

## HEREDITARY ASPECTS OF COMPLEX REGIONAL PAIN SYNDROME (CRPS)

Hooshang Hooshmand, M.D. (Retired), and Eric M. Phillips

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**Abstract:** In a study of 824 complex regional pain syndrome(CRPS) patients treated in our clinic from January 1991 through January 1996, four cases suffering from Ehlers-Danlos syndrome(EDS) were ultimately diagnosed with CRPS (1). Since our report on 824 CRPS patients, we had an additional case referred to our clinic. This case involved twin sisters suffering from EDS-type III (hypermobility type) also diagnosed with CRPS. This additional case gave us five EDS/CRPS cases (six patients) which included two families having other members with both EDS/CRPS.

In our research we have also found five other cases (12 patients) suffering from other diseases such as Fabry' disease(FD), Sjogren's syndrome and lupus erythematosus (LE) that have contributed to these patients developing CRPS.

Over the years there have been very few published reports that have shown the hereditary aspects of CRPS associated with EDS and other diseases. In this article, we will discuss the hereditary aspects of CRPS.

**Keywords:** *Complex regional pain syndrome(CRPS), Ehlers-Danlos syndrome(EDS), Familial CRPS (f-CRPS), Hereditary aspects, Hypermobility.*

### INTRODUCTION

Complex regional pain syndrome (CRPS) has been well documented throughout medical history. In 1864, Doctor Silas Weir Mitchell the father of American neurology gave the first description of what is now known as complex regional pain syndrome(CRPS). He coined the term of causalgia from the Greek words, "Kausos" (heat) and "algos" (pain) to describe this syndrome (2). Since Mitchell's first description of this painful syndrome, there have been many other names given to this complex disease. In 1900 Sudek named it Sudeck's atrophy; in 1937 DeTakats named it reflex dystrophy; in 1947 Steinbrocker named it reflex neurovascular dystrophy and shoulder-hand syndrome; in 1947 Evans named it reflex sympathetic dystrophy (RSD); and in 1994 Merskey, et al. named it complex regional pain syndrome (CRPS) (3-8).

Ehlers-Danlos syndrome(EDS) is a rare genetic disorder of inherited connective tissue. Doctor J.J. van Meek'ren, in 1682 and in 1892 by Doctor A. N. Chernogubov first reported the symptoms of what we now call EDS (9,10). The work by Doctor Edvard L. Ehlers in 1901 and Doctor Henri-Alexandre Danlos in 1908 each had patients with skin laxity a common symptom of the syndrome (11,12). It was not until 1936 when Doctor Frederick Parkes-Weber recommended that the syndrome should be named Ehlers-Danlos syndrome(EDS) since both doctors gave a complete description of the syndrome (13,14). In Russia, EDS is still known as Chernogubov's syndrome named after Doctor A. N. Chernogubov.

The incidents of EDS are estimated at one in 5,000 people (15,16). According to Beighton and Horan, EDS is usually inherited as an autosomal dominant trait (17). They believe that a child who is born to a patient with EDS has a 50 percent chance of developing the syndrome (17).

Due to the rarity of EDS, proper diagnosis and treatment are essential for the health of the patient. The delay of a proper diagnosis and treatment of EDS could endanger the patient's life (18).

The combination of complex regional pain syndrome (CRPS) and Ehlers-Danlos syndrome(EDS) are quite rare diseases. With the lack of knowledge and comprehension of both diseases can produce a poor prognosis for the patient.

CRPS and EDS are two unique syndromes that have been routinely misdiagnosed for other diseases/syndromes. In some cases, EDS may be mistaken for fibromyalgia (19).

Like EDS, CRPS has also been mistaken for other diseases such as a migraine, thoracic outlet syndrome(TOS), shoulder-hand syndrome(SHS) bursitis of shoulder or hip, myofascial injury, frozen shoulder, factitious self-mutilation due to neuroinflammatory changes seen in CRPS, Raynaud's phenomenon (RP) and TMJ disease etc.... (20, 21).

CRPS is a puzzling syndrome with many causes, some of known and some of unknown etiology. The incidents of CRPS are estimated in the millions throughout the United States and worldwide

As we will discuss in this article, EDS is just another syndrome that may cause signs and symptoms of CRPS in some cases.

