Complex Regional Pain Syndrome in Children

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Objectives

1. Review the epidemiology and pathophysiology of CRPS
2. Discuss the clinical presentation, diagnostic criteria, and diagnostic studies
3. Present recent advances in the management, including physical therapy, medications, and invasive techniques

Epidemiology

Complex regional pain syndrome (CRPS1) or reflex sympathetic dystrophy (RSD) is characterized by severe, nondermatomal, chronic pain, vaso- and sudomotor changes, and a movement disorder. It can be preceded by a noxious event, though the presentation is often disproportionate to the inciting injury.

A recent population based study (1) did not find any patients under age 10 and only three patients, one male and two females, in the 10 to 19 age group. Thus, the incidence was 1 to 2 per 100,000 person years at risk and the prevalence was less than 1 per 100,000 people. Large medical centers have reported several case series with a total number of approximately 1000 patients in the pediatric age group. There are only a few case reports of children in the preschool years. (2,3,4). The majority of patients presenting for medical care are in the preadolescent and adolescent age groups. Girls are affected 5 times more often than boys. Whereas adults frequently present with symptoms in their upper extremities, in children, lower limbs are affected 5 times more often than upper ones. (5)

In the 1980’s it was observed that 11 months passed before a diagnosis of CRPS was made. (5) An increased awareness of the syndrome in children seems to have led to an earlier diagnosis. Particularly in cases with an identifiable injury or after surgical procedures children are often referred to pain clinics with the specific question whether this could be CRPS.

Pathophysiology

CRPS presents with findings in the peripheral, the autonomic, and the central nervous system. An etiology has not been identified and the pathophysiology is not fully understood. Abnormalities have been described at all levels of the neuraxis, affecting transduction, transmission, modulation and perception. A genetic predisposition has been considered, particularly in treatment resistant patients. (6) Adrenoreceptor hypersensitivity on the peripheral nerve fiber might be responsible for the perfusion and temperature changes seen with CRPS. Until recently, investigations have primarily focused on changes in the periphery and the sympathetic nervous system. The search for the etiology of CRPS has since been expanded to the central nervous system. Spinal cord and central nervous system sensitization due to persistent nociceptive input might explain allodynia and hyperalgesia. Finally, the recognition that the central representation of somatosensory sensations is changed in patients with CRPS (7) and that the reversal of the tactile impairment and cortical reorganization is associated with a decrease in pain (8) opens a whole new venue for investigation and treatment.

In an early study, psychological dysfunction was considered a significant contributor to the pathophysiology of CRPS in children (9) but more recent assessments in children (14) and in
adults (10) do not support this view. Certainly, chronic pain of any etiology in a child will lead to a disruption of normal family life and can be associated with depression and catastrophizing.

**Clinical Presentation**

Patients will present with a mixture of sensory, autonomic, and motor signs and symptoms. Pain is usually the most prominent complaint. The majority of children will rate it as severe. The quality of the pain can be deep, achy, sharp, stinging or lancinating, or a burning sensation. Patients can report pain due to contact with clothing, bedspread, or water droplets (allodynia) or an exaggerated response to a painful stimulus (hyperalgesia). Pain can be aggravated by environmental factors (cold) or by stressful events.

Transient or persistent skin discolorations from bright red to purple or blue often with whitish or grayish spots are reported and can be observed during examinations. Edema is frequently present. A measurable temperature difference between the affected and the uninvolved extremity is not seen as often. It is our impression that vasomotor changes are much more common in children than sudomotor abnormalities like hyperhidrosis.

Trophic changes involving hair and nail growth tend to be subtle and might require more specific questioning of the patient’s grooming habits. Several months can pass before these symptoms might become apparent.

Motor involvement is most often limited to a decreased range of motion but might include tremors, jerks, and muscle weakness. Dystonia can lead to clenched-fist syndrome or equinovarus of the foot. Contracture can develop if symptoms are allowed to persist without intervention.

**Assessment**

The most important assessment tool in children is an excellent history and physical exam. History should include the current characteristics of the pain and other symptoms in detail. Disease course and progression, previous diagnostic and therapeutic interventions and their outcome should be documented. It is important to include an assessment of the patient’s daily functioning and the health-related quality of life. Children that are frequently missing school or no longer attending school will be much more difficult to rehabilitate. Younger children might not have the vocabulary or the experience to provide a detailed pain history. Observation and parental questioning of the patient’s avoidance behavior can be helpful in this situation.

Routine laboratory studies are usually normal. Their main benefit is one of differential diagnosis if the presentation is less than clear. Plain radiographs can show patchy osteopenia. Nuclear imaging has repeatedly been evaluated for its usefulness to support a diagnosis of CRPS in children. Diffusely decreased bone uptake is often present (11) but the specificity of the scintigraphic pattern (12) and the interobserver reproducibility (13) has been questioned. Hypoactivity at the painful site might support the diagnosis but absence of the finding clearly does not rule it out.

