

A case of challenging pediatric complex regional pain syndrome resistant to conventional treatments and its relationship with FMF

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ABSTRACT

Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy, is a chronic neuropathic pain disorder with important autonomic features. CRPS presents with multifactorial pathophysiology and treatment-resistant pain. Peripheral and sensorimotor abnormalities reflect maladaptive changes in the central nervous system. Invasive treatments may be required as well as non-invasive treatments. Furthermore, CRPS and Familial Mediterranean Fever (FMF) are thought to have some common autoinflammatory pathways. Here, we present a pediatric case who is on follow-up with FMF and presented with the complaint of severe pain after a traumatic event, had pain attacks triggered by emotional stress, and underwent two sympathetic nerve blockades.

Keywords: Complex regional pain syndrome; FMF; sympathetic blockade.

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Geleneksel tedavilere dirençli zorlu pediatrik kompleks bölgesel ağrı sendromu olgusu ve ailevi Akdeniz ateşi ile ilişkisi

ÖZET

Eskiden refleks sempatik distrofi olarak bilinen kompleks bölgesel ağrı sendromu (CRPS), önemli otonomik bozukluklarla kendini gösteren kronik nöropatik bir ağrı bozukluğudur. CRPS'nin patofizyolojisi multifaktöryeldir ve tedaviye dirençli ağrı ile kendini gösterir. Periferik ve sensörimotor anormallikler, santral sinir sistemindeki uyumsuz değişiklikler sonucu ortaya çıkar. Hastalığın tedavisinde invaziv yöntemlerin yanı sıra noninvaziv yöntemler de gerekebilir. Bununla birlikte, CRPS ve ailevi Akdeniz ateşinin (FMF) bazı ortak otoinflamatuvar yollara sahip olduğu düşünülmektedir. Burada FMF nedeni ile takip edilirken, travmatik bir olay sonrası şiddetli ağrı şikayeti ile başvuran, emosyonel stresin tetiklediği ağrı atakları geçiren ve iki kez sempatik sinir blokajı uygulanan CRPS'li bir çocuk olgu sunuldu.

Anahtar Kelimeler: Kompleks bölgesel ağrı sendromu; kompleks bölgesel ağrı sendromu; CRPS; ailevi Akdeniz ateşi; FMF; sempatik blokaj.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a neuropathic pain disorder that usually develops after a trauma, fracture, or surgery. The intensity of the pain is much greater than would be expected at this level of tissue damage and continues after the tissue is healed. Sensory-motor and autonomic changes also occur. These include allodynia, hyperalgesia, sudomotor and vasomotor abnormalities, and trophic changes. Pain does not follow a particular dermatome or myotome but is rather regional (1).

CRPS and Familial Mediterranean Fever (FMF) are two distinct medical conditions with different underlying mechanisms. There is currently no established direct association between CRPS and FMF. However, it is important to note that both conditions could lead to chronic pain and affect the quality of life for those affected. FMF, on the other hand, is an autoinflammatory disorder that primarily affects individuals of Mediterranean descent. It is caused by mutations in the MEFV gene, which leads to episodes of recurrent fever, abdominal pain, and inflammation in various parts of the body, particularly the joints (2). FMF is not directly related to CRPS, and its pathophysiology is related to dysregulation of the innate immune system. It is worth mentioning that individuals with FMF may experience various musculoskeletal symptoms, including joint pain, myalgia, and arthritis. These symptoms may occasionally overlap with CRPS symptoms (3). It is crucial to differentiate between the two conditions and seek appropriate medical evaluation and management.

CRPS management requires different treatment modalities including patient information and education, pharmacological treatments, physical and occupational therapy, and psychological support. The purpose of treatment is to decrease pain and make the extremity useful again. Although the course of the disease is different in every patient and there is no proof that therapy affects its course directly, therapy should not be delayed. Invasive procedures such as sympathetic blockade, surgical sympathectomy, spinal cord stimulation, and even amputation may be required when noninvasive treatment modalities do not work (4).

In this case report, we aimed to discuss an 11-year-old female patient who already has FMF and was diagnosed with CRPS.