### **HEREDITARY ASPECTS OF CRPS**

In recent years there have been some documented reports of familial occurrence in some families with multiple members suffering from CRPS (22). The research work reported by de Rooij et al investigated 31 families who had 53 members diagnosed with CRPS (22). In their study, they believe that CRPS can develop in a familial pattern. In their conclusion, they found no evidence of an inheritance pattern among CRPS patients (22).

In our research, we have identified five families (12 patients) with more than one member of the family suffering from CRPS (Non-EDS cases). These patients were suffering from diseases such as Fabry' disease(FD), Sjogren's syndrome and lupus erythematosus (LE). We also found some cases where members of the same family developed CRPS after an injury or surgery.

- Case #1: Two sisters suffering from Fabry' disease(FD) (lipid metabolism disease of genetic nature). FD selectively involves small blood vessels and secondarily has a high tendency for development of CRPS (or, more frequently, simple sympathetically maintained pain). As it affects the small arteries, it involves the sympathetic nerves surrounding them. It is not CRPS, but the pre-existing genetic disease that made the members of the family susceptible to it.
- Case #2: A mother and her two daughters suffered from CRPS. The mother also suffered from Sjogren's syndrome, and one of the daughters suffered from lupus erythematosus (LE). All three patients had abnormal T-cell lymphocyte ratios. In this family, a strong tendency for an auto-immune disease was seen. The treatment aimed at treating both CRPS and the auto-immune disease due to the family having a strong tendency for an auto-immune disease. It is well known that 5% of patients with auto-immune disease (e.g., rheumatoid arthritis, MS, lupus, etc.) show a hereditary familial tendency.
- Case #3: A brother and a sister suffered from CRPS. The brother developed CRPS after a lightning strike and the sister developed CRPS after a mild lumbar spine injury. Both patients had a rough course with failed treatments and eventually needed infusion pump treatment.
- Case #4: Two sisters and one cousin all diagnosed with CRPS. These three patients developed CRPS from a spinal trauma. Their injuries and diagnosis of CRPS were years apart from one another.

- Case #5: A mother and daughter developed CRPS after knee surgery. Neither patient showed any signs or symptoms of CRPS preceding knee surgery. Was this a case of familial occurrence of CRPS or did the surgery, unfortunately, caused CRPS in both family members?

In 1983, Albert and Ott authored an article where they reviewed a case of Algodystrophy (RSD) of the hip in three brothers (23). Their research suggests a possible genetic predisposition for the disease (23).

Shirani et al, reviewed a cohort study of 69 CRPS cases finding four families with two or more members who suffered from CRPS with nine patients (24).

The research by Veldman et al of 829 CRPS cases found five patients who had one or more blood relatives who also had symptoms of CRPS (25).

Brucas et al, describe familial RSD/CRPS in two brothers who suffered from recurrent RSD/CRPS in the lower extremities (26).

There have been a few documented reports of the familial CRPS (f-CRPS). Realizing that CRPS comprises somewhere between 5-6% of the chronic pain patients, the familial tendency is either coincidence or hereditary diseases rather than the CRPS itself seen as a purely genetic disease.

There needs to be further research into the role that genetic genes play in f-CRPS cases.

### **DO GENETIC GENES PLAY A ROLE IN CRPS?**

Over the years there have been some research studies investigating the role that genetic genes may have in the development of CRPS. These published reports have shown that a small percentage of CRPS cases may have some genetic link to developing CRPS.

According to Mailis and Wade, they observed abnormal human lymphocytic antigens (HLA) elevation in some CRPS patients. Eighty percent of such patients were resistant to treatment. They suggest that a possible association with human lymphocyte antigen(HLA) as a genetic link to CRPS (27).

The research work by Vaneker et al showed 82 out of 161 CRPS patients had the HLA-DR6 and HLA-DQ1 gene. All these patients suffered from the cold type of CRPS (28). They also found tumor necrosis factor alpha (TNF $\alpha$ ) gene in 63 patients suffering from the warm-type of CRPS (28).

Kemler et al, performed a genetic gene study on 52 CRPS patients. They found these 52 CRPS patients to have a high frequency of the HLA-DQ1 gene. Their research show there could be a genetic link to CRPS (29).

According to van Hilten et al had found the HLA-DR13 gene in 26 CRPS patients who also suffered from dystonia (30).

Kimura and colleagues researched the angiotensin-converting enzyme (ACE) gene. They found a link that the ACE gene can contribute to the development of CRPS (31).

A study by Hühne et al investigated 12 CRPS patients from six CRPS families. From their research they did not find the ACE gene to be a predisposing factor for developing CRPS (32).

Given the statistics that a small percentage of CRPS patients may be at risk of developing the syndrome due to a genetic gene, one must determine all factors in the diagnosis of CRPS (e.g. signs, symptoms, nature of onset, and any genetic links that may be the cause of the syndrome).

### **DIAGNOSIS OF COMPLEX REGIONAL PAIN SYNDROME (CRPS)**

The diagnosis of CRPS requires the following four strict criteria:

- Hyperpathic(regional), allodynic (low pain threshold to touch), and neuropathic pain.
- Vasomotor, sudomotor changes, flexor spasm, and secondary thermal changes.
- Intermittent neuroinflammatory edema, skin rash, bulbous lesions, trophic ulcers, and other signs of immune system dysfunction (1,33).
- Disturbance of function of the end organ receiving the neuropathic sensory input, i.e., the limbic system (15).

### **DIAGNOSIS OF EHLER-DANLOS SYNDROME(EDS)**

The diagnosis of EDS (a dominant hereditary, autosomal syndrome) requires strict criteria:

- Easy bruising.
- Hereditary pattern.
- Skin changes with easy bruising of the skin with visible veins.
- Hyper elasticity of the skin, and hypermobility of joints (“Rubberman Syndrome”), and central and peripheral nervous system arrest of development (17,34).

The dysplasia of the nervous system manifests itself in nonspecific complications such as frontal polymicrogyria seizure disorder, poorly developed sensory nerve fibres, and hypoplasia of the cerebellar vermis (35-39).

According to Pauker et al, the diagnosis of EDS should be taken into consideration in young patients who have a dissection of major blood vessel and rupture of an organ (16). EDS patients who have hypermobility of the joints also suffer from musculoskeletal pain (16).

### **EHLER-DANLOS SYNDROME(EDS) AND COMPLEX REGIONAL PAIN SYNDROME (CRPS)**

As we are aware of, EDS is a rare genetic disorder. On the other hand, CRPS has yet to be classified as a genetic disorder. In our clinic, we have seen five cases with six patients having EDS ultimately diagnosed with CRPS. Two out of the five cases had other family members also diagnosed with EDS and CRPS.

- Case #1: A 18-year old female patient has EDS with hypermobility of the joints. She developed CRPS after an injury to her right hand. She does not have any other family members who have EDS or CRPS.
- Case #2: A 29-year old female patient suffers from EDS with hypermobility of the joints for many years. She also had neuroinflammation and skin lesions on both hands and arms. She developed CRPS after an injury to both hands. The patient has other family members diagnosed with both EDS and CRPS. Her younger brother, maternal grandmother, and maternal aunt also suffer from EDS. Her mother and brother were also diagnosed with CRPS. Her other family members were not seen in our clinic. (We were told about the other family members from the patient).
- Case #3: A 21-year old female patient was diagnosed with EDS with hypermobility of the joints in her early teen years. After an injury to her left foot and leg, she was diagnosed with CRPS. She did not have any other family members with EDS or CRPS.
- Case #4: A 15-year old male patient was diagnosed with EDS with hypermobility of the joints and neuroinflammation. He is also double jointed, has handclasp, could put his leg behind his head and has a very high pain threshold. After an injury to his right foot, he was diagnosed with CRPS. He also has three other siblings diagnosed with EDS but not CRPS. His other family members were not seen in our clinic. (We were told about the other family members from the patient).
- Case #5: 16-year old twin females diagnosed with EDS with hypermobility of the joints, and neuroinflammation. They are both double jointed and act like pretzels. CRPS was diagnosed in both patients after injuries to both knees, hips, and lower back.
- Note: Cases #2 and #5 fall under the category of familial CRPS (f-CRPS).

All the EDS patients that we studied in our clinic had hypermobility of the joints. This is a classic symptom of EDS. They also all had neuroinflammation and joint pain. One of the cases also had skin lesions on both arms and hands. A minor injury to the small blood vessels due to hypermobility of the joints maybe one of the contributing factors for these patients developing CRPS (1).

In 2006, Doctors Stoler and Oaklander reported four cases of CRPS patients diagnosed with EDS. Through their research they acknowledged EDS may contribute to the development of CRPS from the following causes: stretch injury to nerves traversing hypermobile joints, trauma from frequent surgery, and fragility of nerve connective tissue (39).

Stern and colleagues reported that 8.3% of the pediatric cases suffering from EDS was also diagnosed with chronic pain syndrome (40).

Chopra and Cooper reported a case of a 12-year old girl with EDS with hypermobility. She had repeated dislocations of her right shoulder and right ankle. She developed CRPS in her right lower extremity with associated dystonic muscle spasms (41).

Weinstock and colleagues recognized that undiagnosed EDS patients who suffer from CRPS could explain some of the familial cases of CRPS reported (42).

Sachati et al also report that chronic pain is a common manifestation of EDS (43).

## COMPLICATIONS OF EHLER-DANLOS SYNDROME(EDS)

EDS has many complications such as joint dislocations and subluxations of the shoulders, temporomandibular joint, and the patella are just some of the many complications found in EDS patients (Table 1).

<b>TABLE 1. COMPLICATIONS OF EDS</b>	
Autonomic dysfunction	Mitral valve prolapse (Barlow Syndrome)
Delayed gastric emptying	Postural orthostatic tachycardia syndrome (POTS)
Headaches(migraines)	Sleep apnea
Irritable bowel syndrome (IBS)	Swelling of the legs
Joint dislocations and subluxations	Syncope

## COMPLICATIONS OF COMPLEX REGIONAL PAIN SYNDROME (CRPS)

CRPS has many various complications often unrecognized and goes untreated for many years. Many of these complications are not well recognized by the medical community treating CRPS patients (Table 2). However, CRPS continues to be a very complex disease to understand and to treat. These various complications can impede the proper treatment against the spread of the disease and the underlying issues that arise from these complications (8).

<b>TABLE 2. COMPLICATIONS OF CRPS</b>	
Cardiac disturbance	Interstitial cystitis
Depression	Intractable hypertension
Disturbance of immune system	Keratitis Sicca (dry eyes)
Endocrine system dysfunction	Limbic system dysfunction
Fatigue	Movement disorders
Gardner-Diamond syndrome (spontaneous bruising)	Respiratory system complications
Gastrointestinal complications	Skin lesions, rashes and ulcers
GERDS	Spread of CRPS
Headaches (migraine)	Tinnitus hearing complications
Insomnia	Urological complications
Internal organ involvement	Visual disturbance

## CONCLUSION

Both CRPS and EDS have had a long complex history in the medical community throughout the years. It is important to understand that both syndromes can be misdiagnosed for other diseases.

From our research and the research by Doctors Stoler and Oaklander, one must consider the possibility that some patients suffering from EDS could have symptoms of CRPS due to stretch injuries to the nerves caused by hypermobility of the joints. The trauma that causes CRPS can be of a minor nature (e.g. sprain of the hand, wrist, foot or ankle) which can cause nerve damage and symptoms of CRPS.

Similarly, the diagnosis of coexistent rare hereditary diseases such as EDS and CRPS required strict diagnosis along with the hereditary pattern of such rare diseases.

Treatment for CRPS and EDS can be very complex for the patient and physician. Most patients with both CRPS and EDS suffer for many years due to misdiagnosis, lack of understanding and lack of proper treatment for both diseases.

Through our research and the research of others, we recognize that there could be a hereditary aspect in some CRPS case.

As we have reported in this article, two groups of five cases (18 patients) with various diseases and injuries developed CRPS. Also, surgery was another cause of developing CRPS. These are just a few examples that other disease can contribute to the development of CRPS either in a single case or in a familiar pattern.

Given the fact, there have been some reported cases of f-CRPS. Further research into the cause of familial CRPS is needed to gain a better understanding on how other disease can contribute to the development of CRPS. Patients who suffer from EDS and other diseases which have developed CRPS could be a helpful link to acquire the answers to the familial causes of CRPS.

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