Expert Opinion

Genetic Causes of Joint Laxity

A 23-year-old woman presents with recurrent right shoulder instability. Surgical stabilization 8 months ago provided only temporary and partial improvement. She can voluntarily sublux the joint and gets spontaneous dislocations with routine motions. She has always been more flexible than her peers. She enjoys several sports, but has had to give up most physical activity because of the shoulder instability and increasingly severe diffuse pain. Physical examination confirms hypermobility in several joints.

BY HOWARD P. LEVY, M.D., PH.D.

Differential Diagnosis

The normal range of joint laxity varies between individuals and over time. Some people are naturally more flexible than others, or have increased their range of motion through stretching, yoga, or other activities. Joint mobility tends to be greater in women than in men, and pregnancy is associated with a further increase in laxity. Young children are usually very flexible, and range of motion tends to gradually decrease throughout life.

Three of the more common genetic causes of joint laxity are Marfan, Stickler's, and Ehlers-Danlos syndromes, but there are dozens of other considerations. Collectively, these are known as heritable disorders of connective tissue, but they should not be confused with rheumatologic connective tissue disorders. There is substantial clinical variability within the specific genetic causes of loose joints, and it can sometimes be difficult to distinguish milder manifestations from the looser end of normal joint mobility.

Many patients with a heritable connective tissue disorder have a high, narrow palate and/or dental crowding. Soft skin, easy bruising, and hernias are also common. Early-onset osteoarthritis is a frequent consequence of joint laxity. Many hypermobile patients also develop functional gastritis, irritable bowel syndrome, and neurally mediated hypotension or postural orthostatic tachycardia.

Other organ system involvement can help to establish a diagnosis.

The most significant concern in Marfan syndrome is aortic root dilation and rupture. Patients with Stickler's syndrome are especially prone to osteoarthritis and skeletal dysplasia. Ehlers-Danlos syndrome is actually a group of six related conditions, all sharing joint laxity and soft skin.

Diagnostic Evaluation

The most important body systems to examine are the skeleton and skin. Joint laxity is assessed by objective and subjective assessment of range of motion. One helpful tool is the Beighton score, which assigns one point for each elbow and knee that can extend more than 10 degrees, one point for each thumb that can be apposed to the flexor surface of the forearm, one point for each fifth finger that can be dorsiflexed more than 90 degrees, and one point for placing the palms on the floor with the knees straight. A score of 5 or more is positive, but a negative test does not rule out joint laxity.

Skin elasticity should be measured in an area without excess skin. The volar surface of the wrist is a better choice than extensor surfaces (such as the back of the elbow or the back of the hand).

An echocardiogram should be obtained in all patients suspected of having a heritable disorder of connective tissue, regardless of age. Follow-up echocardiography depends on initial findings, the ultimate diagnosis, and the age of the patient.

Ophthalmologic examination is appropriate if Marfan or Stickler's syndrome is suspected. An audiogram should be obtained whenever an open or submucous cleft palate (or bifid uvula) is found, or if Stickler's syndrome is being considered.

For most of these conditions, there is no confirmatory laboratory test. Specialized testing of collagen from a skin biopsy can be used to rule in or out certain types of Ehlers-Danlos syndrome. Sequencing of some of the associated genes is clinically available, but is very expensive. Some genetic variants do not result in clinical abnormalities, and not all pathogenic mutations can currently be detected. Therefore, DNA testing always must be interpreted in the context of the clinical presentation. When a specific mutation has been identified and correlated with a patient's diagnosis, this information can be used to test relatives at risk for the same condition.

Management

Avoidance of joint hyperextension, impact activity, and resistance exercise minimizes the risk of subluxation and dislocation. Myofascial release (heat, massage, ultrasound, etc.) provides a few hours or days of pain relief. A lifelong program of low-resistance muscle toning, gradually increasing repetitions and frequency of exercise, helps to stabilize loose joints and might reduce future pain and/or delay the onset of arthritis. Surgical intervention to improve joint stability often fails or provides only temporary benefit.