CASE REPORT

A 12-year-old patient diagnosed with FMF for 6 years presented with complaints of burning in her ankles and severe pain on touch. In the anamnesis, it was learned that the pain started after cast immobilization was applied to the patient 1 year ago due to trauma. The pain in both ankles of the patient limited her daily activities. There was severe tenderness that aggravates even with contact. Acute phase responses were found to be negative. A diagnosis of CRPS was considered due to a few histories of cast immobilization because of recurrent pain and severe tenderness. Mild edema was detected in the subcutaneous fat planes in the dorsolateral at the metatarsal level by magnetic resonance imaging. Electromyography was normal. The patient was diagnosed with CRPS according to the Budapest diagnostic criteria (5). Ibuprofen treatment was used. Because her pain was severe, bone marrow aspiration was performed, and leukemia was excluded. Methylprednisolone and gabapentin therapy was started. The patient whose pain did not regress was evaluated together with a child psychiatrist, and sertraline was added to the treatment regimen. The symptoms of the patient regressed. The dose of methylprednisolone was tapered, and she was discharged. After 1 month of discharge, the patient was admitted because her right foot was cold and had purplish color. Doppler ultrasound revealed no thrombosis. During the follow-up, the patient's complaints did not regress, and gabapentin was switched for pregabalin. However, upon the partial response, the sympathetic nerve blockade was applied by the algologist, pregabalin was stopped, and methotrexate was added to her treatment. Five months later, due to the trigger of emotional stress factors, the patient started to have severe pain. Methotrexate was stopped, and gabapentin was restarted. Tramadol was added to the treatment of the patient, who was evaluated together with the algologist. Physiotherapy continued to be



Figure 1. Foot and ankle swollen and erythematous.



Figure 2. Left foot and leg, cold, and pale.

applied to the patient. Tramadol was stopped when the patient's pain subsided. One year later, pain, tenderness, and swelling in both feet of the patient recurred. The patient had discoloration, tenderness, and coldness in both feet and distal legs. Images of the patient are presented in Figures 1 and 2. Methylprednisolone was started, and she has consulted with algology again. Algologist prescribed morphine sulfate, and the sympathetic blockade was performed again. Sertraline was switched to fluoxetine. After the second sympathetic blockage, the patient's symptoms regressed, and outpatient follow-up continues.

DISCUSSION

CRPS is a rare form of neuropathy that is more frequent in patients with FMF. Common autoinflammatory pathways play a role in FMF and CRPS (3). CRPS is a complex and multifactorial condition that has not been fully understood yet. Although there are multiple treatment options, none of them is curative (6). In this case report, we presented an 11 years old female patient, who also has FMF, and who did not benefit from conventional drugs. Each drug caused a partial decrease in pain intensity. Opiates and antidepressants were also given to the patient. Because of this, the lumbar sympathetic nerve blockade was performed more than 1 time. This patient was treated with a multidisciplinary approach, including pediatric rheumatology, algology, physical therapy and rehabilitation, orthopedics, and child psychiatry departments.

Invasive procedures may be required in CRPS cases unresponsive to conventional treatments. The sympathetic blockade is performed in different invasive ways to relieve pain. Recently, cases of pediatric CRPS with different treatment modalities have been reported. Zyluk et al. (7) reported successful tre-

atment with epidural anesthesia in two pediatric patients. Wössner et al. (8) reported successful treatment of complex pain syndrome after foot amputation with pregabalin in a 4-year-old patient.

Epidermal Growth Factor Receptor Inhibitors (EGFR-I) have been used in the treatment of various cancers for many years. Some studies have shown chronic single infusion of the EGFR-I cetuximab and placebo in crossover design, followed by a single open-label cetuximab infusion. Pain is associated with EGFR mutations and EGFR-I also reduce neuropathic pain. A trial was done to assess the effectiveness of EGFR-I cetuximab with 14 patients, who either have chronic neuropathic pain and CRPS. Patients were given either a single infusion of cetuximab or placebo and a single open label cetuximab infusion. 36% of patients who received cetuximab and 14% of patients who received placebo had reported more than 50% reduction in pain. Although this result is not statistically meaningful, cetuximab decreased pain, and further research might result in new treatment options (9).

A Scoping Review study conducted by Zernikow et al. (10) evaluated 173 pediatric patients, 83% of whom were girls. In this study, it was emphasized that placebo-controlled studies on invasive treatment were incomplete, the differences between children and adults were not adequately investigated, the effectiveness of invasive treatment was uncertain, and the data for the decision on invasive treatment type were insufficient.

The association between FMF and CRPS was first reported by Bodur et al. (11) Many causes trigger CRPS, including arthritis, chronic diseases, and emotional stress. Although our patient had a pathology triggered by trauma, we think that the severity of the symptoms increased due to the association with FMF.

CONCLUSION

CRPS can be resistant to a variety of drugs and interventions and is a challenging condition that needs careful multidisciplinary management. In CRPS, invasive interventions seem to be an effective option for better pain control in cases that do not respond to conventional treatment or to avoid the long-term use of glucocorticoids. Comorbid diseases such as FMF can affect the severity of pain. It is important to distinguish between psychological disorders and somatization disorders in pediatric patients. Comprehensive studies are needed on the diagnosis and treatment approach in the pediatric age group. It should be taken into account that psychological factors can be exaggerated. A multidisciplinary approach, including physical therapy, algology, psychiatry, and rheumatology units, is important.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

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