Narrative Review

Noninvasive Treatments for Pediatric Complex Regional Pain Syndrome: A Focused Review

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This is a review of current literature of noninvasive treatments for pediatric complex regional pain syndrome (CRPS). There are a variety of noninvasive approaches to the treatment of pain, but few pediatric-focused studies have been published in regard to CRPS. In comparison with adult CRPS, there is a greater need for behavioral approaches in children to enable coping with difficult symptoms. Current gaps in knowledge include mechanisms triggering CRPS, pediatric-focused diagnostic criteria, validated tests that are diagnostically specific, definitive treatment protocols, age-based medication recommendations, and validation of specific noninvasive treatments in pediatric populations. Intensive multidisciplinary treatment is supported by high recovery rates and a family-centered approach that allows continuation of goals into the community environment.

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INTRODUCTION

The purpose of this article is to review evidence for noninvasive treatments for pediatric complex regional pain syndrome (CRPS). In general, much of the treatment for pediatric CRPS has historically been extrapolated from the adult literature. Pediatric CRPS can often be treated using noninvasive methods [1]. CRPS can be separated into 2 categories: type I and type II [2]. Type I typically arises from a minor injury (sprain/fracture), and type II indicates the likelihood of a specific nerve injury causing the symptoms [2].

Pediatric CRPS type I develops more commonly in girls of white ethnicity, with the incidence rising around puberty [1,3]. This condition often arises after minor trauma and is more common in the lower extremities (versus upper extremity in adults) [1,3]. CRPS type II has been reported to occur in equal numbers in boys and girls [1]. Before diagnosis and treatment, some patients may undergo immobilization, which has been noted to increase pain levels [4]. CRPS may result in nearly immediate disability, and swift therapy referral is indicated [5]. In comparison to adults, triple-phase bone scan is a less reliable diagnostic method [1,6].

The focus of this article is to review the evidence for the type of treatment provided in our program, along with some emerging treatments that may contribute to the treatment of pediatric CRPS.

LITERATURE SELECTION

A literature search identified studies relevant to noninvasive treatments for CRPS in children. Databases used included PubMed (National Center for Biotechnology Information via PubMed.gov), CINAHL (Cumulative Index of Nursing and Allied Health Literature via EBSCOHost), and PsycINFO (American Psychological Association via Ovid). Because of the small volume of literature on the pediatric population, database-specific controlled vocabulary (subject headings or index terms) were not used, and keyword searching produced a comprehensive and manageable yield. The following search strategy was used:

((complex regional pain syndrome) OR (reflex dystrophy AND (sympathetic OR neurovascular)) OR (amplified OR complex OR chronic) AND (neuralgia OR pain) AND...
musculoskeletal) AND (Rehabilitat* OR (physical OR occupational OR recreation* OR mirror OR alternative OR complementary OR integrative) AND (therapy OR therapies OR therapeutic)) OR (transcranial AND magnetic AND stimulation) OR (graded AND motor AND imagery) OR (physiotherapy OR acupuncture OR psychotherapy) AND (child* OR adolescent* OR pediatric*). Initial search results were limited to English-language articles. The results were then narrowed to exclude those that focused solely on other diagnoses, such as unspecified musculoskeletal pain or fibromyalgia. Search results were also narrowed to avoid invasive treatments. Case reports and case series were excluded unless the literature on a given treatment was extremely limited. The references in the selected articles were used to identify additional relevant sources. In addition, the authors identified a limited number of articles or chapters from personal readings.

**REVIEW OF EVIDENCE**

**Diagnostics**

The diagnosis of CRPS can be challenging, but reliability can be improved by use of diagnostic criteria such as the Budapest criteria (most recent International Association for the Study of Pain [IASP] criteria) (Figure 1) to ensure correct diagnosis [7]. CRPS is characterized by a continuing regional pain that is disproportionate to the usual course of any known trauma or other lesion [7]. Pain is regional; it includes predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings; and it shows variable progression over time [7]. Diagnostic workup may include studies to rule out other etiologies as causes of symptoms or to confirm the suspected diagnosis, and can include electromyography/nerve conduction studies, radiography, magnetic resonance imaging, bone scintigraphy with technetium 99m, and/or a sympathetic nerve block [2]. Emerging diagnostic studies include quantitative sensory testing, thermography, laser Doppler flowmetry, and sudomotor function tests [2,8]. A review of diagnostic studies can be helpful in ruling out other causative factors for the presenting symptoms.

