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Original Article

Complex regional pain syndromes in children and adolescents

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Abstract ***Background***: The purpose of the present paper was to assess efficiency of treatment and long-term functional outcome of complex regional pain syndromes (CRPS) in children who were treated in the chronic pain clinic at a major tertiary hospital in Israel.

Methods: The files of 14 children with CRPS were analyzed retrospectively. Demographic data, initiating event, referring source, time needed for referral to pain clinic, clinical evaluation, treatment, recurrence and complications were recorded.

Results: Fourteen children with CRPS types I and II were included in the study. Girls were affected in 71%. Lower extremities were affected in 57%. The median time from onset of symptoms to seeking medical help was 4.46 weeks (range 2–82 weeks). The median time to referral to pain clinic was 24.51 weeks (range 1.2–94). In 45% the referral source was the pediatrician. A total of 85.8% of patients were referred to various consultations before the pain clinic. Most children had reduced pain and improved function on non-invasive treatment approach. Invasive treatments were used in 28.5%. Full or partial recovery was accomplished in 93%. Recurrence was observed in 29%.

Conclusions: CRPS in children and adolescents is still underdiagnosed, although many of the epidemiologic features of pediatric CRPS are similar in different countries/cultures. Early recognition and management is the major factor in improving outcome and preventing resistant CRPS, but even children with delayed diagnosis still have a good outcome. The management of this disease by an experienced multidisciplinary team is recommended. Because psychosocial factors play an important role, it is recommended to provide psychological evaluation and cognitive behavioral treatment as soon as possible.

Key words children, complex regional pain syndromes, outcome, treatment.

Complex regional pain syndrome (CRPS) is a painful syndrome, typically affecting the hand or foot. Regional pain, sensory changes (e.g. allodynia), abnormalities of temperature, abnormal sudomotor activity, edema and an abnormal skin color that usually occurs after an initiating noxious event such as trauma are the main features.[1] Two types of CRPS have been recognized: CRPS I corresponds to reflex sympathetic dystrophy (RSD) and occurs without a definable nerve lesion. CRPS II (causalgia) refers to a case in which a definable nerve lesion is present after a nerve injury, but the clinical picture is not limited to the distribution of the injured nerve.

Complex regional pain syndromes were regarded as rare in children until the 1970s, when several case series were reported.[2,3] But in the last decade it has become a well-established entity in children and adolescents, although it remains probably underdiagnosed.[4] Failure to distinguish CRPS leads to delayed management, unnecessary investigations and improper treatment, which may worsen the situation and aggravate suffering. Early diagnosis, appropriate referral and treatment are essential in reducing pain and improving function in children and adolescents with CRPS.[5]

The aim of the present study was to examine the efficiency of treatment and long-term functional outcome of CRPS at the Chronic Pain Clinic of Schneider Children's Medical Center of Israel.

Methods

For the purposes of the present study, the written files of patients who were referred with a suspected diagnosis of CRPS types I and II from 2003 until 2005 to the Chronic Pain Clinic Schneider Children's Medical Center of Israel, a major tertiary-care and teaching facility, were analyzed retrospectively. The files consisted of patient reports, results of check up and investigations. The study was approved by the institutional ethics committee.

Evaluation

The following patient-related parameters were recorded from the medical files: sex, age, weight, referring source, time from onset of symptoms to seeking medical help, and time needed for referral to the Pain Clinic. The time needed for the referral to the Pain

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Clinic was calculated as the time from the first examination of the patient by the primary physician until the referral to Pain Clinic. The number and type of previous consultations and investigations that were carried out in an effort to make the diagnosis, and treatments used before referral to Pain Clinic, were recorded, based on objective information from specialist letters.

The disease-related parameters included an initiating event (if identifiable), location (which extremity), clinical evaluation, treatment, recurrence and complications. The data were collected systematically through the patients' reports during regular examinations.

Hyperalgesia was defined as a lowered sensory threshold to noxious (pinprick), thermal and mechanical stimuli compared to the unaffected side. Allodynia was defined as pain in response to a normally non-noxious stimulus, such as light touch judged against the unaltered side. Dystonia was defined as tremors or involuntary, sustained muscle contractions in the affected extremity. A skin temperature change was defined as >1.1°C difference between the affected and contralateral uninvolved extremity.[6] The temperature difference was measured using a skin temperature probe.

We used the clinical diagnostic criteria for CRPS proposed by the Budapest International Association for the Study of Pain (IASP) consensus group (Table 1).[7]

All the patients were evaluated by the Pain Clinic psychologist and standard clinical psychological intake and anamnesis were obtained. Children with learning difficulties, those in special education classes or with documented learning disabilities were defined as poor students.

A senior specialist in pediatric pain made the final diagnosis in all cases based on the clinical diagnostic criteria for CRPS proposed by the Budapest IASP consensus group. The time from the first examination of the patient in the Pain Clinic to recovery was recorded. Full recovery was defined as complete resolution of disease-related signs and symptoms and resumption of age-appropriate activity, including school attendance. Partial recovery was defined as incomplete resolution of disease-related signs and symptoms, but accompanied by significant lowering of pain and resumption of age-appropriate activity. Follow up lasted 6 months after recovery, and the patients were evaluated at the end of this period. The evaluation included physical assessment, pain scores, limb function, and school attendance.

The number of children who relapsed during that time was identified. The treatments used for the relapse and the time needed for recovery from the relapse were recorded.

Results

Nineteen patients were referred with the diagnosis of CRPS types I and II. Five of these patients were diagnosed as suffering from erythromelalgia ($n = 1$), sprained ankle ($n = 2$), conversion reaction ($n = 1$) and angiomatosis of the lower extremity with osteoporosis due to disuse ($n = 1$). In the remaining 14 patients the diagnosis was confirmed: 12 with CRPS type I (RSD) and two with CRPS type II (causalgia). The average age was 11.85 ± 3.18 years (range 7–16 years). Seventy-one percent of the patients were girls. Lower extremities were affected in 57% of patients.

The initiating event was identified in 13 patients (92.8%) and consisted of minor trauma in seven cases, major trauma in one case, prior operation of the extremity in three cases, and pre-existing low extremity arthritis in one case. In one patient the CRPS type I started after infliximab infusion for Crohn's disease.[8] The case in which no initiating event was identified was considered a spontaneous presentation.

The average time from the onset of the symptoms to seeking medical help was 4.46 weeks (range 0.2–82 weeks). The average time of the referral to Pain Clinic was 24.51 weeks (range 1.2–94 weeks). Twelve patients (85.8%) were referred to various consultations before the Pain Clinic. Eight were investigated by

Table 1 Clinical diagnostic criteria for CRPS

Continuing pain, which is disproportionate to any inciting event	
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 color changes and/or skin color asymmetry
Sudomotor/Edema	Reports of edema 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)
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 color changes and/or asymmetry
Sudomotor/Edema	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
There is no other diagnosis that better explains the signs and symptoms	

[†]A sign is counted only if it is observed at time of diagnosis.
CRPS, complex regional pain syndrome.

an orthopedic surgeon, two by a pediatric neurologist, two by a vascular surgeon, one by a pediatric psychiatrist, three by a physiotherapy specialist, five by a day-care pediatrician and one by a pediatric rheumatologist; an average of 1.8 consultations per child. Several specialists examined five of the patients (35.7%).

Before the diagnosis was made eight of the children (57.1%) had some form of investigation: six had had radiographs; six had isotope bone scan; two had ultrasound; two had computed tomography; two had magnetic resonance imaging and three had had electromyography; an average of 2.6 investigations per child.

Prior to the referral to the Pain Clinic, all children had some form of treatment. Eight received non-steroidal anti-inflammatory drugs (NSAIDs), seven were treated with paracetamol, two with amitriptyline, one with carbamazepine, one with antibiotics and one with tramadol. Twelve patients had physical therapy (PT) and one had occupational therapy (OT). Four of the eight affected by lower limb CRPS type I had a period of time of non-weight bearing, either using crutches ($n = 3$) or in a wheelchair ($n = 1$). Three of the patients with an affected upper limb were treated with an arm sling.

On admission, Pain Clinic senior specialist in pediatric pain evaluated all the patients. On clinical examination the mechanical hyperalgesia and hyperalgesia to cold were present in 100% of cases, allodynia in 100%, temperature difference between affected and non-affected extremities in seven patients (50%), color changes in 13 (92.8%), atrophic changes in four (28.5%), edema in 10 (71.4%) and hyperhydrosis in six patients (42.8%). Average visual analog score (VAS) on admission was 8.78 ± 0.97 (range 7–10).

The Pain Clinic psychologist evaluated all of the patients. Family and/or socioeconomic problems were present in six patients: two families were new immigrants with a low socioeconomic status, in two the parents were divorced, in one case the father was suffering from chronic painful osteopathy and the younger brother from enuresis and hyperactivity. In one family the mother was extremely overprotective and controlling. Only seven of the patients (50%) were excellent students and participated in competitive sports activities. Nine of the patients reported truancy from school more than twice a week.

Once diagnosis was made all the patients received intensive PT four times a week in a 2 h session. The patients we instructed to perform the exercises twice a day at home. This schedule of PT was continued until the end of the treatment.

