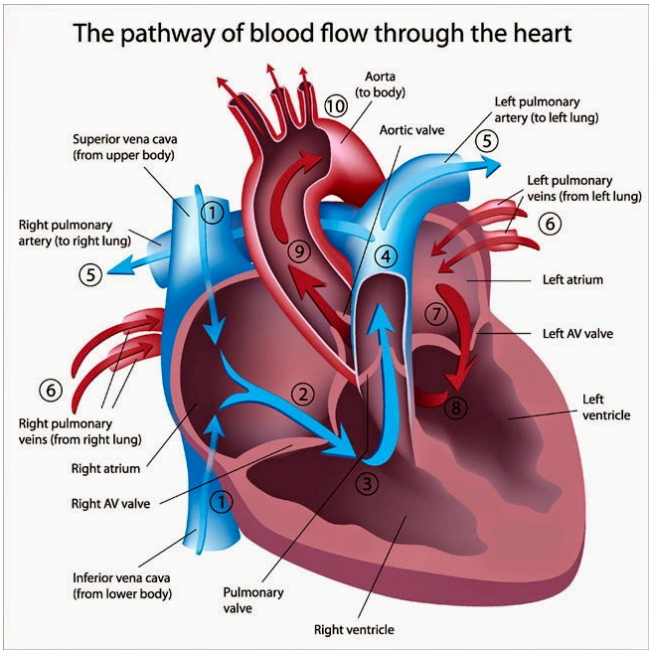

Fig. 1 - Pathway of Blood Flow Through the Heart

2. Loeys-Dietz Syndrome

Loeys-Dietz syndrome (LDS) is an autosomal dominant genetic disorder caused by mutations in several different genes that are related to the TGFβ pathway (*TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*). LDS was described in 2005 by pediatrics geneticists, Bart Loeys and Harry Dietz. In the past, the condition was misdiagnosed as Marfan or Ehlers-Danlos syndrome, therefore the exact prevalence is unknown.

LDS is a multisystemic connective tissue condition with vascular, cardiovascular, cutaneous, craniofacial and skeletal involvement. Craniofacial features include craniosynostosis (premature fusion of one or more cranial suture), widely spaced eyes and a bifid uvula/cleft palate. Skeletal issues are characterized by scoliosis, joint laxity or contractures, and chest anomalies. Skeletal overgrowth in LDS is seen to a lesser extent than in MFS. Cutaneous features include easy bruising, dysmorphic scars, velvety and translucent skin. Unlike MFS, myopia is less frequent and retinal detachments and ectopia lentis are either rare or not observed, respectively. Arterial tortuosity (abnormal twists and turns of the arteries) frequently involves the head and neck vessels but can be generalized with uterine rupture during pregnancy and delivery. Arterial aneurysms or dissections within the cerebral, thoracic, and abdominal vascular trees are common findings.

Cardiovascular issues are the major cause for early morbidity and mortality within LDS. These issues include dilation of the aorta, predisposition for aortic dissection and rupture, MVP (with or without regurgitation - Figure 2), and enlargement of the proximal pulmonary artery. Aortic dissections have been reported in children, ages 6 months and older. Additionally, unlike MFS and other connective tissue disorders, smaller aortic dimensions in LDS confer a greater risk of dissection and rupture. Therefore, the threshold to perform surgery in adults with LDS is when the ascending aorta dimension approaches 4.0 cm versus 5.0 cm, as we see in MFS.

Learning issues are not common in LDS. However, developmental delays are seen in a minority of cases and are most frequently associated with craniosynostosis and or/hydrocephalus (fluid buildup in brain). There are reports of two unrelated individuals with microdeletions (chromosomal loss of genetic material) encompassing the *TGFB2* gene, who presented with LDS and mild developmental delays.

