



Clinical note

Patients with Ehlers Danlos syndrome and CRPS: A possible association?

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Abstract

Rare patients are left with chronic pain, vasodysregulation, and other symptoms that define complex regional pain syndrome (CRPS), after limb traumas. The predisposing factors are unknown. Genetic factors undoubtedly contribute, but have not yet been identified. We report four CRPS patients also diagnosed with the classical or hypermobility forms of Ehlers Danlos syndrome (EDS), inherited disorders of connective tissue. These patients had been diagnosed using standard diagnostic criteria for CRPS and for EDS. All had sustained joint injury; in three this had been surgically treated. The association of these two diagnoses leads us to hypothesize that EDS might contribute to the development of CRPS in one or more of the following ways: via stretch injury to nerves traversing hypermobile joints, increased fragility of nerve connective tissue, or nerve trauma from more frequent surgery. We review the clinical presentation of the different Ehlers Danlos syndromes and provide clinical criteria that can be used to screen CRPS patients for EDS for clinical or research purposes.

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1. Introduction

Patients with complex regional pain syndrome (CRPS), also known as reflex sympathetic dystrophy (CRPS-I) or causalgia (CRPS-II), complain of chronic pain, vasodysregulation, and other symptoms that persist after apparent healing of limb trauma. Patients with type 2 CRPS are defined as having a known nerve injury and patients with type 1 CRPS do not (Table S1), although the identification of axonal losses in CRPS-I patients (van der Laan et al., 1999; Oaklander et al., 2006) challenges the validity of this dichotomy.

Little is known about why some patients develop CRPS after traumas that usually do not have long-term sequelae. Age is important, with the average patient being 30–40 years old (Veldman et al., 1993). It is not known why it is less prevalent among older patients, who have increased risk of neuralgic pain in other conditions (e.g., post-herpetic neuralgia, trigeminal neuralgia, and small-fiber neuropathies). Spontaneous resolution is more likely in children than adults (Wilder et al., 1992). Genetic factors may influence susceptibility to CRPS. The number of patients with more than one episode is greater than that expected by chance alone (Devor, 2004). Specific HLA types (Kemler et al., 1999; van de Beek et al., 1999) but no specific genetic disorders have been associated with CRPS.

Within the last few years, we have identified several patients evaluated at the Pain Center and Genetics Ser-

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vice of the Massachusetts General Hospital who meet diagnostic criteria for both Ehlers Danlos syndrome (EDS) as well as CRPS (using the current diagnostic criteria of the International Association for the Study of Pain (Table S1)), which raises the possibility of an association between these conditions.

EDS is a group of conditions involving the skin, ligaments, tendons, and vasculature, due to inherited disorders of connective tissue. The overall incidence of EDS is about 1 in 5000 at birth, and the prevalence varies by type. Since most go cases go undiagnosed, this figure is believed to be a significant underestimate. EDS is subclassified by clinical presentation and specific genetic defect, if known (Table S2). Diagnosis is made using consensus clinical criteria, because laboratory test confirmation is not usually possible. Examination reveals some combination of hyperextensible and fragile skin, unusual scars, early varicose veins, and joint hypermobility. The Beighton hypermobility scale is used to grade hypermobility. It is a nine-point scoring system, with a score of 5/9 or above considered positive (Table 1).

Most EDS patients remain undiagnosed, even after treatment for EDS complications, due to most physicians' unfamiliarity with EDS. Yet, diagnosis could help to reduce the risk of serious complications, including preterm labor, joint dislocations, wound dehiscence, aortic dissection, and organ rupture. Since chronic pain is a common problem for EDS patients, pain specialists who are knowledgeable about EDS can improve the health of entire families by identifying pain patients whose history or examination suggests EDS and referring them for genetic evaluation. Furthermore, by learning how EDS might predispose to CRPS, we gain insights relevant for the vast majority of CRPS patients, who do not have EDS.