Referral to a clinical geneticist is useful to establish or confirm the diagnosis and to determine if any laboratory testing is appropriate. Genetic counseling should include discussion of the risk to parents, siblings, and current or future children, as well as more distant relatives.

More information about these and related disorders of connective tissue is available at GeneTests (www.genetests.org).

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Hypermobility Ups the Odds for Osteoporosis, Other Risks

BY DENISE NAPOLI
Assistant Editor

Patients with hypermobility have a significant and often unappreciated risk for osteoporosis, according to one expert.

The prevalence of osteopenia and osteoporosis is very high in this cohort, said Dr. Eric P. Gall, chief of rheumatology and allergy at the Chicago Medical School, North Chicago.

"In my patient population, this is something that I'm well aware of and I tend to screen for osteoporosis sooner rather than later, particularly if there are any other risk factors." said Dr. Gall during an audioconference on the subject organized by the American College of Rheumatology.

Additional complications reported in hypermobile patients include problems with proprioception, osteoarthritis, mitral valve prolapse, hernias, passing out, palpitations, chest pain, fatigue, and also heat intolerance.

"These patients don't just complain of pain in their joints; they complain of lots of things," he said. "They maybe have headaches and chronic pain. Sometimes pain disrupts their sleep and they get secondary fibromyalgia. [They could have] problems with sexual relations. They may have injuries and [psychological] reactions to the injuries. They have resistance to local anesthetics."

One of the reasons why hypermobility can be difficult to diagnose is that patients may not always have pain in the affected joints.

"If a patient has pain, they protect their joint and develop arthritis in the joint," he said, reducing range of motion and disguising the hypermobility.

One specific type of hypermobile disease is Ehlers-Danlos syndrome, which has 10 subtypes, all characterized by slightly different associated comorbidities and risk factors.

One of the most serious of these (type 4) may be fatal, but is also especially rare, with an estimated prevalence of 1 in 250,000, said Dr. Gall.

Hallmark signs are vascular aneurysms; bowel and organ rupture; milder hyperextensibility compared with other types; translucent skin; pinched nose; dystrophic scars; and severe ecchymosis, which can often lead doctors to think that the sufferer is being physically abused.

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This composite slide shows two patients with Ehlers-Danlos syndrome: Note the hyperextensible skin.

"So how do we manage these people?" asked Dr. Gall. He mentioned that screening for mitral valve prolapse—both by listening and, if indicated, echocardiogram—is very important.

He added that "We discourage the hypermobile activities of daily living, although in the musician and the dancer we have to put practicality together … and make compromises." Additionally, physical therapy can help these patients, as can measures to protect fragile skin. Recurrent dislocations can be treated with surgery, but sutures must be very carefully and closely placed, with "careful hemostasis." "All [of the patients] who have severe disease are in need of genetic counseling" as well, he added.

Another serious hypermobility disease is Marfan syndrome. The criteria for a Marfan diagnosis is complicated, but Dr. Gall said that from a practical standpoint, if a patient's arm span measures more than 1.1 times his height, that is a good sign that Marfan syndrome may be present.

These patients can suffer complications like scoliosis, pectus excavatum, and pectus carinatum, also known as a "pigeon chest." "That can be so severe that it actually can compress the heart," said Dr. Gall.

These patients also often have a high, arched palate.

In Marfan syndrome, Ehlers-Danlos syndrome, and all hypermobility disorders, Dr. Gall emphasized that "management is multidisciplinary. People really have to work together as a team: The patient, the rheumatologist, the orthopedist, and the primary care providers all need to work together with the physical and occupational care therapist in dealing with these diseases," Dr. Gall said.

"I have seen more and more [hypermobility] in patients that I see for other things. … You have to look for them," he added.

Dr. Gall said he had no conflicts of interest to disclose in relation to his presentation.

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