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TREATMENT OPTIONS IN COMPLEX REGIONAL PAIN SYNDROME IN ADULTS AND CHILDREN – REVIEW

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Abstract

Complex regional pain syndrome is a complex disease characterized by neuropathic pain out of proportion to the injury, followed by neurological malfunctions or circulation issues, swelling, sweating or trophic changes. The disease in most cases is affecting limbs, and is often connected with fractures, injuries or traumas. Exact pathomechanisms underlying CRPS are not fully understood. Diagnosis is made based on physical examination, patient's history, neurological examination and laboratory tests. Among radiological scans that are used in the diagnostic process one can find radiography, magnetic resonance imaging, dual-energy X-ray absorptiometry or scintigraphy. The gold standard in making a diagnosis of CRPS are Budapest clinical criteria. Management methods in CRPS include physiotherapy, pharmacotherapy, psychotherapy, physical therapy and invasive methods. The main goal is to relieve pain and to improve the functioning and the quality of life of the patient.

Key words: complex regional pain syndrome, CRPS, neurology, orthopaedics

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Introduction

Complex regional pain syndrome (CRPS), previously known as "reflex sympathetic dystrophy", "causalgia", "algoneurodystrophy", or "Sudeck atrophy", is a condition characterized by persistent and intense pain disproportionate to the injury, that is often impacting the limbs [1]–[3]. It is frequently linked to issues with the autonomic nervous system and small fibre polyneuropathy. Trauma, injury, surgery or illness is typically the underlying cause of CRPS, and the disease usually develops six weeks after such events [1], [2]. Most frequently the disease occurs after minor injury, such as extremity fractures, joint sprain or carpal tunnel syndrome [3], [4].

CRPS is most frequently connected with painful sensations that can last for an extended period of time, and their intensity exceeds the magnitude of the initial injury [2]. It is a rare disease with estimated incidence in adults varying from 5.5 to 26.2 per 100,000 patients [1], [2], [5]. A Canadian study done by Baerg et al. revealed the incidence of CRPS in children of 1.14 per 100,000 patients [6]. CRPS was the most common among children of 12 years and older [6]. Fractures are responsible for up to 40% of CRPS cases [2]. The disease tends to occur two to four times more often in women than men [2], [3]. In paediatrics, the typical patient is a early adolescent female with the lower limb affected, but in literature one may find cases of CRPS in the upper extremities [7]–[9]. Paediatric patients tend to present reduced absorption of bone which is revealed in scintigraphy [10]. Generally it is believed that children and adolescents present more favourable results [10], [11]. On the other hand, a study conducted by Wong et al. revealed that a small percentage of individuals who had CRPS during childhood show no symptoms or signs of the condition in adulthood and their quality of life tends to be lower compared to a typical sample from the general population [9]. This was also confirmed in the study performed by Tan and co-workers [12]. The work by Sherry and colleagues revealed that differences between children with prior trauma and those without it are slight and minimal, when it comes to CRPS diagnosis [10]. Researchers found out that in childhood a CRPS traumatic event as an initiating factor is less significant [13].

Table 1 outlines the symptoms associated with this syndrome [1], [2].

Tab. 1. Symptoms of CRPS

Symptoms of Complex regional pain syndrome
Pain out of proportion to the injury
Oedema
Change of skin colour
Hypersensitivity to touch
Burning or tingling sensations
Changed skin temperature
Problems with blood circulation
Trophic changes – hypergrowth of hair ornails
Increased sweating

Symptoms of CRPS seem not to be specific, what leads to the fact that this disorder is considered as diagnosis of exclusion [1]. When the disease progresses to chronic phase, decreased skin temperature, a slowdown of nails and hair growth, limb atrophy and decreased range of motions are noticed [14]. Research conducted by Sobeeh and colleagues revealed that adult patients with CRPS typically suffer from reduced sensitivity to temperature and pressure, along with enhanced sensitivity to pain [5]. In contrast, sensory abnormalities in adolescents and children with CRPS are in most cases less severe [5].