2. Case reports

2.1. Case #1

This 30-year-old woman was referred to the Pain Center for treatment of chronic, left greater than right,

knee pain. Her most recent knee surgery, anterior tibial tubercle osteotomy and patellar realignment, initiated her most severe pain problem, which involved her left knee and medial lower leg. Her pain, rated at 6–7 on a 1–10 scale, was worsened by activity, weather changes, and prolonged sitting. Paresthesias radiated from her left knee down her medial calf to her foot and toes, and up to her left hip. She also noted intermittent edema of her left lower leg, and color and temperature differences between her left and right legs. Her non-CRPS right knee pain was less severe, did not radiate, and was not associated with edema or vascular dysregulation. Her medications were sodium naproxyn and three tablets daily of hydrocodone. In the past, rigorous physical therapy, ibuprofen, acetaminophen, amitriptyline, and tramadol had been ineffective.

Her medical history revealed recurrent spontaneous dislocations of her patellae since age 15. Polyarthralgias, worse in her knees, developed when she was in her mid-20s. Her first knee surgery, right tibial tubercle osteotomy with medial transfer and lateral retinacular release in 1997, provided only temporary improvement in right knee pain. She delivered four children vaginally, three of whom were born prematurely due to cervical incompetence. There was no known family history of recurrent dislocations, although her mother reportedly had “arthritis” and “knee pains”.

Examination revealed a normal female habitus, hyperextensibility of both of her knees and elbows, and bilateral left greater than right mild prepatellar edema. She had normal motor function and reflexes. Sensory examination revealed mechanical allodynia and hyperpathia medially at the left knee and left calf. This patient met the three criteria for a diagnosis of CRPS-II (Table S1) from left saphenous nerve injury.

She was referred to the Genetics Service for possible EDS based on her history of recurrent joint dislocations, preterm labor, and signs of joint hypermobility. Additional history obtained there included myopia and no problems with healing or easy bruising. Examination there revealed soft, smooth, and slightly hyperextensible skin without stretch marks, varicosities, or easily visible veins. Her surgical scars were neither hypoplastic nor unduly wide. She had finger, wrist and ankle hypermobility, spontaneously dislocatable thumbs, and flat feet. Her Beighton score was 6 out of 9. She had pectus excavatum and mild scoliosis. Hypermobility EDS was diagnosed on the basis of two major criteria (joint hypermobility and hyperextensible skin) and one minor criterion (recurrent non-traumatic joint dislocations).

Over the next months, trials of adequate doses of gabapentin, sustained-release oxycodone, nortriptyline, desipramine, and doxepin provided only partial relief. Surgical exploration of her left saphenous nerve revealed neither neuromas nor compression in the subsartorial

Table 1
Beighton hypermobility scoring system (Beighton, 1993)

Feature	Scoring ^a
1. Ability to passively dorsiflex the fifth finger >90°	One point for each hand
2. Passive extension of the thumb to the forearm	One point for each hand
3. Elbow hyperextension beyond 10°	One point for each arm
4. Knee hyperextension beyond 10°	One point for each leg
5. Can place palms flat on the floor while forward bending with straight knees	One point

^a Five or more out of a total of nine are considered consistent with significant joint hypermobility.

canal. Subsequently, she had surgical implantation of a temporary, and then a permanent, stimulator of her left saphenous nerve, which provided initial relief. However, migration of the paddle electrode eventually caused discomfort and she discontinued use of her stimulator and resumed medical management.

2.2. Case #2

This 21-year-old woman was evaluated at the Pain Center for severe right wrist and hand pain that had developed four months earlier when she awoke to find her shoulder out of its socket. Although this reduced easily without medical care, the pain worsened and spread to her shoulder. She complained of numbness, weakness, and atrophy of her right arm, and tingling in her fingers. She noted hyperhydrosis and intermittent edema of her right hand. Cold exacerbated her symptoms. Her history revealed multiple prior spontaneous shoulder and patella dislocations. Recurrent right ankle sprains had required right ankle ligament reconstruction. She reported no difficulty with either healing or abnormal scarring. She had a history of a language-based learning disability and depression. Both her mother and maternal grandmother also had joint hypermobility.

On examination at the Pain Center, she guarded her right arm and hand, and the plantar surface of her wrist was tender to palpation. There was atrophy of the first right dorsal interosseous muscle and decreased pin sensation in the ulnar distribution of the right hand. A Tinel's sign was elicitable at the right supraclavicular fossa. Edema and trophic changes of the skin or nails were absent. Generalized joint laxity was noted. Electrodiagnostic study, which required intravenous sedation to perform, was interpreted as normal. She was diagnosed with CRPS-II after presumed stretch injury to the medial cord of her brachial plexus or her ulnar nerve. Nortriptyline and a topical lidocaine patch were prescribed. She found the nortriptyline, but not the patch, partially efficacious.

She was referred to the Genetics Service because of concern about possible EDS based on her history of recurrent spontaneous joint dislocations and signs of joint hypermobility. Examination there revealed very soft and smooth skin with well-healed surgical scars. Her skin was neither hyperextensible nor translucent. She had no varicosities or easily visible veins. Striae were prominent across her lower back and trunk. She had gingival recession, mild scoliosis, and widespread joint hypermobility (Beighton score 8 out of 9) with hyperextensible fingers, wrists, and elbows. She was diagnosed with hypermobility EDS on the basis of two major criteria (abnormally soft smooth skin and joint hypermobility) plus one minor criterion (recurrent non-traumatic dislocations).

2.3. Case #3

The Genetics Service evaluated this 40-year-old woman for a connective tissue disorder. She had a history of dislocations and subluxations of many joints; these had required eleven surgeries at various hospitals. These included reconstructions of both ankles, fusions of both hands, left and right rotator cuff repairs, and reconstruction of her right shoulder to treat multi-directional instability. This last surgery was immediately followed by new chronic pain, paresthesias, and edema of the dorsum of both of her hands. She reported intolerance of light touch on her hands or water running over them. Her pain was exacerbated by changes in temperature and with activity but also was present at rest. Her medical history also revealed gastroesophageal reflux with hiatal hernia treated by fundoplication and cholecystectomy. She had a history of easy bruising and increased joint mobility. She had one term pregnancy that produced a daughter with increased joint flexibility. Examination of the dorsum of her hands revealed allodynia to touch, decreased pin sensation, and edema. Electromyography and nerve conduction studies of both upper extremities had been interpreted as normal. Clinical and radiological evaluations of her cervical spine had revealed no abnormalities. She had been diagnosed elsewhere with reflex sympathetic dystrophy (CRPS-I) and treated with methadone and nerve blocks in both of her hands.

Examination in Genetics Clinic showed velvety, slightly hyperextensible skin, and many scars from minor trauma as well as from surgery. Some of the surgical scars were narrow and well healed, whereas others were abnormally atrophic and broad. No cutaneous varicosities or translucency were noted. She had a high arched palate and no gingival recession. She had hyperextension of her fingers and knees, and could place her palms on the floor without bending her knees, yielding a Beighton score of 5 out of 9. This was considered artifactually low because her previously hypermobile elbows and shoulders had been surgically tightened. She was diagnosed with classical EDS on the basis of two major criteria (widened atrophic scars and joint hypermobility) plus two minor criteria (smooth velvety skin and complications of joint hypermobility) (Fig. 1).

2.4. Case #4

This 33-year-old woman was evaluated at the Pain Center for severe chronic left lower leg symptoms after injury to her left anterior-cruciate-ligament from a soccer injury a year earlier. The immediate cause of her symptoms was surgical repair of her anterior cruciate ligament and menisci that was performed two weeks after her injury. This was complicated by intra-operative penetration of a surgical screw through her tibia into her



Fig. 1. This patient with classical EDS can passively extend her thumb to touch her forearm.

popliteal artery, which caused intra-arterial thrombus formation. This was identified and treated with thrombolytic and anticoagulant therapy, which lysed the clot but initiated arterial bleeding into her leg. This produced severe lower leg pain, numbness, and increased limb girth. Compartment syndrome with critical ischemia and elevated pressures was documented and treated the next day by fasciotomy and repair of her left popliteal artery using a right saphenous vein graft. In the immediate postoperative period, she complained of severe lancinating pain radiating down her left lower leg to her toes, numbness and stimulus-independent pain at the dorsum of her left foot, lower-left-limb edema, and hyperhidrosis. She also noted tactile hallucinations of bugs crawling on top of her left foot. She denied mechanical allodynia. Despite good recovery from surgery, these symptoms persisted, and a few months postoperatively similar though less-severe symptoms developed at the mirror-image location on her right lower leg. Autonomic testing had documented left-right asymmetries in lower-limb skin temperature and sweating. Electrodiagnostic study had revealed reduced amplitude of compound motor action potentials in her left peroneal and tibial nerves, and spontaneous activity in the left gastrocnemius but not tibialis anterior muscles. Triple-phase bone scan identified abnormally increased uptake in both calves and at the left proximal tibia. Treatment with gabapentin, amitriptyline, and occasional oxycodone had been partly efficacious. The bottom of her left foot had improved more than the top of her foot. A consultant identified no rheumatological cause for her chronic pain.

Her pertinent medical history included one earlier traumatic shoulder dislocation and sleep apnea treated

with nocturnal continuous positive airway pressure. A heart murmur had prompted echocardiography, which was said to show multivalvular leakage. Family history revealed that her mother had mitral valve prolapse and an abdominal aortic aneurysm. Her father had unspecified knee problems, and several family members were said to have increased joint mobility.

Examination at the Pain Center revealed normal athletic female habitus. Spontaneously dislocatable thumbs and elbow and knee hyperextension suggested EDS. There was color asymmetry between her two feet, but no overt edema nor changes in skin and nails. Motor function was intact. Sensory examination demonstrated hypesthesia to pinprick, light touch, and cold on the dorsal left foot and calf (medial worse than lateral). Her left ankle reflex was diminished. She met all criteria for and was diagnosed with CRPS-II caused by injury to the left common peroneal and tibial nerves. The proximate cause of nerve injury was felt to be ischemia from her documented compartment syndrome. The recommendations were to switch from amitriptyline to nortriptyline to try to reduce amitriptyline-related orthostatic hypotension and to consider evaluation for possible EDS.

Evaluation at the Genetics Clinic revealed no history of easy bruising or difficulty with wound healing. Examination revealed broad surgical scars and persistent scars from minor injuries such as cat scratches. Her skin was hyperextensible (>4 cm of extension at the neck) and soft, but not velvety. There was neither cutaneous translucency nor varicosities. There was no gingival recession, pectus excavatum or scoliosis. There was joint hypermobility with a Beighton score of 6 out of 9 (although mobility of her left knee was reduced because of prior surgeries) with hyperextensible thumbs, wrist, elbows, and right knee. She was diagnosed with classical EDS based on three major criteria (skin hyperextensibility, widened atrophic scars, and joint hypermobility) (Fig. 2).



Fig. 2. Hyperextensibility of the skin of the forearm in a patient with classical EDS.

3. Discussion

EDS is divided into several different types, based on clinical and molecular criteria (Table S1). Reviews of the different types of EDS can be found at <http://www.ednf.org>; <http://www.ehlers-danlos.org> and <http://www.genetests.org>. Classical EDS comprises 90% of cases (Steinmann et al., 2002). The diagnosis is based on skin hyperextensibility (>4 cm of skin extension at the neck), broad atrophic scars, and joint hypermobility (Beighton, 1993; Beighton et al., 1998). Patients' skin is typically smooth and velvety. Complications include hernias, pelvic organ prolapse, premature arthritis, joint pain, and cervical insufficiency. The severity is variable; type II EDS designates patients with milder manifestations, particularly those lacking widened atrophic scars (Wenstrup et al., 1996). Classical EDS is autosomal dominant and mutations in the COL5A1, COL5A2 genes (responsible for type V collagen synthesis) or in the COL1A1 gene (encoding one of the subunits of type I collagen) (Wenstrup et al., 2000) have been identified in about 30% of cases.

Hypermobility EDS (formerly type III) is less common and involves fewer skin abnormalities. Diagnosis is based on joint hypermobility, frequent dislocations, and hyperextensible skin that heals normally (Beighton, 1993; Beighton et al., 1998). Chronic joint pain is common. Mutations in two genes have been found in a few cases, COL3A1 (responsible for type III collagen) (Narcisi et al., 1994) and Tenascin-XB (Zweers et al., 2003). Most cases are autosomal dominant, although Tenascin-XB mutations are autosomal recessive.

Vascular EDS (EDS IV), the most dangerous form, accounts for only 4% of cases and has a prevalence of less than 1 in 100,000 (Byers, 1995). Affected individuals have thin translucent skin, easy bruising, tissue fragility, and a characteristic thin face with large eyes. There may also be hypermobility of small joints, acrogeria, and gingival recession. Potentially lethal complications include development of aneurysms or pneumothoraces, and rupture of arteries or hollow organs, including the gravid uterus. It is autosomal dominant and caused by COL3A1 mutations.