It must be mentioned that the Budapest convention did not address pediatric CRPS. Our search did not locate consensus-based pediatric diagnostic criteria for CRPS such as those published for adult CRPS. Prior publications have discussed the discrepancy in pediatric versus adult CRPS symptoms [3,6,9,10] (Table 1). Patients have frequently seen multiple providers before formal diagnosis. Review of prior diagnostics is important, as noted by Kachko et al., who reported 5 patients with alternative diagnoses among 19 patients referred for CRPS (these included erythromelalgia, ankle sprain, angionatosis of the lower extremity with osteoporosis due to disuse, and conversion reaction) [11]. Overall, the diagnosis of CRPS is a clinical diagnosis [2].

**Medical Management**

Medication management varies among providers and may include medications such as bisphosphonates, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, anticonvulsants, opioids, topical anesthetics, free radical scavengers (dimethylsulphoxide and N-acetylcysteine), N-methyl-D-aspartate (NMDA) antagonists (ketamine, memantine, magnesium sulphate), baclofen, benzodiazepines, corticosteroids, vitamin C, calcium channel blockers, and intranasal calcitonin [2,12]. There are no known large, prospective, randomized clinical trials of medications for pediatric CRPS. Patients have different tolerances and focus to their symptoms, and this can guide the necessity for medications or

**Figure 1. Budapest clinical diagnostic criteria for complex regional pain syndrome (CRPS).** This figure has been reproduced with permission from the International Association for the Study of Pain (IASP). The figure may not be reproduced for any other purpose without permission.
other treatments. Unfortunately, in many medications, use may result in side effects, and safety of medications for specific age-groups has not been studied in this population of patients. To allow tolerance to therapy, medical management may also be required to treat symptoms such as autonomic dysfunction, headaches, sleep cycle disruption, psychological dysfunction, osteopenia, orthopedic changes, spasms/dystonia/movement disorders, and edema. Unanswered questions in the pediatric CRPS patient population include the long-term effects of medication use on the central nervous system and also effects on CRPS recurrence.

Despite the lack of large pediatric-focused studies regarding medication management in pediatric CRPS, there may be indications for the use of vitamin C, anticonvulsants, and topical ketamine. In regard to the adult literature, vitamin C has been noted to decrease the risk of CRPS after fracture [13]. Vitamin C could be considered for children with CRPS who have a fracture, soft tissue injury, or surgical intervention (such as wisdom tooth extraction). Topical ketamine has been beneficial in reduction of allodynia in adult populations but has not been studied in pediatric populations [14-16]. In the pediatric literature, Wilder et al noted benefit with treatment of tricyclic antidepressants included with other treatments (multidisciplinary therapies, and another subset required sympathetic blocks) [17]. Benefit has also been noted in 2 pediatric case reports of management using gabapentin, but is also supported in the adult literature [2,18,19]. Low et al found that a large number of children (70%) required adjunct pain medications (amitriptyline or gabapentin) to enable participation in physical therapy [1]. There is conflicting evidence in regard to the benefit of steroids, and perhaps appropriate clinical indicators for use of steroids have not been elucidated [17]. Low-dose naltrexone has not thus far been heavily studied in CRPS populations, but may also prove to be beneficial, especially in dysyonic symptoms [20]. Authors such as Sherry et al have also advocated the use of no medications and yet have had excellent recovery outcomes [10]. Medications cannot be viewed as curative, but can be initiated for symptom reduction and to allow participation in therapies [1,17]. At this time, numerous approaches exist regarding medication management of pediatric CRPS and may vary significantly, depending on the training background of the physician.