One can distinguish two types of CRPS – type 1 and type 2 [2]. Type one, which accounts for 90% of CRPS cases, can be described as reflex sympathetic dystrophy, while type two as causalgia. Type one is characterized by an injury with no nerve involvement. On the contrary, type 2 is diagnosed when there is a nerve injury confirmed in neurophysiological tests [2], [15]. In children, the incidence of type 1 CRPS is 95% [7]. There is a subtype of CRPS, described as CRPS-NOS – not otherwise specified, which is diagnosed less commonly [4], [14]. This subtype is diagnosed in patients who do not meet the diagnostic criteria for CRPS, or when they do not have any other condition or illness that could explain their symptoms [4], [14].

The pathophysiology of complex regional pain syndrome has not been fully discovered yet, but it is believed that the cause is multidimensional [2]. It is probably connected with central and peripheral nervous system disfunction [3]. Among potential reasons one may list inflammatory cascade, direct injury of nerve fibres, sympathetic nervous system malfunction, prolonged immobilization, disrupted pain processing, emotional responses or autoimmune reactions [2], [15]. Genetic factors may play a role in the development of the condition, but as of now, no strong associations have been conclusively confirmed [2].

There are several risk factors that are vital to take under consideration when suspecting CRPS in patients. It is crucial as early detection plays a role as an important prognostic factor. Risk factors are listed in table 2 [3], [4], [15].

Tab. 2. Risk factors of complex regional pain syndrome

Risk factors of CRPS
Psychiatric history of patient
Psychological factors
Type of surgery performed
Female gender
Fracture
Drug abuse

On the other hand, there are some conditions linked with lower rates of CRPS – including diabetes, obesity, anaemia and hypothyroidism [3].

Material and methods

To conduct this review, we searched the PubMed and Google Scholar databases for articles related to complex regional pain syndrome in adult and paediatric populations. We used key words such as 'complex regional pain syndrome', 'CRPS', 'complex regional pain syndrome' paediatrics' and 'CRPS paediatrics'. Our focus was on articles published between 2017 and 2023, including their references. We assessed the papers by titles, abstracts and full texts. Articles were included to the review if they were raising the problem of management of CRPS in adults and children. Other papers were excluded from our review.

Diagnostic methods

CRPS is a set of symptoms characterized by sensory, motor, vascular and autonomic dysfunction based on multiple mechanisms [14], [16]. The clinical diagnosis of CRPS is made in light of a thorough physical examination, history, and neurological evaluation. Allodynia and signs of autonomic dysfunction may be present on neurological examination. The International Association for the Study of Pain (ISAP) in 1994 proposed diagnostic criteria for CRPS types I and II, but these criteria are not specific, leading to overdiagnosis [17]. The Budapest criteria developed by the International Association for the Study of Pain can be helpful in making the diagnosis of CRPS, in addition to other laboratory and imaging tests. Their sensitivity was 99% and specificity was 68% for CRPS [2].

The CRPS Syndrome Severity Score (CSS) is used to assess the severity of CRPS. The updated version created in 2017 consists of 8 signs and 8 symptoms [14].

Currently, there is no objective test to confirm the diagnosis and monitor the course of the disease. However, it is important to remember that radiological imaging and blood tests are used to exclude other diagnoses, including orthopaedic, neurological and rheumatological disorders. [4]. The basic laboratory tests that should be performed in patients with suspected CRPS-I are a complete blood count, CRP, erythrocyte sedimentation rate (ESR), creatinine kinase and antinuclear antibody (ANA). Usually, laboratory test results will remain normal [17].