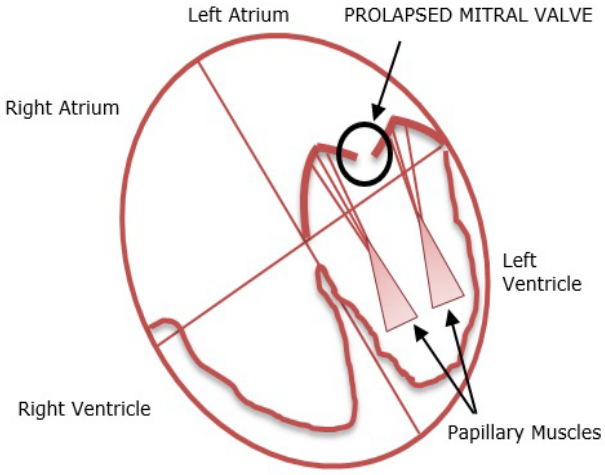

Fig. 2 – Mitral Valve Prolapse

3. Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders. There are now many genes described with EDS but the most common ones include *COL5A1* and *COL5A2* (Classic), *COL3A1* (Vascular), *PLOD1* (Kyphoscoliosis), *COL1A1* and *COL2A2* (Arthrochalasia), and *ADAMTS2* (Dermatosparaxis).

Based on the Villefranche Classification (1997), there are six major forms of EDS that have a combined prevalence of 1 in 5,000:

- Classic type – AD (1/20,000-40,000 people)
- Hypermobility type – AD (1/15,000 people)
- Vascular type – AD (1/250,000 people)
- Kyphoscoliosis type – AR (very rare)
- Arthrochalasia type – AD (very rare)
- Dermatosparaxis type – AR (very rare)

These group of conditions present with a certain degree of overlap, but may be distinguished by specific clinical features. Here we will briefly review the Classic, Hypermobility, and Vascular forms of EDS.

Individuals with the Classic form demonstrate easy bruising and velvety, hyperelastic skin that is fragile and prone to trauma, with delayed healing and wide scars that have a “cigarette-paper” like appearance. They also have issues with joint hypermobility including dislocations of the shoulder, patella (knee caps), digits, hip, radius, and clavicle. Other features include primary muscular hypotonia (low muscle tone), leading to delayed motor development including walking. Unlike Marfan syndrome and Loeys-Dietz, MVP, aortic root dilation, and spontaneous ruptures of the large arteries occur less frequently but baseline surveillance is warranted.

The Hypermobility type of EDS is usually the least severe, although individuals may have severe musculoskeletal pain. Common features include degenerative joint disease and joint instability and laxity, resulting in subluxations and dislocation. These occur both spontaneously or with minimal trauma. Psychological dysfunction and emotional problems are frequently seen in response to chronic pain and fatigue. Aortic root dilation is typically mild and there does not appear to be a high chance of dissection.

The Vascular form is a serious condition characterized by arterial, intestinal, and/or uterine fragility. Dissection or rupture, gastrointestinal perforation, or organ rupture is what frequently brings these individuals to clinical attention and diagnosis. Clubfoot (8%) and congenital hip dislocation may be seen in newborns. Children have an increased chance for recurrent subluxations and dislocations, inguinal hernia, and pneumothorax (collapsed lung). In addition, individuals may have thin, translucent skin with easy bruising. The extremities, but particularly the hands can have an aged appearance. In terms of facial appearance, the nose may seem narrow, with prominent eyes, thin upper lip, and small jaw. The death rate approaches 5% in pregnant women due to peripartum arterial rupture or uterine rupture.

Unlike Marfan syndrome or homocystinuria, ocular involvement including, myopia, lens dislocations, and retinal detachments are either not observed or occur at lower frequencies in the various types of EDS. With the exception of muscle hypotonia and delayed motor milestones, intellectual disabilities are not associated with EDS.

4. Shprintzen-Goldberg Syndrome

Shprintzen-Goldberg (SGS) is an autosomal dominant condition caused by alterations to the *SKI* gene, which has a role in the TGF-β pathway. It presents with many similar features to MFS and LDS, making the exact prevalence unknown.

Like LDS, a common feature in people with SGS is craniosynostosis and distinctive facial features, including a long, narrow head, widely spaced and protruding eyes, a high, narrow palate with a small lower jaw, and low-set ears that are rotated backward. A broad or bifid uvula, as well as, cleft palate has also been reported in SGS.

Like Marfan syndrome, they have chest anomalies, long limbs, and scoliosis. In addition, they may have bent fingers (camptodactyly) and even more significant hypermobility. Other features include heart (aortic root dilation and valvular anomalies-seen at a lower frequency than in MFS and LDS), brain anomalies (Chiari I malformations, hydrocephalus), low muscle tone, hernias, minimal subcutaneous fat, club foot, and arterial tortuosity.

Unlike many of the other conditions presented here, individuals with SGS have developmental delays and mild to moderate intellectual disability which may require special education.

5. Homocystinuria

Homocystinuria caused by Cystathionine Beta-Synthase (CBS) Deficiency is an autosomal recessive condition (incidence 1:300,000) in which individuals cannot process the amino acid, homocysteine, to the molecule, cystathionine, in the metabolic pathway. This results in methionine and homocysteine building up to toxic levels in the blood, with some excretion into urine (Figure 3).

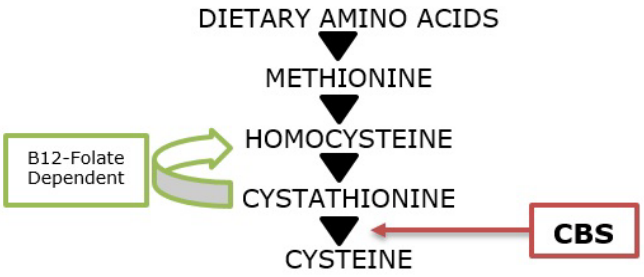

Fig. 3 — Methionine Metabolic Pathway

There are two different types of homocystinuria caused by (CBS) Deficiency: B_6-responsive (typically milder) and the B_6-non-responsive. This form of homocystinuria is due to genetic alterations in the *CBS* gene. Although a metabolic condition, we review it here due to the phenotypic overlap with Marfan syndrome.

Homocystinuria is characterized by poor growth, delays in motor and language milestones, serious learning and intellectual deficiency, behavioral and emotional issues, dislocation of the ocular lens, skeletal issues, and thromboembolic complications (obstruction of blood flow through vessels due to a blood clot).

Ectopia lentis typically occurs after one year of age and is usually present in untreated children by 8 years of age. Other features include glaucoma (untreated can cause blindness) and high myopia.

Individuals with homocystinuria are often tall and slender with a Marfaniod-like habitus. About half shows signs of osteoporosis by the time they are teenagers. Other common skeletal features include scoliosis, chest anomalies, and a high-arched palate.

Thromboembolisms are the major cause of early death, leading to heart disease and stroke. Although cerebrovascular events occur more frequently in young adults, they have been reported in infants. Pregnant women have an increased risk for thromboembolisms.

A major distinguishing feature from Marfan and other conditions presented here are the neurologic complications. Often the first sign of homocystinuria are developmental delays (both motor and language milestones). The FSIQ ranges from 10 to 138. B_6 responsive individuals have a mean FSIQ of 79, whereas B_6 non-responsive individuals have a mean FSIQ of 57. With identification through the newborn screen program, early treatment and compliance, the mean FSIQ is 105 for B_6 non-responsive individuals. Seizures occur in about 20% of untreated individuals. Individuals with homocystinuria develop various psychiatric issues which include psychotic episodes, depression, obsessive compulsive behaviors, anxiety, and personality disorders.

Management

1. Marfan Syndrome

Marfan syndrome requires a multidisciplinary team including genetics, cardiology, ophthalmology, and surgery for effective management. The life expectancy of individuals with Marfan syndrome reaches that of the general population with proper cardiovascular management.