Acupuncture is a treatment with origins in China that uses needles to stimulate the nerves in the skin and muscles at anatomic points known commonly as acupuncture points [21]. Other styles of non–needle-based approaches may include use of acupressure, heat (moxibustion), magnetic therapy, laser, cupping, Shonishin, or electrical stimulation [22]. Acupuncture can be viewed as noninvasive with a low risk of side effects, but use of non–needle-based approaches can further reduce risk [22-23]. The reviewers place acupuncture in a noninvasive category, especially with less relative risk in comparison to many oral medications; however, needle-based treatments are not without risk [23]. Published guidelines exist from the World Health Organization on currently approved uses [26]. Large high-quality studies have demonstrated benefit in regard to chronic pain, but no large studies have been located for acupuncture in adult or pediatric CRPS [24]. Case reports exist showing the possible benefit of specific types of acupuncture treatment, such as Chinese scalp acupuncture or combinations of auricular and body point therapy [27,28]. A retrospective case series of 47 pediatric patients with chronic severe pain who underwent acupuncture reported that many patients found it to be pleasant (67%) and the treatment to be beneficial for their pain symptoms (79%) [29]. Zeltzer et al also found evidence for utility in chronic pediatric pain including CRPS, and suggested larger studies to explore this treatment modality [30]. Two studies reviewing the safety of pediatric acupuncture noted overall safety when performed by appropriately trained practitioners, with a 1.55 adverse event risk occurring in 100 treatments [25,31]. Korpan et al studied placebo and treatment groups using traditional Chinese acupuncture; however, the study was of 14 patients and thus of small study size, making comparison difficult [32]. There are more recent indications using electro-acupuncture, auricular acupuncture, scalp acupuncture, and other techniques that would purport to enhance the treatment effect of acupuncture in general. The wide availability of this treatment, the ability to titrate treatments to various symptoms and tolerance, and the diverse styles of treatments available makes acupuncture worth further research to establish its usefulness in CRPS.

Interventional analgesic therapy has historically included sympathetic blocks, intravenous regional anesthetic blockade, epidural and intravenous infusions, intrathecal medications, and implantable stimulators [2,12]. Sympathetic nerve blocks can offer pain relief so that patients are able to engage in therapies more effectively [2]. Sympathetic blocks are typically most effective in cold-limb CRPS. Tunneled epidural catheters can offer direct reduction of pain symptoms with titratable pain control [2]. CRPS patients do not present as a homogenous population, and there may be indications for these treatments that are out of the scope of this review. We have mentioned these treatments because some of these techniques are present in multidisciplinary pediatric pain rehabilitation programs after failing interventional approaches.

Physical, Occupational, and Recreational Therapies

Therapy treatment for CRPS may include physical therapy (PT), occupational therapy (OT), and recreational therapy (RT) [33,34]. Limited articles of strictly therapy interventions for CRPS exist, especially in the pediatric setting. Westdocks et al evaluated the utility of various therapy approaches, in a retrospective chart review, in 24 pediatric patients (mean age 13 years) with an average time to diagnosis of 9 months [35]. The investigators noted benefit to
components including progressive pressure and tactile desensitization, hot/cold packs, graduated weight bearing, and aquatic walking exercises [35]. Adult studies such as Oerlemans et al compared PT and OT interventions for upper extremity CRPS, finding usefulness and cost-benefit of both therapies in comparison to treatment in control group, which was social work (SW) interventions [36]. In this study, however, patients did receive medical treatment, using free radical scavengers. The authors also noted improvement in all 3 categories (PT, OT, and SW), which they attributed partially to education. They found the cost-benefit ratio in PT greater than in OT interventions but both stronger than SW. OT had a more favorable effect on disability in this patient population. They also proposed that treatment in a multidisciplinary setting might reduce the amount of new specialist consultations or additional treatments that significantly contributed to cost of treatment [36].

Initially, outpatient therapy should be tried, with intensive inpatient or day hospital treatment program being indicated if outpatient therapies fail to improve function [34,37]. There are many factors leading to greater treatment in an inpatient basis in pediatric CRPS populations, including high functional disability in portion secondary to predominant pediatric lower extremity involvement in comparison to that in adults. Other factors may include disruption of psychological functioning, dysfunctional family dynamics, and high levels of pain-related disability [34,38-40].

Functional rehabilitation promotes individual achievement of maximal functional independence, independence in activities of daily living, and return to desired activities. Thus, in pediatric CRPS, “functional rehabilitation” is defined as recovery of impairments affecting the home, school, and community settings [5,10,41]. In CRPS, it is based on a progression from gentle active range of motion to weight bearing [10,41]. Patients may initially require use of assistive devices, but use should be minimized, as it can lead to avoidance behaviors [42]. Strengthening and mobilization are important to prevent further weakness and debility, as well as osteopenia [5,36]. Altered sensory perception is present in a large portion of patients [43]. Reconditioning has been theorized in chronic pain states to improve endorphin relief as well as to engage in central nervous system remodeling necessary for recovery [10].

Functional use of the affected extremity, active range of motion, edema, coordination, sensory components, activities of daily living, and school participation are evaluated by OT [5]. Targeted sensory re-education reduces allodynia and edema, and improves range of motion, body mechanics, and ergonomics [36,37].

Increasing functional use of the affected extremity while improving weight bearing, active range of motion, and strength is a focus of PT. Casting/functional splinting may improve positioning during rehabilitation interventions and promote increased circulation. Individualized home exercise programs can be modified throughout recovery, promoting autonomy [37]. Techniques such as graded motor imagery and myofascial release may facilitate reaching functional goals [5,44]. Modalities such as transcutaneous electrical nerve stimulation (TENS), contrast baths, fluidotherapy, and elastic therapeutic tape (e.g., Kinesio Tape) may also be used to assist with symptom management [33,36,45]. Elastic therapeutic taping is used by many therapists, but no focused studies were located for use in this population.

Aquatic therapy is beneficial because of buoyancy and sensory properties provided while promoting weight bearing in a reduced-gravity environment, and can be a component of RT [5,46]. The mild compressive force of the water may assist in edema management as well [5]. RT encourages use of the affected extremity by providing opportunities for children to engage in preferred leisure activities [5]. Patients may be more inclined to incorporate their affected extremity if they are participating in a desired therapy [5]. Therapy appears to be universally indicated; however, the intensity and focus varies among the studies reviewed. Overall, there is consensus support for education, desensitization, introduction of weight bearing, and functional use of the affected extremity.

**Psychological Interventions**

Psychosocial treatments are an important component of a treatment plan for CRPS. The primary goals of psychosocial treatments are to enhance pain management skills and to restore normal activity. Behavioral and cognitive-behavioral interventions (e.g., contingency management for parents, progressive muscle relaxation, diaphragmatic breathing, cognitive coping) can be particularly helpful in influencing pain perceptions and behaviors, altering environmental and behavioral triggers, and reducing the severity and frequency of pain. Psychosocial approaches can also be valuable for facilitating understanding and acceptance of pain, supporting patients as they participate in their rehabilitation therapies, and improving emotional adjustment and familial functioning. If serious mental health issues (e.g., severe depression, suicidal ideation or plan) are present, referral for psychiatric care is indicated. Studies that have examined psychosocial treatments as part of a comprehensive treatment for CRPS have supported their effectiveness. Numerous positive outcomes have been reported, including improvements in pain intensity, physical functioning, school attendance, anxiety, parental anxiety, depression, illness, and decreased medication use [10,33,40,47,49].

Sherry and Weissman reported psychological overlay and its impact on pediatric chronic pain symptoms; they also noted effects on family function, school participation, and higher somatic overlay in comparison to other diagnoses, including arthritis or back pain [38]. CRPS versus non-CRPS limb pain patients show increased somatization and phobic anxiety [49]. Comparisons of back pain, local neuropathy, and CRPS found that no childhood trauma predisposed to any particular diagnosis, and also noted no contributions of a “nonorganic” (conversion syndrome) etiology for the
patient's symptoms [30]. The 3 categories were psychologically similar, but CRPS patients experienced a higher level of disability in comparison to patients with back pain and local neuropathy [30]. Higher risk has been noted for somatic symptoms and emotional distress in CRPS, especially anxiety [39]. Furthermore, there is preliminary evidence for deficits in attention and working memory, which bears further investigation [39]. Patients with chronic CRPS type I symptoms are noted to have perceived harmfulness of activities, which worsens functional limitations [51]. Conflicting results are noted in psychological history as a predisposition for CRPS, but anxious personalities may contribute to development of CRPS without establishing causality [52-55]. CRPS patients require psychological support and family support to ensure success with community re-entry and the challenges related to school and family participation [56].