Bone demineralization is often described in CRPS-I, but it must be remembered that it is common in parts immobilized after trauma. Evidence of bone demineralization is imaged by radiography or magnetic resonance imaging (MRI). In children with CRPS-I the values of serum markers of bone formation and bone resorption were normal. Many dual-energy X-ray absorptiometry (DXA) studies have shown decreased bone mineral density after immobilization. The DXA method only allows two-dimensional measurements and does not separate trabecular bone from cortical bone [4]. Scintigraphy has been used for many years and has proven to be useful in the early diagnosis of children with CRPS-I. Abnormal uptake can be visualized and usually manifests as cold spots. The described three stages of disease progression in adults were also documented in a 12-year-old boy [18]. Blood flow at the time of diagnosis

of CRPS-I is reduced compared to the unaffected side during phases 1 (1 minute) and 2 (another 4 minutes). Two hours after radionuclide injection, in phase 3, the uptake is low. Several months later, differences can still be detected, manifesting as livedo reticularis sign and cold extremities. Even more accurate measurements of bone morphology parameters are possible using computed tomography (CT). High-resolution peripheral quantitative computed tomography (HR-pQCT) compared to the DXA method allows separate measurements of trabecular and cortical bone density and trabecular bone volume. Using this method, the thickness of trabecular and cortical bone can be determined. This is a promising method in imaging and monitoring the course of CRPS-I [4]. A change in the nerve types in affected limbs has also been shown during peripheral nerve biopsy, in which the density of C-type and Aδ-type neuron fibres was revealed as decreased [19]. Damage of the peripheral nerves during the course of CPRS was confirmed in the study conducted by Oaklander and co-workers. The damage tends to be minimal [19]. In a study by Parkitny, et al. it has not been confirmed that an increase in systemic cytokines is associated with the subsequent development of CRPS [17]. However, it cannot be ruled out that an excessive inflammatory response does not play a role in the development of CRPS. This study found that psychological and non-immune mechanisms of pain rather than an abnormal immune response play a greater role in the development of CRPS [17]. In their study Shulman et al. confirmed that Pedi-Sense is useful in assessing mechanical allodynia in adolescents with CRPS [20]. This test, also known as The Paediatric Tactile Sensitivity Test of Allodynia, is especially useful in assessing mechanical allodynia in adolescents with CRPS. Pedi-Sense helps rehabilitation physicians assess mechanical allodynia at the patient's bedside and using simple equipment [20]. In a study reported by Mesaroli et al. the Paediatric PainSCAN screening tool was used in CRPS in children [21]. The available literature does not provide precise data on importance of diagnostic criteria in the paediatric population. This topic needs further research in the future.

In 2003, the Budapest clinical criteria for the diagnosis of CRPS were established by second IASP consensus. These criteria are regarded as the gold standard in CRPS diagnosis, with the current version demonstrating increased accuracy, sensitivity, and specificity, as the previous version had a tendency to overdiagnosis due to its low specificity [19], [22]. The criteria are presented in table 3 [19], [22].

Tab. 3. Budapest clinical criteria for the diagnose of CRPS.

1.	Continuing pain, which is disproportionate to any inciting event.	
2.	Must report at least one symptom in three of the four following categories:	
	Sensory	reports of hyperesthesia and/or allodynia
	Vasomotor	reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
	Sudomotor/oedema	reports of oedema and/or sweating changes and/or sweating asymmetry
	Motor/trophic	reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
3.	Must display at least one sign at time of evaluation in two or more of the following categories:	
	Sensory	evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement).
	Vasomotor	evidence of temperature asymmetry and/or skin colour changes
	Sudomotor /oedema	evidence of oedema and/or sweating changes and/or sweating asymmetry.
	Motor/trophic	evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
4.	There is no other diagnosis that better explains the signs and symptoms.	

Management

Treatment methods for CRPS can be divided into active and passive. The first group includes physiotherapy and psychotherapy (often cognitive-behavioural therapy (CBT)). Passive methods include pharmacotherapy (PhT), physical therapy (PT) and invasive procedures [2], [23]–[27]. The mentioned therapeutic elements can be combined. Their goal is to alleviate pain, improve physical functioning and psychological well-being, and improve the patient's quality of life [23], [26]. The improvement of sensory perception, strength, motor skills and body perception are achieved through physiotherapy and occupational therapy techniques. Meanwhile, a gradual reduction of anxiety is supported by psychological interventions. Intervention treatments should be used in special cases [26]. Early and aggressive therapy can prevent the development of chronic pain in patients with CRPS. The use of bisphosphonates and a short course of oral corticosteroids at this time can significantly improve pain sensation in CRPS patients, according to data [2].

