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Surgical Management of Shoulder and Knee Instability in Patients with Ehlers-Danlos Syndrome: Joint Hypermobility Syndrome

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Ehlers-Danlos Syndrome (EDS) is a hereditary disorder of the connective tissue, which has been classified into numerous subtypes over the years. EDS is generally characterized by hyperextensible skin, hypermobile joints, and tissue fragility. According to the 2017 International Classification of EDS, 13 subtypes of EDS have been recognized. The majority of genes involved in EDS are either collagen-encoding genes or genes encoding collagen-modifying enzymes. Orthopedic surgeons most commonly encounter patients with the hypermobile type EDS (hEDS), who present with signs and symptoms of hypermobility and/or instability in one or more joints. Patients with joint hypermobility syndrome (JHS) might also present with similar symptomatology. This article will focus on the surgical management of patients with knee or shoulder abnormalities related to hEDS/JHS.

Keywords: *Knee dislocation, Shoulder dislocation, Ehlers Danlos syndrome, Joint hypermobility*

Ehlers-Danlos Syndrome (EDS) has been described as a multiorgan disorder resulting from various abnormalities in collagen primarily affecting the skin, musculoskeletal tissues, and vessels.[1] Based on the most recent classification of EDS in 2017, 13 subtypes are currently recognized.[2] This newer classification (Table 1) was believed to be more clinically oriented and "user-friendly" compared to the previous classifications of EDS that were mostly based on genetics. Although it was not developed based on the genetic defects associated with EDS, the 2017 classification is particularly useful in cases of EDS diagnosis without the presence of a genetic defect. EDS might also be classified according to the genetic and pathogenetic mechanisms involved in each type and that result in the production of proteins with similar biological effects.[2] The Villefranche Nosology classification of EDS was published in 1998 and it has been widely used in clinical practice; however, with the description of new EDS subtypes over the last 2 decades, another classification was necessary. The clinical diagnosis of hypermobile type EDS (hEDS) needs the simultaneous presence of all 3 criteria presented in Table 2. A diagnosis of joint hypermobility syndrome (JHS) is made in the presence of 2 major criteria, 1 major and 2 minor criteria, 4 minor criteria, or 2 minor criteria in the presence of an unequivocally affected first-degree relative (Table 3).

Genes that encode collagen or collagen-modifying enzymes are involved in the pathogenesis of EDS.[2] Due to this, patients with EDS often present with skin hyperextensibility or wound healing abnormalities, joint hypermobility or instability, and easy bruising.[1,3] Orthopedic surgeons may encounter patients with hEDS due to chronic pain and joint instability. Hypermobile EDS is an autosomal dominant disorder but the gene responsible for its clinical manifestations is currently unknown.[3] Therefore, the diagnosis of hEDS is clinical.[4] Malfait et al.[2] have described the diagnostic criteria for hEDS, which include the presence of JHS. It is important to notice that JHS and hEDS constitute 2 distinct inherited disorders of the connective

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Table 1. EDS Classification According to the Newer Classification: 2017 International Guidelines

Ehlers-Danlos subtype	Inheritance pattern	Gene involved in pathogenesis
Classical EDS	AD	COL5A1, COL5A1 rare: COL1A1 c.934C > T, p. (Arg312Cys)
Classical-like EDS	AR	TNXB
Cardiac-valvular EDS	AR	COL1A2 (biallelic mutations that lead to COL1A2 NMD and absence of pro a2(I) collagen chains)
Vascular EDS	AD	Major: COL3A1 Rare: COL1A1 c.934C > T, p. (Arg312Cys) c.1720C > T, p. (Arg574Cys) c.3227C > T, p. (Arg1093Cys)
Hypermobile EDS	AD	Unknown
Arthrochalasia EDS	AD	COL1A1, COL1A2
Dermatosparaxis EDS	AR	ADAMTS2
Kyphoscoliotic EDS	AR	PLOD1 FKBP14
Brittle Cornea syndrome	AR	ZNF469 PRDM5
Spondylodysplastic EDS	AR	B4GALT7 B3GALT6 SLC39A13
Musculocontractural EDS	AR	CHST14 DSE
Myopathic EDS	AD or AR	COL12A1
Periodontal EDS	AD	C1R C1S

EDS: Ehlers-Danlos syndrome, AD: autosomal dominant, AR: autosomal recessive. Malfait et al.[2)]

Table 2. Summary of the Diagnostic Criteria for hEDS

Criterion	Clinical finding
Criterion 1	Generalized joint hypermobility
Criterion 2	Two or more of the following features must be present: Feature A—systemic manifestations of a more generalized connective tissue disorder (a total of 5 out of 12 must be present) Feature B—positive family history, with 1 or more first-degree relatives independently meeting the current diagnostic criteria for hEDS Feature C—musculoskeletal complications
Criterion 3	All these prerequisites must be met: absence of unusual skin fragility, exclusion of other heritable and acquired connective tissue disorders including autoimmune rheumatologic conditions, and exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity

hEDS: hypermobile type Ehlers-Danlos syndrome.

Table 3. Diagnostic Criteria for Joint Hypermobility Syndrome

Major criteria	Minor criteria
1. Beighton score of ≥ 4/9	1. Beighton score of 1, 2, or 3
2. Arthralgia for > 3 months in ≥ 4 joints	2. Arthralgia of ≥ 3 months in 1 to 3 joints or back pain of ≥ 3 months; spondylosis, spondylolysis, spondylolisthesis
	3. Dislocation/subluxation in > 1 joint or in 1 joint on > 1 occasion
	4. Soft-tissue rheumatism in ≥ 3 lesions (e.g., epicondylitis, tenosynovitis, and bursitis)
	5. Marfanoid habitus (tall, slim, span: height ratio of > 1.03, upper : lower segment ratio of < 0.89, arachnodactyly)
	6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring
	7. Eye signs: drooping eyelids or myopia or antimongoloid slant
	8. Varicose veins, hernias, or uterine/rectal prolapse

tissue with significant overlapping in clinical manifestations (hyperextensible skin, recurrent joint subluxation/dislocation, chronic arthralgia, limping, and positive family history). Because of this, it was previously suggested that these 2 diagnostic entities could be considered syn-

onymous in clinical practice.[5] The surgical treatment of joint instability in hEDS/JHS patients is under-reported in the literature. This current review will focus on the operative management of shoulder- and knee-related problems in patients with hEDS/JHS.

SHOULDER INSTABILITY IN hEDS/JHS PATIENTS

Clinical Presentation

The majority of patients with shoulder instability related to hEDS/JHS often experience joint subluxation or dislocation following an atraumatic or low-energy traumatic injury. Patients with JHS/hEDS have been reported to have impaired shoulder function, increased intensity of shoulder pain, decreased health-related quality of life score and significantly increased rate of generalized pain in comparison with healthy controls.[6] The last was the result of a cross-sectional survey including 110 patients diagnosed with hEDS/JHS and 140 healthy patients from the general population (controls).[6]

The examiner must be careful when evaluating patients with signs and symptoms of shoulder instability in order to determine whether their clinical presentation is related to an underlying connective tissue disorder. It is important to ask the patient about the degree of voluntary control of the shoulder instability and whether or not they have family history of joint (any) dislocation. As mentioned above, no genetic test is available to confirm the diagnosis of hEDS, which is based on the updated clinical criteria.[2] It is important, however, to distinguish between JHS and hEDS given that the latter might be associated with abnormalities in multiple organ systems.[1] For example, patients with hEDS might be at higher risk of bleeding during surgery due to the inherited fragility of the blood vessels.[7,8] Delayed tissue healing (such as wound healing or healing of the repaired or reconstructed tissues) is another possible complication that might negatively affect the surgical outcomes of patients with underlying disorders of the connective tissue.[9]