Multidisciplinary Management

Combined therapy approaches, including OT, PT and RT, are essential in the treatment of CRPS [5,37]. The ability to administer different levels of therapies may affect treatment intensity, length, and type of treatment, whether it be inpatient, outpatient, day hospital, or home exercise-based therapies. The largest/pediatric studies have included Sherry et al (n = 103) and Wilder et al (n = 70) [10,57]. Sherry et al had a better reported rate of recovery with a lower rate of recurrence than Wilder, who used other treatments including TENS, psychotherapy, sympathetic blocks, and antidepressants [10,17]. Combinations and intensities of desensitization, exercise, weight bearing, electrical stimulation, aquatic, home exercise program, TENS, sensory stimulation, and massage have been used [1,4,10,17,33,37,46].

Treatment in the inpatient setting may be required based on functional mobility status, may help to interrupt the pain and disability cycle, and has been proposed to shorten recovery time in comparison to outpatient treatment [4,46]. Brooke et al reviewed charts and a follow-up telephone survey of 32 children admitted for inpatient multidisciplinary treatment of their CRPS, and found that 95% of patients had restoration of physical function. Of these patients, 34% had resolution of symptom by discharge, and 89% had resolution of symptoms at the time of follow-up [34]. Key points noted in this study include weaning of CRPS-specific medications, and noninvasive treatments were described; however, patients were allowed as-needed acetaminophen or ibuprofen for headache or soreness [34]. The study was small and lacked a control group; the patient population was representative of the complex patient population, with the majority of patients falling 1 or more treatment regimens before admission [34]. Length of follow-up telephone calls ranged from 6 to 43 months, supporting prolonged success of treatment in regard to lower pain levels and continued higher physical functioning, although not all patients participated in the telephone follow-up [34]. The greatest reduction in pain levels was seen in the 2 months after admission, and no major differences were noted in the recurrence rate (37%) compared to those in other studies; but skills learned from treatment purportedly prevented further medical interventions secondary to these recurrences [34]. Interestingly, patients in this study who were believed to have failed the intensive therapy program were those with atypical pain distribution, which could be proposed as an additional screening tool to judge possible success of proposed intensive treatments [34]. Most importantly, in our opinion, is the evidence that patients failing other approaches can still have positive outcomes with intensive multidisciplinary treatment even if there is a delay in diagnosis [1,10,11,17,34]. The option of day hospital approaches can also be beneficial if inpatient hospitalization is not required [37]. Initial inpatient hospitalization, with stepwise transition to home environment via day hospital, could be beneficial for targeting the variety of factors affecting patient functional level, including pain, sleep, nutrition, social factors, emotional factors, family dynamics, academics, activities of daily living, and mobility [1,4,34,37,46,56].

Emerging Treatments

Graded motor imagery (GMI) is a rehabilitation approach that can be used to treat pain and movement-related problems that are secondary to central nervous system changes caused by CRPS [58]. GMI aims to alter sensory-motor processing in 3 stages, including left—right limb judgment tasks, imagined movements of the affected limb, and mirror therapy; this allows gradual movement without pain production [44]. The goal of this treatment is to successively activate cortical motor areas without triggering protective pain responses [58]. Sequence of the treatments appears to be important to the success of the treatment [59]. GMI has been successfully used in adult CRPS; however, no pediatric studies were found [60]. Improved pain and swelling have been reported using GMI in adult CRPS patients, but there is some conflicting evidence regarding treatment protocols and whether GMI leads to improved functional recovery [44,60,61]. Potentially, GMI could be incorporated into the treatment program for pediatric CRPS at the early phase of therapies, which could lower pain-related fear and promote progress in subsequent mobilization. The conservative nature of GMI, along with the benefit of improved body awareness, would also promote its use. Pediatric-focused studies would clarify the use and application of this treatment.