Reducing pain and increasing function in people with CRPS-I may be accomplished through physiotherapy modalities such as mirror therapy, transcutaneous electrical nerve stimulation (TENS), and multimodal physiotherapy. However, the evidence for this is uncertain [27]. The goal of physiotherapy is to restore normal limb function, including joint mobility [4].

In contrast, TENS and acupuncture reduce swelling and relieve pain. Another anti-oedema method is manual lymphatic drainage [4], [26]. Alleviating allodynia may be possible when physiotherapy is combined with sensory rehabilitation [4]. Occupational therapy (OT) is one of the key components of a multidisciplinary approach to the treatment of CRPS, whose interventions may include sensory re-education, functional use of the affected limbs, psycho-education, patient and family education, among others [28].

Multimodal treatment often includes a psychological form of pain therapy, such as cognitive behavioural therapy. It can also be carried out in groups with other patients. Indications for psychotherapy include cases that are difficult to treat and patients who are under significant stress [26]. An essential element of CRPS treatment is the use of physiotherapy methods with elements of CBT. The goal of such treatment is to normalize sensory-motor integration. For this purpose, gradual exposure to force and movement, visual-tactile stimulation and discrimination are used [26]. The combination of PT and CBT can lead to a reduction in pain symptoms and increase patients' functionality [24], [29]. Lee et al. conducted a prospective, randomized, single-blind study that included 28 CRPS patients aged 8–17. They were divided into two groups—A (PT once a week for 6 weeks) and B (PT three times a week for 6 weeks). Both groups participated in 6 sessions of CBT. Both groups experienced improvements in pain perception and physical function at short- and long-term follow-up, with no significant differences [29].

Pharmacotherapy relies on off-label drugs, but evidence of their effectiveness is limited. Among the drugs used to treat CRPS are bisphosphonates, glucocorticoids, gabapentinoids, tri/tetracyclic antidepressants, ketamine, botulinum toxin type A and N-acetylcysteine [2], [4], [26]. Prednisone, methylprednisone and prednisolone significantly reduce pain in patients with CRPS. In studies, they found that prednisone use was associated with an improved range of motion and function. It is suggested that the maximum benefit from glucocorticoid treatment occurs within six months of the onset of the disease. There are indications that intra-articular injections of glucocorticoids may alleviate pain in the affected limb [14]. Iloprost administered 6 hours a day for 3 days has a pain reducing effect. However, there are side effects including headache, flushing, vomiting, and lowering of systolic blood pressure within the first 30 minutes of administration [24]. Relapses can occur during iloprost use. There is evidence that non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are not effective in reducing pain in patients with CRPS [30]. Studies on the use of gabapentinoids for pain in CRPS are thought to be insufficient. However, several randomized trials have found that the use of gabapentin results in a reduction in pain. There are known cases in which the use of pregabalin has benefited patients with short term illnesses who are under psychiatric care [31]. The study by Brown et al. involved 34 patients aged 7–18 who were diagnosed with CRPS-I or neuropathic pain. Each was assigned treatment with amitriptyline or gabapentin. After 6 weeks of follow-up, there was a reduction in pain, an improvement in sleep quality in both groups – the differences between the groups were not statistically significant [32]. In the early stages of CRPS, corticosteroids, bisphosphonates or ketamine, among others, can be used [33]. Ketamine reduces pain for a short period of time with no improvement in function [30].

Among the invasive procedures used to treat CRPS are dorsal root ganglion stimulation (DRGS), intrathecal baclofen (ITB), intravenous regional blocks (IVRB), regional sympathetic nerve blocks, spinal cord stimulation (SCS), surgical and pharmacological sympathectomy, epidural drug infusion, continuous epidural anaesthesia, trigger point injections (TPI) and amputation.