Cognitive behavioral treatment (CBT) that included guided imagery, biofeedback and/or relaxation techniques was provided for 11 patients. Drug treatment consisted of amitriptyline 0.2–1 mg/kg per day ($n = 13$) and carbamazepine in one patient 20 mk/kg per day. Our practice is to obtain electrocardiogram before starting tricyclic antidepressant therapy and to evaluate the patients every week while escalating to a full therapeutic effect. In addition, two patients were treated with NSAIDs, two with cyclooxygenase-2 enzyme inhibitors and one with topiramate. Two patients consulted the adolescent psychiatrist and depression was diagnosed in one of them.

Most children had reduced pain and improved function with a non-invasive drug and a rehabilitative treatment approach. Invasive treatments were used in four cases (28%) after the failure of a non-invasive treatment approach. One patient was hospitalized and a lumbar epidural catheter was inserted for PT. In one patient with left upper extremity CRPS type I the series of stellate ganglion blocks was done once a week. Because the patient's response to the blocks was good but symptom regression was very slow, we had to complete 12 procedures until the full recovery.

Two patients with CRPS type I of the foot received ankle blocks in order to facilitate physiotherapy. One of the patients who received ankle blocks had to undergo Achilles tendon lengthening to restore full range of motion to the affected extremity.

We continued the medications until the end of the treatment in both groups of patients (invasive and non-invasive).

Average time of treatment was 8 weeks (range 2–28 weeks). Full recovery was accomplished in 78.5% of the patients. Partial recovery was achieved in 14.5% of the patients. Those children continued PT at home with our evaluation once in 3 months. In one girl (7%) the treatment failed and the parents decided to continue the treatment in another clinic. This patient was lost to follow up.

Recurrence was observed in four patients (28.5%): two children with upper extremity CRPS type II, one-with CRPS type I of the foot and one with CRPS type I of the upper extremity (the one previously treated with stellate ganglion blocks). In all cases the recurrences were in the same limb and occurred after a new event (minor trauma in three cases and operation of the extremity in one case). The disease course of recurrent CRPS was milder than the first presentation. VAS on admission was 6.5 ± 0.57. The treatment consisted of amitriptyline 0.5–1 mg/kg per day and PT with average duration until recovery of 2.4 ± 0.54 weeks. No patient needed invasive treatment.

Discussion

Characteristic features of CRPS include pain, allodynia, hyperalgesia, edema, skin color and temperature changes, and limited range of motion of one or more extremities,[4,5,9] The pain is often burning in quality.

The present study confirms several unique features of pediatric presentation, reported previously (Table 2).[4,5,10,11] Girls were affected more often than boys (3:1), and the most common age of onset was young adolescence. But the lower extremity was almost equally affected as the upper extremity (1:1.14), contrary to the literature, in which the incidence of lower extremity predominance ranged from 1:2[4] to 1:7.[10]

Table 2 Contrasts in pediatric and adult CRPS

	Children	Adults
Site	Lower > upper	Upper > lower
Sex ratio	Marked female predominance	Moderate female predominance
Prognosis	Excellent recovery in most cases	Variable; long-term disability relatively common

CRPS, complex regional pain syndrome.

Most publications reported that a significant number of children attribute the onset of the CRPS to some episode of trauma, which may be only minor.[10–14] It was proposed that in the pain clinics, where a high percentage of referrals come from orthopedic surgeons and neurologists, the percentage of identifiable events would be higher.[4] We were able to recognize some kind of traumatic episode that seemed to trigger CRPS in >90% of cases, even though 45% of all referrals were by pediatricians. Interestingly, even though a supracondylar fracture at the elbow only very rarely produces CRPS in children and adolescents,[1] the youngest of the present patients (7 years old) suffered an episode of CRPS type II after this fracture.

The diagnosis of CRPS can be performed on clinical judgment with a number of symptoms present at the time of establishing the diagnosis,[7,9] but the mosaic clinical picture of this syndrome leads the patients to be evaluated by a spectrum of specialists. In agreement with published data,[9–11] we found that in a large number of patients there was a significant delay before presentation to Pain Treatment Clinic. Although the average time from the onset of symptoms to seeking medical help was relatively short, it took a long time for the patients to be referred to the Pain Clinic (almost 6 months), mostly because of unnecessary consultations and diagnostic investigations. In the present study, before correct diagnosis was made, the average number of professionals consulted was 1.8 and the average number of investigations was 2.6 per child. These results are close to the 2.3 and 2.2 respectively reported by Murray *et al.*[10] Computed tomography or nuclear magnetic resonance imaging were carried out to exclude any organic disease. Even though radiographs of extremities and isotope bone scans contributed to establishing the diagnosis, it is worth mentioning that in all but one case the clinical picture on admission was very characteristic.

The present study confirms the previously recognized fact that a large number of children had inappropriate treatments before the diagnosis was made.[10,12] Fifty percent of the patients had some form of immobilization that had aggravated the condition. Even though 85.7% of the patients had had PT before referral to Pain Clinic, the treatment was ineffective often because of incorrect diagnoses.

Several studies have investigated different treatment modalities in children with CRPS. Choice of therapy often seems to depend more on the type of clinician who sees the patient, rather than on evidence derived from prospective controlled clinical trials.[4] Nevertheless, an agreement exists across medical specialties that active PT/OT and restoration of normal extremity function is a cornerstone of treatment. A dedicated PT team is usually required for successful application of physical modalities in these patients.[11,12,15–19] The same special PT group with the expertise in CRPS management treated all of the present patients.

Most studies agree on the importance of early diagnosis and treatment in children and adolescents with CRPS,[5,10–12,19,20] although Murray *et al.* could not confirm the relationship between early onset of treatment and fast recovery.[10] In the present study all four patients who received invasive treatments were referred late to the Pain Clinic (average time from onset of disease, 63 weeks). In addition, one of them had to undergo further surgical correction of the affected limb.

There is some inconsistency regarding the use of medically based interventions in the management of children with CRPS. A recent Cochrane review could not determine a conclusion concerning the effectiveness of regional anesthetic techniques for CRPS treatment.[21] Some of the discrepancies in treatment approaches may reflect in part the specialties involved. For example, among the patients in case series reported by pediatricians, pediatric rheumatologists and orthopedic surgeons,[10,19,22,23] the use of invasive procedures has generally been avoided. Conversely, the treatment in pain clinics, conducted by the anesthesiologists, seems to be more aggressive, especially in severe cases.[11,12,24–26] Our practice is to proceed with the invasive modalities in pediatric patients with CRPS who have not responded to 4 weeks of treatment with systemic medications, PT or CBT. Blocks are used primarily to increase the participation of the patients in PT/CBT.

The relapse rate is a major concern in pediatric CRPS. The reported incidence ranges from 25% to 33% and signs and symptoms often spread from one extremity to another.[5,10,12,23,27] As in other groups, the recurrence in the present cohort was high, but all episodes occurred in the same limb. Of note, two of four patients who had relapsed, suffered from CRPS type II and one of them had two episodes. We recommend that children and adolescents with CRPS type II especially should not be lost to follow up for at least 2 years.

Psychological factors contribute to the development of pediatric CRPS and sometimes a particular psychological profile can be seen in children with CRPS.[10,11,28–30] Most commonly, the patients are high achieving, compliant, preadolescent girls, participating in competitive sports. In the Sherry and Weisman study these patients comprised 71% of the group.[30] School problems, family discord or divorce, and enmeshment with one parent are other psychological issues found.[11,29] In the present patient cohort only 50% were high achievers, but family and/or socioeconomic problems were present in 42.8%. These results differ from the 25% reported by Murray *et al.*[10] We speculate that these data may reflect the special aspect of Israel, given the high level of immigration and accompanying significant psychological stress. In any case, we consider psychological evaluation of all the patients with CRPS to be obligatory during the first visit.

We think that the delays in referring patients to the pain clinic were an indication of lack of pediatrician awareness of this disease. Since carrying out this study we have established a plan of lectures and round-table meetings on the subject of CRPS in children and adolescents among pediatricians. We emphasize that failure to suspect the condition may cause serious disability in these patients.

Limitations to study

Use of retrospective analysis was the main study limitation. Because the current study represents the authors' experience with CRPS types I and II, we cannot compare the morbidity between two conditions because of the small number of patients. A multicenter study would be needed to answer this question. Another limitation of the study is the fact that we did not use gabapentin or pregabalin (during the present study those drugs were approved in Israel only for the treatment of refractive epilepsy).

Conclusions

In our experience, CRPS in children and adolescents is still underdiagnosed, although many of the epidemiologic features of pediatric CRPS are similar in different countries/cultures. We consider early recognition and appropriate management to be the major factor in improving the outcome and preventing resistant CRPS. Although earlier diagnosis will shorten the period of misery and uncertainty for these children, the evidence from the present study suggests that even those children who had delayed diagnosis still mostly had a good outcome. The management of this disease by an experienced multidisciplinary team is recommended. Because psychosocial factors play an important role, it is recommended to provide psychological evaluation and CBT as soon as possible.

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