Studied methods of noninvasive neurostimulation have included repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation [2]. Transcranial magnetic stimulation is a method of brain stimulation using brief magnetic pulses that pass through the scalp and skull to produce a current in underlying cortical tissue, which aims to cause change in areas of the brain including somatosensory,
thalamocortical, limbic, and cognitive areas. This treatment may affect sensory, emotional, and cognitive spheres of the pain experience [62]. The goal is to lead to cortical changes that last past the treatment, leading to decreased states of pain. No pediatric studies have been found to date regarding rTMS treatment of CRPS. Lefaucheur et al observed, in their study, that motor cortex rTMS showed transient relief of drug-resistant neuropathic pain; however, no CRPS patients were included in this study [63]. Benefit has been shown in central pain after spinal cord injury and CRPS type 1 [64,65]. Site and origin of pain affect the success of this treatment [63]. Further research is suggested in pediatric CRPS to establish the usefulness of rTMS and transcranial direct current stimulation.

Scrambler Therapy (ST) is a new noninvasive neuro-modulation approach to the treatment of chronic neuropathic pain [66]. The underlying theoretical perspective does not rely on the Gate Control theory but instead on the theory that the nervous system is a cybernetic system that responds to coded information [67]. In chronic pain, nociceptors have theoretically been damaged and produce erroneous pain codes that can be produced independent of a sensory source (eg, phantom limb pain) [68]. Neuromatrix theory postulates that the pain signals must be reinterpreted by the brain to return to homeostasis and thereby no longer produce chronic pain [69]. ST is thought to interfere with the pain neuromatrix by providing nonpain codes [66]. Initially developed as a treatment for oncological neuropathic pain and chemotherapy-induced peripheral neuropathy, ST has been used successfully on a variety of chronic pain symptoms, but there has not been a focused large-scale study of this method in the pediatric population [66]. Recent investigations of the efficacy of ST have all demonstrated excellent results with various forms of adult neuropathic pain (eg, neuropathy, neuralgia, CRPS, failed back syndrome) [66]. The results of ST with 173 consecutive adult admissions demonstrated significant improvement across multiple diagnostic groups, including CRPS, with improvement maintained for 6 months in 75% of the patients treated [66]. Studies on ST in pediatric CRPS appear to be indicated.

**AUTHORS’ CLINICAL EXPERIENCE**

The pediatric pain rehabilitation program at our facility is a Commission on Accreditation of Rehabilitation Facilities (CARF)-accredited 3-week program in an intensive multidisciplinary setting using medical treatment, PT, OT, RT, psychology, SW, school, and family and patient education targeting improvement in function with a focus on return to school, community, and sports activities [70]. Most patients experience improvements in level of pain; however, the primary focus of the program is improving function and coping skills. In the first 2 weeks of the program, children are admitted to the inpatient rehabilitation unit, where treatment is often delivered apart from their parents. Our view is that the inpatient setting maximizes the potential for successful control of the environment (eg, activity, diet, sleep) and for the interdisciplinary structure to adhere to a common treatment philosophy [4]. In addition, in our experience within the pediatric population, program compliance can be difficult because of limited ability to comprehend all treatment strategies. Inpatient treatment allows 24-hour supervision, with goals of improving compliance and increasing intensity of services. Separation of children and parents serves to interrupt maladaptive interactions that are maintaining or worsening pain behaviors and facilitates acquisition of more healthy behavioral habits. In the final week, children participate as outpatients in a day hospital setting and leave with their parents at the end of each day. They continue the activities of the prior weeks but have more opportunities to apply their new skills. Throughout the program, parents and other family members are provided with structured education on how best to help their children return to normal functioning. An important objective of the final week is planning for a successful re-entry into home, school, and other community settings.

**CONCLUSIONS**

There is evidence that children respond better to noninvasive approaches to pain management [4] (Table 2). There are a small number of intensive pediatric pain rehabilitation programs in the United States, and evidence for this style of treatment is growing [17,34,37,48]. In pediatric patients, behavioral components cannot be overlooked and are key factors to successful rehabilitation [48]. Noninvasive approaches offer areas for further research, which the reviewers believe offer promise for symptomatic relief to allow progress in therapies. Approaches need to be tailored to the individual personality of the patient [39]. A treatment algorithm should include initial outpatient PT/OT unless the level of functional disability requires an initial intensive therapy approach. Depending on the severity of symptoms, medication use and psychology referral may also be required. Family-centered therapies offer support and education that help create patient autonomy in the face of a disabling condition. In our opinion, the multidisciplinary care model

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REFERENCES