Cardiovascular issues require frequent monitoring by echocardiography, as well as, periodic CT and MRA scans. Beta-blockers are often used to reduce hemodynamic stress on the aorta. They are usually started at the time of diagnosis or detection of progressive aortic root dilation. However, aortic root surgery should be considered in adults when the enlargement of the aorta is more than 5.0 cm, there is progressive enlargement of 1.0 cm per year, or severe aortic regurgitation. As we also see with LDS, family history of early aortic dissections need to be taken into account and may necessitate a more aggressive management plan. Severe mitral valve regurgitation with ventricular dysfunction (Fig. 2) is the primary cause for cardiovascular surgery in children. For children and adults, valve-sparing procedures may be necessary. It is essential to explain to children with MFS the importance of avoiding aggressive and competitive sports. Aerobic activities should be done in moderation.

Ocular issues are managed by eyeglasses and surgical removal with artificial lens replacement in those with lens dislocation. Orthodontic and skeletal treatment follows standard protocols and surgical interventions when necessary.

2. Loeys-Dietz Syndrome

Loeys-Dietz syndrome families should also be managed by a multidisciplinary team with appropriate therapy and continuous monitoring and imaging. Considering the gravity of aneurysms, guidelines recommend frequent MRA or CTA (head to pelvis) evaluation since valvular disease is not limited to the aortic root.

Aggressive surgical intervention is necessary for aneurysms. Therapy with beta-blockers can be useful to reduce the stress on the vessels walls and blood pressure. Surgery should be considered in children with an ascending aorta that exceeds the 99^{th} percentile and aortic annulus measures greater than 1.8-2.0 cm. In adults, surgery needs to be performed when the aortic root dimensions are at or below 4.0 cm. Although guidelines exist, particular attention and early interventions should also be based on family history. Skeletal, craniofacial, and ocular issues follow standard management guidelines.

3. Ehlers-Danlos Syndrome

The management of EDS is dependent on the type and features in each individual. Cardiovascular issues should follow standard management procedures including baseline echocardiograms and appropriate surveillance thereafter.

Standard management procedures are also recommended for other systemic issues. Individuals with the Classic and Hypermobility forms often seek physical therapy, anti-inflammatory medications, assistive devices, psychiatric services, etc. for chronic pain and joint instability. Physical therapy is also initiated in children with delayed motor milestones.

Individuals with the Vascular form benefit from surgical intervention (often life-saving) but minimal exploratory procedures are the recommendation due to the risk of unintended damage to other tissues. The risks and benefits of elective surgery should be discussed with a qualified medical professional and any individual with Vascular EDS must seek immediate medical attention for sudden and unexplained pain.

4. Shprintzen-Goldberg Syndrome

The management of SGS is much the same with routine surveillance for cardiac issues and typical treatment measures for craniofacial, skeletal, physiotherapy, and special education needs.

5. Homocystinuria

Thanks to early diagnostic and intervention efforts of the Newborn Screen programs, we are seeing improved control of plasma homocysteine levels and better neurologic outcomes. The goal of the therapy is to reduce the level of homocysteine by using Vitamin B_6 (pyroxidine) therapy in those who are responsive, protein-restricted diets, methionine-restricted diets in those who are B_6 non-responsive, betaine treatment for an alternative metabolic pathway (converts excess homocysteine to methionine), and folate and vitamin B_{12} supplementation (optimizes conversion of homocysteine to methionine). Early initiation of intervention therapies, individualized education plans and exceptional learning classes are key to helping children with developmental delays and intellectual deficiency.

Conclusion

Early diagnosis, easily accessible guidelines and diagnostic criteria, robust gene panels, aggressive surveillance and management, attention to family history, and movement towards personalized medicine is heralding in a new era for individuals with connective tissue disorders and related conditions. These measures are improving quality and quantity of life thanks to the efforts of a vast network of people including researchers, programs like the Newborn Screen, medical specialists, and families advocating for a hopeful tomorrow.

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes. Pediatric Genetics University of Florida Box 100296 Gainesville, FL 32610.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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