Shoulder instability in patients with hypermobile joint of any etiology can be classified into type 1 or unidirectional, type 2 or bidirectional, and type 3 or multidirectional. Bidirectional anteroinferior instability has been reported to be more prevalent than multidirectional shoulder instability in patients with hEDS/JHS.[10] Nourissat et al.[11] compared the clinical and radiologic data of patients with hEDS (study group) who sustained a shoulder dislocation with the signs and symptoms of a control population with shoulder instability but without diagnosis of hEDS; In this last study, patients in the study and control groups underwent shoulder stabilization surgery. The authors found that bilateral shoulder instability was more prevalent in patients with hEDS than in the controls.[11] In addition, pain during shoulder dislocation was more frequent in patients without EDS; however, post-reduction pain was more frequent in EDS patients.[11] The majority of EDS patients were less than 14 years old and of female gender in this last study.[11] Lastly, the percentage of patients with shoulder external rotation > 85° (a classic sign of joint hyperlaxity) was not different between EDS and non-EDS patients.[11] Based on the above, the authors concluded that EDS should be suspected in young, female patients who present with global hyperlaxity and describe reduced pain during a shoulder dislocation event compared to post-reduction.[11]

Another study evaluated the acromiohumeral distance between 29 female patients diagnosed with hEDS or JHS and 20 healthy controls by evaluating the relative amount the supraspinatus tendon occupies in the subacromial area, using ultrasound.[4] The measurements were performed in 45° and 60° of active arm elevation in the scapular plane. This last study found that hEDS/JHS patients had a larger subacromial space outlet than did the control group.[4] In addition, both groups had increased occupation of the supraspinatus tendon in the subacromial area when the arm was elevated compared to the resting position. The last was an indication that narrowing of the subacromial space occurs with arm elevation regardless of the presence of hEDS/JHS syndrome.[4] By identifying that patients with hEDS/JHS has a larger subacromial space outlet than healthy patients during arm elevation, the impact of hEDS/JHS on the biomechanical function of the shoulder joint might be better understood and treatment protocols can be modified accordingly when managing these patients.[4,12,13]

Shoulder Stabilization Procedures in Patients with hEDS/JHS

Shoulder instability is a complex clinical problem and may become even more challenging in patients with hEDS/JHS. As stated above, patients with these disorders may experience voluntary or atraumatic shoulder subluxation or dislocation episodes.[10] In addition, significantly increased capsular redundancy has been observed during the intraoperative evaluation of the shoulder joint in patients with hEDS/JHS compared to patients with shoulder instability without underlying connective tissue disease.[14,15] Therefore, shoulder stabilization procedures that have been proven to be effective in patients without hEDS/JHS might

not yield equally successful outcomes in patients with connective tissue disorder. For this reason, bony augmentation procedures that increase the articular surface of the shoulder and rely less on the stabilization properties of the soft tissues might be preferred in patients with hEDS/JHS.[16]

Vavken et al.[17] examined the outcomes of open inferior capsular shift for multidirectional shoulder instability in 15 adolescents with EDS or JHS, who had failed nonoperative therapy. The authors reported significant improvement of the American Shoulder and Elbow Surgeons score and the 11-item version of the Disabilities of Arm, Shoulder and Hand score at 7.5 years postoperatively. In the same study, 64% of the patients returned to sport following the procedure.[17] Aldridge et al.[18] also reported resolution of bilateral shoulder instability (multidirectional) in a 9-year-old patient with hEDS following bilateral arthroscopic thermal capsulorrhaphy of the shoulder. Successful short-term outcomes (follow-up ranged from 4 months to 3 years) were observed in a 28-year-old female with hEDS and a 10-year history of recurrent shoulder subluxations, who underwent bilateral anterior and posterior glenohumeral stabilization using Achilles tendon allograft. However, long-term follow-up was not available for this last patient.[19]

Armstrong et al.[20] have proposed an all-arthroscopic technique to address recurrent multidirectional instability of the shoulder in patients with EDS. In this technique, extra-articular bone grafting of the glenoid was used to augment the plicated capsule both anteriorly and posteriorly. According to the authors, the main advantage of this procedure was the preservation of the subscapularis muscle and coracoid-conjoint complex with concomitant soft-tissue and bony support.[20] The clinical outcomes of this surgical technique have yet to be reported in patients with hEDS/JHS.

Although studies that report the clinical outcomes of shoulder stabilization surgery often include patients with hEDS/JHS, comparative studies that show the differences in the efficacy of the above procedures between hEDS/JHS patients and patients without an underlying connective tissue disorder are missing.[15,21] Future research should examine whether the above described procedures offer clinical benefit in patients with hEDS/JHS. Lastly, the efficacy of the currently established techniques for the treatment of shoulder instability in non-EDS patients must be assessed for those with underlying disorders of the connective tissues.

KNEE ABNORMALITIES IN PATIENTS WITH hEDS/JHS

Clinical Characteristics

Knee issues are another common manifestation in patients with EDS.[22] A review of pediatric patients with EDS found that the most common site of issue was the knee, primarily involving the patella.[23] A different study reported patellar instability in 57% of 300 hEDS patients and chronic pain in 85% of EDS patients.[7] These numbers were similar to the results of the survey by Rombaut et al.[24] in 2010, in which 81.5% of patients with hEDS reported knee pain and 40% reported patellar dislocations. In terms of the biomechanical function of the patellofemoral joint, Sheehan et al.[25] showed that differences exist in patellofemoral and tibiofemoral kinematics in patients with patella maltracking with versus without joint laxity. In this last analysis, patients with EDS were found to have a relatively large lateral tilt (7.6° higher than normative).[25]

Knee instability (any type) in hEDS may be partially explained by substantial muscle weakness in the quadriceps and hamstrings, and it is hypothesized that 1 cause of hEDS muscle weakness is related to defective collagen function, leading to abnormal muscle extracellular matrix composition.[26-28] This may influence muscle function by reducing force generated and transmitted through tendons. Other contributors to muscle weakness may include chronic pain and increased fatigue.[27] Joint hypermobility might also be associated with increased risk of anterior cruciate ligament (ACL) injury.[27,29] A previous study found that patients with ACL injury were 4.4 times more likely to have joint hypermobility.[29] The same authors also reported an association between joint hypermobility and female gender, where ACL injury is more common.[29] Patellar tendon ruptures can also occur in patients with EDS, with most ruptures occurring at the inferior pole of the patella.[30,31] It is hypothesized that this is a result of tendon weakness in this category of patients and is a primary concern for orthopedic surgeons.[31]

Knee Surgical Procedures in Patients with hEDS/JHS

Patellar stabilization procedures

Medial patellofemoral ligament (MPFL) reconstruction is a widely accepted procedure to treat recurrent patellar instability in young patients.[32] Little has been reported on the outcomes of this procedure in patients with hEDS. A recent study found no difference in clinical outcomes following MPFL reconstruction in patients with versus without JHS (defined as Beighton score 4 or greater).[33] In this last analysis, JHS was inversely related to patient age

and it was more common in female patients. Howells and Eldridge[34] examined the results of MPFL reconstruction using semitendinosus autograft in 25 patients with joint hypermobility (Beighton score equal to or greater than 6) in comparison with 50 patients who underwent the same procedure but their Beighton score was < 4. In this study, although both groups showed significant improvement in functional outcomes at 15 months postoperatively, the functional improvement was significantly less in patients with joint hypermobility. Therefore, attention must be paid when managing patients with patellofemoral joint instability and hEDS/JHS due to the risk of inferior surgical outcomes. It is worth noting that autograft tissue was used in this last study for the reconstruction of the MPFL. Since EDS/JHS patients are known to have defective collagen tissue, using an autograft might have contributed to the inferior outcomes in this group.[34] Finally, successful outcomes were recently reported in a 35-year-old female with hEDS and bilateral iatrogenic medial and lateral patellar instability who was treated with simultaneous medial and lateral patellofemoral ligament (MPFL and LPFL) reconstruction.[35]

Patellar tendon repair-reconstruction

Rupture of the patellar tendon might occur in patients with systemic or chronic diseases (systemic lupus erythematosus, rheumatoid arthritis, chronic renal failure, etc.), including EDS.[36] These patients often present with the classic signs and symptoms of patellar tendon rupture (knee pain, swelling, and inability to extend the knee joint), but they often report a low-energy mechanism of injury or absence of trauma.[36]

Iacono et al.[37] reported a case of a 21-year-old male with a history of EDS, who presented with bilateral simultaneous patellar tendon rupture when rising from the sitting position and failed initial management with primary repair of the patellar tendon in both knees. The patient underwent reconstruction of the knee extensor mechanism of 1 knee using frozen bone-patellar ligament-bone allograft with satisfactory outcome and had already elected to proceed with the same operation on the contralateral knee at the time of follow-up. Further, a 13-year-old female with hEDS was successfully treated with bilateral patellar tendon repair using a suture anchor technique protected temporarily with a cerclage wiring.[30] This last patient experienced spontaneous bilateral rupture of the patellar tendon of proximal insertion following a trivial trauma.[30] There is lack of studies comparing the efficacy of the commonly used patellar tendon repair or reconstruction techniques in patients with versus without connective tissue abnormalities, which would be helpful to determine whether new techniques must be considered for this special patient population.

Reconstruction of the cruciate ligament of the knee

No evidence exists regarding the graft choice and outcomes for cruciate ligament (anterior or posterior) reconstructions in patients with hEDS or other connective tissue disorders.[38] Simonian and Luck[39] reported a case of a 21-year-old female who successfully underwent synthetic posterior cruciate ligament reconstruction and who had also received a lower extremity prosthesis following a below-the-knee amputation related to EDS.[39] Other case reports have reported the outcomes of ACL reconstruction in patients with this condition. Williams et al.[40] treated an 18-year-old male with EDS and deficient ACL with ACL reconstruction using a hamstring autograft combined with a Ligament Advanced Reinforcement System. The authors reported good radiographical and functional outcomes at 2 years after this combined procedure. Another case of a prepubescent with Ehlers-Danlos syndrome and congenital ACL insufficiency (bilateral), who underwent physeal-sparing iliotibial band ACL reconstruction and revision to an all-epiphyseal ACL reconstruction with allograft, has been described. This patient was a 7-year-old girl with type IV EDS, who experienced repeated episodes of falls and initially had positive Lachman and pivot shift tests in both knees. At 28 months after the revision ACL reconstruction procedure in 1 knee, the patient had a stable Lachman test and excellent functional outcome based on the Pediatric International Knee Documentation Committee score and Lysholm knee questionnaire.[38]. No studies have explored the outcomes of the above procedures in larger groups of patients with EDS or other connective tissue disorders, and therefore, future investigation in this field is warranted.

CONCLUSION

The surgical management of shoulder and knee instability in patients with EDS can be challenging due to likely inferior biomechanical properties of the collagen-containing structures. More research is necessary to determine potential differences in tissue quality and joint mechanics between patients with joint instability and EDS versus those without connective tissue disorders. The efficacy of already established surgical techniques to address knee or shoulder instability must be examined in larger groups of EDS patients in order to assess their suitability for this patient population. The optimal surgical treatment for shoulder and knee instability in patients with hEDS or

JHS has yet to be established in the literature. Therefore, it is imperative that the treating surgeon identify patients with hEDS and JHS prior to attempting surgical stabilization procedures. A preoperative diagnosis of hEDS or JHS will allow for informed consent of the patients with regard to their higher level of surgical risks, as well as preparing the treating surgeon for the increased risk of perioperative complications, which can occur in this patient population.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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