DRGS may be a promising treatment for CRPS, with an efficacy comparable to spinal cord stimulation (SCS). It leads to a reduction in pain [23], [34]. The ACCURATE trial achieved ≥50% pain relief and DRGS success in 81.2% of patients after 3 months [35]. The analysis by Huygen et al. (2020) included 217 patients, 63% of whom had ≥50% pain relief. The most common complications reported were pain at the treatment site (10.2%), electrode fracture (5.9%), electrode migration (5.9%), and infection (5.1%). However, it can be concluded that DRGS is a safe method [36].

Another method is ITB, which can result in pain reduction in patients with CRPS. The continuous administration of ITB with a pump is reported to reduce dystonia, but it is associated with a high risk of complications, including nausea and vomiting, as well as headaches. It is therefore necessary to monitor patients for possible complications [23], [26].

IVRB is also practiced, which involves injecting a local anaesthetic into a limb where a tourniquet was previously placed. This allows the anaesthetic to diffuse into the surrounding tissues, which will ensure that the sensation of pain is reduced. This procedure is well tolerated by patients [23].

Regional sympathetic nerve blocks, on the other hand, involve the injection of a local anaesthetic under the guidance of an imaging study, such as ultrasound. The goal of this procedure is to block sympathetic ganglion activity – lumbar ganglia for CRPS of the lower limb, and stellate ganglion for the upper limb [23]. A study conducted by Yoo et al. on a group of 48 patients showed that regional blockade of the lumbar sympathetic ganglion with botulinum toxin type A leads to decreased pain, but increased the temperature of the affected foot for 3 months [37]. The use of botulinum toxin type A is associated with decreased allodynia and increased time of reduced pain sensation after each subsequent injection of the product [14].

Another method is SCS, which involves implanting a device under the skin that delivers electrical impulses to the spinal cord. This occurs when pain signals are interrupted before they reach the brain. This results in reduced pain, improved function and reduced medication. SCS is used when other methods have failed to reduce pain and the degree of dysfunction in patients with CRPS [23], [38], [39]. The use of therapy that combines physiotherapy with SCS has been shown to provide greater pain

relief than physiotherapy on its own [40]. The evidence suggests that DRGS presents fewer adverse effects and is more durable than SCS [26].

The next therapeutic option is a surgical sympathectomy, which is rarely performed compared to other invasive methods. The efficacy of both pharmacological and surgical sympathectomy has been demonstrated to be comparable. Regrettably, there is a dearth of studies on both methods, thus their implementation in practice should be accompanied by caution [23].

Epidural infusion of opiates, 2-adrenergic receptor agonists, and local anaesthetics can reduce pain in patients with CRPS, but it is associated with side effects, such as hypotension and sedation. The occurrence of complications during the repetition of these procedures, such as bleeding, infection, and neural injury, is uncommon when performed by an experienced specialist [23]. A study using clonidine found a reduction in pain sensation and a degree of sedation that was dose-dependent [41].

Donaldo et al. conducted a retrospective study involving a review of the medical records of 102 patients treated between 2003 and 2014 with continuous epidurals or peripheral perineal infusions of local anaesthetics. Subsequently, patients were also treated for rehabilitation. Information on pain and functional scores was collected from the first appointment and follow-up visits (4 months before and after hospital admission) and each day during hospitalization. During hospitalization and follow--up, improvements were observed. A total of 70% of patients benefited, which was 56% reduced pain and 40% increased functionality [25].

A trigger point is defined as a tense band or knot of muscle that causes pain and tenderness. TPI involves cannulating the tense tissue with a needle and injecting a small amount of local anaesthetic or botulinum toxin. The upper limbs, trapezius and supraspinatus muscles are treated with this method. There may be minor muscle pain after the procedure; however, patients should remain active to reduce the risk of recurrence at the same trigger point [23].

If all therapeutic approaches fail in patients with severe CRPS and poor quality of life, amputation may be considered, as shown in a study by Domerchie et al. [14], [42].

There are not enough studies to clearly determine the order of treatment for the paediatric population, but the described therapeutic approaches for CRPS may be considered.

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