If neurologic testing is pursued CRPS type 2(causalgia) can be found in some patients. No difference in response to rehabilitative treatment or to the eventual outcome was observed in this subgroup. (14)

**Treatment:**

CRPS is a syndrome with pathophysiological changes in all parts of the nervous system. Therapeutic interventions in children have been more rehabilitative and non-interventional in nature when compared to those in adults. No randomized studies exist to assess whether a more aggressive approach would lead to a better outcome. Peripheral, sympathetic or epidural nerveblocks are usually reserved for children in whom more conservative therapies failed.
Pain relief is the child’s and the family’s primary concern but improved mobility, function, and a return to age-appropriate activities should be a goal, as well. A multi-disciplinary approach seems to be most effective in achieving this goal. Lee et al. evaluating combination of physical therapy (PT) and cognitive-behavioral interventions in a prospective, randomized trial found significant improvements for the majority of children. (14) There was no difference in outcome between PT sessions once a week versus three times a week for six weeks. Almost 90% of the children had excellent improvements in functional status at long-term follow-up, although 50% of the children had at least one recurrence and a third of them received sympathetic blockade within a year of initial treatment. In another prospective study Sherry et al. evaluated the effectiveness of short-term, intense PT (up to 6 hours a day for 6 to 14 days): 92% of the patients became symptom free. A recurrence was seen in 31% of the children. (15) Transcutaneous nerve stimulation is occasionally added to the PT approach. (16)

Pharmacological therapies are largely based on experience gained in adult patients with neuropathic pain syndromes. These therapies are generally off-label uses and not specifically FDA-approved for CRPS. Prospective class I studies in adults have shown significant improvement with pulsed corticosteroids in early CRPS. Children are much more frequently treated with anti-inflammatory agents like NSAIDs, although no studies support this approach. Tricyclic antidepressants have been found to be effective for at least 30% of the adults taking them for neuropathic, non-CRPS pain. The recent FDA black box warning concerning antidepressant prescriptions for adolescent patients has complicated the matter. Physicians will have to decide for themselves whether they can comply with the increased need for monitoring in their particular practice setting. Anticonvulsants like gabapentin might be as effective as antidepressants and possibly better tolerated. Compliance and convenience might be an issue as anticonvulsant have to be taken two to three times a day versus the once a day dosing suggested for tricyclics.

Multiple case reports in adults and rare ones in pediatric patients or small case series without control groups describe therapeutic interventions with transdermal clonidine and lidocaine, intranasal calcitonin and bisphosphonates, ketamine and dextromethorphan, anti-TNF treatment with infliximab, and treatment with a prostacyclin analog. (17) Short-term and/or long-term side effects need be considered before initiating these therapies.

Regional anesthetic approaches include peripheral, somatic, sympathetic nerve blocks and the central neuroaxial infusions. The goal is a reduction in pain and facilitation of physical therapy. In two recent case series a complete resolution of symptoms was demonstrated with initiation of the block. In the first, Suresh et al. used 0.5 mg/kg of ketorolac and 2 mg/kg of lidocaine for an IV regional anesthetic (Bier block) in 2 children. (18) In the other study continuous popliteal and axillary nerveblocks with an equal volume mixture of 0.5 ml/kg of 1% lidocaine and 0.5 % ropivacaine with 1:200,000 epinephrine after an initial Bier block led to a universal resolution of symptoms in all 13 children studied. (19) An accompanying editorial by Berde and Lebel points out the weaknesses of the latter study: limited follow-up and non-randomized design. (20)

Surgical procedures, like implantation of spinal cord stimulators, intrathecal drug delivery systems or sympathectomies are rare enough to justify case reports. (21) Clearly, these procedures should not be recommended easily, considering the high rate of recurrence and spread to other extremities in children.
Outcome:

Outcome in children has been thought to be more favorable than in adults, though it is very difficult to state this with any kind of authority. Adult have preferably been treated with interventional therapy whereas children have primarily, and often exclusively, been exposed to physical therapy and behavioral cognitive interventions. The gloomy picture for adults with CRPS was not supported by a recent population based study where three out of four cases resulted in resolution. (1) Up to a third of pediatric patients have recurrences either in the same extremity or in another part of the body. The risk for recurrences seems to be highest during the first 6 months after therapy. Occasionally, continuous spread beyond the initial presentation site is seen though reports of this occurrence are few. It is unclear whether children and adolescent who had CRPS are at any increased risk for other painful syndromes in their adult lives. Clearly, much more research is needed to further elucidate complex regional pain syndrome in children.

References:


