Ehlers-Danlos Part 2

II: Joint Hypermobility Syndrome or Joint Hypermobility Spectrum Disorder.

The joint hypermobility syndrome, also abbreviated JHS and the hypermobility spectrum disorder, also known as HSD are new terminology often used to describe the most common hereditary disorder of connective tissue diseases. Connective tissue diseases include joint hypermobility syndrome, or the hypermobility spectrum disorder, Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, Stickler syndrome. Connective tissue disease disorders do not generally include lupus, rheumatoid arthritis, Sjogren's disease, scleroderma, mixed connective tissue disease, vasculitis and other related rheumatologic diseases, although these diseases can give pain throughout the body and joints and muscles. They are usually not associated with connective tissue disorders unless there are two separate disease entities existing.

Joint hypermobility syndrome is present in up to 10-20% of the general population as estimated, although we believe a number of 3%, which is often quoted in the literature, is often more accurate. There are several types of Ehlers-Danlos syndrome, and type III is known as the hypermobile type. Joint hypermobility syndrome and hypermobile Ehlers-Danlos syndrome are probably the same disease problem. The main clinical features of joint hypermobility syndrome include joint hypermobility and skin fragility. Widespread pain throughout the body, chronic fatigue, autonomic dysfunction and gastrointestinal side-effects are also present. Generally, to diagnose joint hypermobility syndrome, or Ehlers-Danlos hypermobility type, the Beighton score is used. The Beighton score involves a 9 point scoring system. Two points are given for passive dorsiflexion, or bending backwards of the fifth finger greater than 90 degrees if both the right and left fifth finger are involved. Two points are given if passive movement of each thumb to the flexor surface of the forearm can be accomplished easily with elbows extended and the hand pronated. If the patient has the ability to use only hand to do this then they only get one point, but a total of two points is awarded if both thumbs can be flexed to the forearm with both hands. Hyperextension of each elbow greater than 10 degrees, and this can be measured with an instrument called a goniometer with the hand supinated and the elbow fully extended and shoulders fully abducted, award a point for each arm for a total of two points. If one can hyperextend the knee beyond 10 degrees when standing upward and the feet both touching each other, a point will be given for each leg, and a total of two points is awarded if both knees are involved. If the patient can place the palms flat on the floor with the knees fully extended and both feet touching each other, that is the feet together, then a point is given for this. We also give a point if the patient could do this in the past, but cannot do it now because of degenerative changes in the lumbar spine. This maneuver assesses the spine, whereas the other maneuvers assess the elbow, knees, and hands. A total of nine points is awarded if the patient is positive in all areas. The Beighton score greater or equal to five is the criteria used for generalized hypermobility. However, as one ages, their joint mobility decreases, and some experts have said for children before puberty, a score greater than or equal to six is needed, and for those greater than 50, a score greater than or equal to four is sufficient. A rheumatologist or a trained physician in autonomic dysfunction can score each patient for

hypermobility. Generally, we ask patients if then can or ever could put their hands on the floor without bending their knees, of if they can touch their thumb to their forearm, and generally we get a positive response from people with hypermobility. People with hypermobility often have a history of being double jointed in addition. They also give a history of dislocating shoulders, knees, ankles and other joints. While with the Beighton score, we do not test for cervical mobility or jaw hypermobilities are important and was to cover in the history_____???

If a person is hypermobile with a score of at least five, they qualify for hypermobility. However, does that automatically make them diagnostic criteria for hypermobile Ehlers-Danlos syndrome? Since Ehlers-Danlos syndrome has no characteristic blood test or gene testing, it is clearly a clinical diagnosis. Therefore, strict criteria have been established for whether a person with hypermobility can be classified as Ehlers-Danlos syndrome. We believe this is just a matter of semantics since if you are very hypermobile and have diffuse pain, whether you are labeled an Ehlers-Danlos syndrome or not is irrelevant as the treatment is the same, and autonomic dysfunction is often seen in most of these patients. At any rate, the criteria used are the following:

Criteria I: Is the patient generally hypermobile? As mentioned above, a Beighton score can be performed for this.

Criteria II: Does the patient have at least two of the following three items.

A. 1) the skin is soft and hyperextensive (the extensor surface of the joints have more than 2 cm of skin stretching, such as over the hand, 2) does the patient have unexplained stretch marks or recurrent hernias; a history of hiatal hernia may also be included, 3) does the patient have scars on the skin that shrink. These are known as atrophic scars and are linear scars from lacerations that form. Also, the patient has rectal or uterine prolapse; this will count towards criteria II. An arm span greater than one's height also can count in criteria II as long as they do not have Marfan syndrome. An aortic root dilatation on echocardiogram would also support one of the features for criteria II.

B. Also, a positive family history counts towards one point in criteria II. A first degree relative should meet the diagnostic criteria for Ehlers-Danlos syndrome.

C. A patient should have pain at least of two or more extremities for at least three months, or chronic widespread pain for three months, or history of recurrent dislocations, which are spontaneous and not due to trauma.

Criteria III.

A third criterion is the absence of other diseases which can cause a syndrome of hypermobility, such as Marfan syndrome. A history is often important. If there is no skin fragility, one should look for an alternative diagnosis.

If the patient has all three of these criteria they have Ehlers-Danlos syndrome. That is, if they have generalized hypermobility (criteria I), evidence of a syndrome of musculoskeletal complications of a systemic syndrome or a family history (criteria II), or if they have exclusion of alternate diagnoses (criteria III). Oftentimes, the diagnosis is based on establishing criteria II, as criteria I and III are easily made. If a family history of first degree relatives is made, that would qualify as evidence of criteria II, but in the absence of such, as can occur in patients who develop this disease de novo, or who do not know their family history well, have a syndrome complex of diffuse pain throughout the body for more than three months or at least two joints are required.

While hypermobility offers advantages to dancers and athletes as well as people involved with gymnastics, this unfortunately creates significant pain especially later on in life in multiple joint areas and diffusely. There is also associated fatigue, exercise intolerance, gastrointestinal symptoms, anxiety and other associated symptoms that become more disabling as one gets older. Recurrent joint subluxation or incomplete dislocations is often an extremely important disability.

Also, patients oftentimes have loss of balance due to loss proprioception. They need to hold onto objects when they stand, or are unstable when they walk. We do balance testing on most of these patients and find abnormalities, and oftentimes balance therapy is effective in these patients with Ehlers-Danlos syndrome, or hypermobility syndrome.

III: Autonomic Dysfunction.

The majority of patients with joint hypermobility syndromes, or Ehlers-Danlos syndrome, have autonomic dysfunction features. The most common is orthostatic intolerance, that is when they stand up for periods of time they get brain fog, dizziness, and feel as though they will faint and are relieved when lying down. Many of them have tachycardia on standing up and palpitations with a rapid heart rate, also relieved with lying down. This is known as postural orthostatic tachycardia syndrome or POTs syndrome and can be diagnosed with various types of testing. In our laboratory, we have autonomic testing working with heart rate variability and with tilt testing, which can aid in diagnosing whether an individual has this postural orthostatic tachycardia response. Strict criteria requires the heart rate to rise over 30 in a 10 minute period of time, and or to go above 120 beats per minute, although there are patients who show trends toward postural orthostatic tachycardia that do not quite meet this criterion but do have all of the features of it, and for most practical purposes are treated similarly. We often look at the slope with the rise of the heart rate with standing on a cardiorespiratory test that we perform to give us an indication of orthostatic intolerance and heart rate responses.

Gastrointestinal symptoms are also important features that reflect dysautonomia, such as alternating diarrhea and constipation, nausea and gastroparesis, which is delayed emptying. Interestingly, many patient's who have postural orthostatic tachycardia have rapid gastric emptying, which also can cause nausea. Fatigue is a hallmark symptom of dysautonomia often

due to orthostatic intolerance, that is when standing symptoms become worse. It is almost invariably found in all patients with Ehlers-Danlos syndrome.

Echocardiogram is often done because patients have fainting or pre-fainting symptoms. Rarely do we find aortic root dilatation and oftentimes this is not marked. Rarely we find mitral valve prolapse in these patients. These two entities are more common in a Marfan syndrome, which is a disorder of collagen tissue in which the aorta can become quite enlarged and the aortic valve can leak, and the mitral valve can be quite floppy and prolapse significantly and can leak significantly also. In Marfan syndrome, patients often have ocular symptoms whereas this is rare in Ehlers-Danlos syndrome. The paper-thin skin often seen in Marfan syndrome and easy bruising can also be seen in other collagen vascular entities, but is not as common. Marfan patients also have scoliosis, kyphosis and ectopia lentis, not seen in Ehlers-Danlos syndrome.

IV: Treatment:

Treatment of Ehlers-Danlos syndrome focuses on relief of pain and improving exercise intolerance and orthostatic intolerance. Patient education is important. Physical therapy and balance therapy are also important features. Exercise is an important component, and we often have people begin with swimming or using a rowing machine with non-vertical exercise. Low-impact exercises are more important than high level aerobic exercises. Occasionally, splints or orthoses are used improving joint alignment. For chronic pain, we attempt to avoid narcotics and use antidepressants, especially those with anticholinergic capabilities, such as tricyclics or some SNRIs, and sometimes we can even use antiseizure medicine. Anticholinergic medicines are particularly important if autonomic testing suggests cholinergic excess, and we do have testing modalities which can suggest that. Anxiety and depression oftentimes need to be handled with cognitive behavior therapy or psychological and psychiatric help, but is not the primary but the secondary symptom complex. Many of these patients present with a diagnosis of primary anxiety or depression that has not been properly diagnosed by their prior physicians.

Genetic counseling is of limited value. However, since each individual with hypermobile EDS has a 30% chance of inheriting the disorder, this should be explained. However, there is marked variability and it is difficulty to predict severity in offspring.

We have found an antioxidant cocktail involving alpha lipoic acid, Coenzyme Q10 and L-carnitine as well as an antiinflammatory regimen involving omega-3 to be beneficial to both the autonomic function and the pain syndromes in patients with hypermobile Ehlers-Danlos syndrome. For the fatigue factor, we have used nitric oxide boosting preparations of beetroot, and in patients older than 40 years of age, precursors to nitric oxide, such as L-citrulline and L-arginine.

In individuals with orthostatic intolerance and postural orthostatic tachycardia syndrome, lowering the heart rate with beta-blockers or a medicine called Corlanor, oftentimes is effective in relieving rapid heart rate symptoms and heart pounding symptoms. However, the key is to make sure the veins transport the blood from the legs to the heart on standing properly.

Therefore compression stockings, fluids, salt and venoconstriction medicine, such as Midodrine are oftentimes effective. Occasionally, we use Mestinon in people who cannot tolerate Midodrine. Florinef, a mineralocorticoid, is often helpful also as an adjunct to Midodrine, and we can use low doses of both agents at the same time and avoid potential side-effects at higher does of either one alone.

V: Types of Ehlers-Danlos Syndrome:

Ehlers-Danlos syndrome is an inherited group of connective tissue disorder with abnormal collagen synthesis, which affects skin ligaments, joints, blood vessels and organs. It is believed that it was first described by Hippocrates in 400 B.C. However, in 1901, Edvard Ehlers recognized the condition as a distinct disease entity. In 1908, Henri-Alexander Danlos suggested that the skin extension and fragility were significant features of the syndrome. Then in 1998, Beighton published a classification system.

Patients with this disorder have hyperextension of the skin, hypermobility of the joints, tissue fragility with easy bruising, delayed wound healing and atrophic scarring. Both Ehlers and Danlos were dermatologists.