Extremely rare forms of EDS include Kyphoscoliosis (EDS VI), Dermatosparaxis (EDS VIIC), and Arthrochalasia EDS. Kyphoscoliosis EDS is autosomal recessive, caused by mutations in the lysyl hydroxylase gene and consists of generalized joint laxity, keratoconus, scoliosis, and scleral and vascular fragility. Dermatosparaxis is autosomal recessive due to a deficiency of procollagen I N-terminal peptidase and consists of lax redundant fragile skin and large hernias. Arthrochalasia EDS is autosomal dominant, due to specific mutations in the COL1A1 and COL1A2 genes resulting in abnormal cleavage of the precursor type I procollagen to collagen. Affected individuals have congenital hip

dislocation, joint hypermobility, recurrent dislocations, scoliosis, and short stature. There are also other rare forms of EDS that are not well characterized (Steinmann et al., 2002). Confirmatory testing is available for the Vascular, Kyphoscoliotic, Arthrochalasia, and Dermatosparaxis types of EDS. Genetic testing is unavailable for patients with hypermobility EDS and most patients with classical EDS.

These four patients were diagnosed with CRPS-I or CRPS-II according to the criteria of the International Association for the Study of Pain (Table S1) (Merskey and Bogduk, 1994). A clinical geneticist also diagnosed each with EDS. Two patients were diagnosed with classical EDS and two with hypermobility EDS. Chronic pain is common in EDS (Sacheti et al., 1997), particularly in the hypermobility and classical forms. Usually the cause is premature joint or tendon wear, or injuries, however some chronic pain in EDS is due to post-traumatic neuralgia. There are a few previous reports of patients with EDS-associated nerve injury (Kayed and Kass, 1979; Bell and Chalmers, 1991; Chattopadhyay et al., 1995; Galan and Kousseff, 1995) including one vascular EDS patient, six hypermobility EDS patients, and two classical EDS patients. The nerves involved were the brachial plexus, lumbosacral plexus, sciatic nerve, and common peroneal. These had been injured by fracture, traction, sling, or normal activities of daily living. The outcome varied, but incomplete resolution was common. Tomaculous neuropathy with pressure related nerve injuries has also been associated with EDS (Schady and Ochoa, 1984).

Our cases demonstrate the development of CRPS in patients with EDS by two distinct ways, specifically: stretch injury to nerves by joint dislocation or hyperextension and increased exposure to medical procedures such as surgery. Medical procedures have been linked to the onset of CRPS in a number of studies. Veldman et al. (1993) showed that 23% of 829 CRPS patients underwent an invasive procedure (surgery, injection or intravenous infusion) just before the development of their symptoms. Medical procedures (surgery, casting, or phlebotomy) immediately preceded onset of CRPS-I in 16/18 subjects in a recent study (Oaklander and Brown, 2004). Of our four cases, it is unclear whether the first patient sustained her presumed saphenous nerve injury from patellar dislocation or subsequent knee surgery. Case 2 had sustained joint dislocation only, without surgical procedures. Case 3 attributed her CRPS to a surgery that immediately preceded onset of symptoms, and in Case 4, CRPS was clearly a complication of surgery.

We suggest a third possible link between EDS and CRPS for which there is no direct evidence. It is possible that the nerve connective tissue is fragile in EDS patients and less able to protect the axons within from trauma. Type V collagen, one of the components of nerve tissue (Rothblum et al., 2004), is abnormal in some cases of

classical EDS. While we are unaware of testing of the strength of nerve connective tissue in EDS patients, other tissues that contain type V collagen, such as skin, tendons, and ligaments, are more fragile in classical EDS patients. More work is needed to define the relative contributions of these factors. An existing rabbit model of EDS (Sinke et al., 1997) is a potential tool for such studies.

In conclusion, it is important for physicians to consider EDS when evaluating a patient with multiple joint problems. We recommend that physicians caring for CRPS patients consider the possibility of an underlying connective tissue disorder in patients with histories or examinations revealing joint laxity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.pain.2006.02.022](https://doi.org/10.1016/j.pain.2006.02.022).

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