There are several types of Ehlers-Danlos syndrome. The most common type is type III, in which there is mostly skin laxity, velvet skin, joint hypermobility and recurrent joint dislocations. This is almost always associated with autonomic nervous system dysfunction. This is the type of Ehlers-Danlos syndrome that we see almost always in clinical practice. There is no genetic testing for it. In the classical, or type I and type II types of Ehlers-Danlos, there is abnormal type V collagen. These patients have muscle hypotonia and increased incidents of hernias in addition to skin laxity, scars and joint hypermobility. The scarring can be quite significant. Type IV is known as the vascular type, which is due to abnormal type III collagen. In this entity, which is the most serious, arterial ruptures, easy bruising, hypermobility of small joints and varicose veins are often seen. A family history of vascular ruptures, such as aortic aneurysms or viscus ruptures, such as the intestines is often given. This is a rare type but needs to be identified. Type VI is known as the kyphoscoliosis type, and in this there is a deficiency of lysyl hydroxylase. Joint laxity, muscle hypotonia in infants, scoliosis from birth and scleral fragility are seen. The type VII type, arthroclasia, is a deficiency in chains and type I collagen. In dislocation hypermobility, skin laxity and easy bruisability, muscle hypotonia and also kyphoscoliosis may be seen. This is extremely rare. Another of type VII is dermatosparaxis, which is a deficiency in enzyme in type I collagen, and there is redundancy of the skin with a sagging rough doughy skin texture, easy bruising and premature rupture of fetal membranes has been identified.

Almost always the type seen is type III, or the hypermobile type in which there is no blood or genetic testing.

Ehlers-Danlos syndrome disorders are more common than appreciated. The prevalence has been estimated between 1 in 2,500 and 1 in 5,000 according to prior literature. However, we see a much higher percentages of patients with hypermobility, as mentioned earlier, and many

of these patients who have been carefully screened do meet criteria for Ehlers-Danlos syndrome. The exact instances is unknown. Also, the degree of abnormality and penetrance can vary and many times there are very mild cases, which still do not ensure that the autonomic dysfunction associated with it will be mild.

Again, it is important to make sure that an individual presents with hypermobile Ehlers-Danlos syndrome and not one of the other subtypes. It is also important to exclude other collagen vascular entities, such as Marfan syndrome and Loeys-Dietz syndrome, which are more serious entities. Cardiovascular manifestations do not account for significant comorbidity and mortality in Ehlers-Danlos syndrome as they do in the other two entities just mentioned. When there is a question, oftentimes the expertise of a cardiologist, a geneticists and a rheumatologist is needed to differentiate these entities.

VI: Conclusion:

Ehlers-Danlos syndrome is a very complicated area of diagnosis and treatment. It is basically synonymous with a diffuse hypermobility syndrome with chronic pain and fatigue, and autonomic dysfunction being present in the patients. A multisystem approach to diagnosis and treatment is indicated. The most disabling features of diffuse pain, dislocation of joints, fatigue, scarring, orthostatic intolerance and other autonomic dysfunction symptoms, gastrointestinal side-effects and balance issues need to be addressed to improve quality of life.

VII: Addendum:

Physicians should not take hypermobility or Ehlers-Danlos syndrome disorders lightly. The quality of life impairment and morbidity associated with EDS disorders can be marked. While the life expectancy of hypermobile EDS is usually normal, there are exceptions where more severe cases are accompanied by Chiari neurological malformations with cerebral spinal complications, colonic motility disorders with obstruction complications, collapsed lungs, poor wound healing and sepsis complications, severe bleeding disorders associated with EDS, cranial vertebral instability caused by trauma and other complications of other organ systems which can abbreviate life expectancy and cause significant morbidity to patients. The vascular type of EDS has a life expectancy of less than 50 years due to vessel or viscus rupture, and this generally is more serious than hypermobile types and needs to be diagnosed early also. More research is needed in order to treat EDS, especially these severe forms, both hypermobility and vascular as well as the other types which we have mentioned.

There are other disorders associated with EDS. Celiac disease has been associated with EDS. Also, small fiber neuropathy is seen in a significant number of patients with EDS and is associated with autonomic dysfunction. Ocular problems and large fiber neuropathies can also be associated with EDS.