Complex regional pain syndrome type I in children: What is new?

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A B S T R A C T

Complex regional pain syndrome type I (CRPS-I), although first described by the French surgeon Ambroise Paré as far back as the 16th century, nevertheless remains shrouded in mystery. The most common symptoms are pain in an entire hand or foot, alldynia, functional impairment induced by the pain, local oedema and skin color changes and transient sweating abnormalities. Most cases occur after a minor injury (i.e., a sprain or fracture), although there may be no identifiable triggering event, particularly in children. Primarily cold CRPS-I is by far the most common variant in children. Development of the Budapest criteria has benefited the diagnosis. These criteria are clinical and no specific diagnostic investigation is available. In vitro and in vivo studies have established that several pathogenic mechanisms can be involved concomitantly. However, there is no satisfactory explanation to the full clinical spectrum. Blood tests and imaging studies are useful for ruling out other diagnoses then monitoring the course of the condition, which may involve the development of demineralisation or osteopenia. High-resolution peripheral quantitative computed tomography may be helpful, as it provides quantitative assessments of the cortical and trabecular bone. CRPS-I has several specific characteristics in children compared to adults and whether the condition is the same entity in these two age groups is a legitimate question. The optimal management involves an early diagnosis followed by a multidisciplinary management programme of functional rehabilitation therapy and cognitive behavioral therapy. Analgesics are useful only during the phase of acute pain and to facilitate physical therapy. Studies in adults showed that bisphosphonates were effective within the first 12 months after symptom onset and calcitonin in longer-lasting cases. No high-quality clinical research studies into the aetiopathogenesis and treatment of CRPS-I in children and adolescents are available to date.

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1. Introduction

Complex regional pain syndrome type I (CRPS-I) manifests as pain, usually in a hand or foot, combined with sensory, motor and autonomic nervous symptoms. In children and adolescents, the presentation of this severe condition differs from that seen in adults and elderly individuals [1]. The insidious onset and slow progression of CRPS-I often delay the diagnosis, thus jeopardizing the chances of recovery [2]. The exact cause of CRPS-I is unknown. The many contributors to the development and severity of CRPS-I include psychological factors [3]. The relationship between the child and parents clearly has an influence. A vicious circle of pain, autonomic disorders, stiffness and psychological ill-being becomes established. Early multidisciplinary management can prevent progression of the symptoms. Nevertheless, a full recovery may not be achieved, and the condition may become chronic.

The objective of this conference is to review the data on CRPS-I, a condition that continues to disconcert not only the patients and their families, but also physicians and other healthcare workers. Our goal in discussing current data is to provide insights into the nature of CRPS-I, role for investigations, existence of factors associated with greater severity, differences between the patterns seen in children and in adults, aetiopathogenic mechanisms and therapeutic principles. Clearly, a vast field of research is unfolding and carefully designed, prospective, multicentre studies are indispensable to produce advances that will benefit our patients.

2. Definition of complex regional pain syndrome type I (CRPS-I)

In the fourth edition of CRPS guidelines, published in 2013, Harden et al. state that ‘CRPS is a syndrome characterized by a continuing regional pain that is seemingly disproportionate in time
or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, and/or trophic findings. The syndrome shows variable progression over time.

Claude Bernard (1813–1878) is considered to have provided some of the earliest evidence that pain can be linked to autonomic nervous system (ANS) disorders. One of his students, Mitchell (1829–1914), coined the term ‘causalgia’ to designate the pain seen in veterans of the American Civil War (καύσιμος, kausos, burning sensation; and αλγος, algos, pain). The term ‘reflex sympathetic dystrophy’ introduced by Evans in 1946 was widely used in the 20th century but finally proved inappropriate. After the international conference held in Orlando in 1994, the International Association for the Study of Pain (IASP) defined the following criteria for chronic pain [4]:

- the presence of an initiating noxious event or a cause of immobilization;
- continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event;
- evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain;
- this diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

To improve specificity, motor criteria were added at the conference held in Budapest in 2004. The Committee for Classification of Chronic Pain of the IASP validated the new ‘Budapest criteria’. These criteria are clinical and are now used to diagnose CRPS-I (see Box 1) [4]. The diagnosis requires at least three of four symptom categories to be positive and at least one physical examination sign in at least two of the four categories. With these decision rules, sensitivity is 85% and specificity 69%.

**Box 1: Diagnostic criteria for complex regional pain syndrome type I (Budapest, 2004)**

1. Continuing pain, disproportionate to any inciting event.
2. At least one symptom in three of the following four categories:
   - sensory: history of hyperalgesia and/or allodynia;
   - vasomotor: history of temperature asymmetry and/or skin color change and/or skin color asymmetry;
   - sudomotor/oedema: history of oedema and/or sweating changes and/or sweating asymmetry;
   - motor/trophic: history of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia), and/or trophic changes (hair, nails, skin).
3. During the evaluation, at least one sign in two or more of the following four categories:
   - sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or to deep somatic pressure and/or to joint movement);
   - vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry;
   - 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, nails, skin).
4. There is no other diagnosis that better explains the signs and symptoms.

3. **Patterns of complex regional pain syndrome (CRPS)**

Three subtypes of CRPS have been defined [4]:

- CRPS-I, the topic of this conference, previously designated reflex sympathetic dystrophy syndrome;
- CRPS-II, previously known as causalgia, defined as CRPS with clinical and/or electrodiagnostic evidence of nerve damage;
- and CRPS-NOS (not otherwise specified), which only partially meets CRPS criteria but is not better explained by any other condition.

It is worth noting that the distinction between types I and II is unclear, as the nerve deficits are ill defined.

4. **Potential usefulness of investigations**

The diagnosis of CRPS-I is clinical and rests on the Budapest criteria (Fig. 1). To date, no objective test for confirming the diagnosis and monitoring the course is available. Nevertheless, imaging studies and blood tests are helpful in ruling out other diagnoses. Bone denormalisation may be visible by radiography or magnetic resonance imaging (MRI). Bone scintigraphy may reveal abnormal uptake, which usually consists in cold spots. Computed tomography (CT) and, with even greater accuracy, micro-CT provide quantitative measurements of bone morphology parameters.

In paediatric patients, the blood and urine levels of biological markers for bone turnover vary normally with pubertal development and growth rate. In studies of children with CRPS-I, values were normal for serum markers of both bone formation (osteocalcin and bone alkaline phosphatase) and bone resorption (tartrate-resistant acid phosphatase 5b, C-terminal telopeptide of collagen type I). In CRPS-I, the limited extent of the bone turnover abnormalities, which are confined to an extremity, results in overall biological changes that are too small to be identified.

Radiographic evidence of denormalisation is often described (Fig. 2a). However, bone loss is extremely common at sites that are immobilized after an injury. Thus, many dual-energy X-ray absorptiometry (DXA) studies showed decreases in bone mineral density and content of the entire lower limb after immobilization to treat a fracture. This regional abnormality, affecting the entire limb from the calcaneus to the hip, is normally reversible within about 6 months [5]. Decreases in bone density parameters measured by DXA were reported in the affected side compared to the unaffected side in a 29-year-old male with residual pain from CRPS-I that

![Fig. 1. 11-year-old girl with CRPS-I in the left foot: note the oedema, purplish color, and livedo reticularis. Transcutaneous electrical nerve stimulation.](image-url)
developed at 13 years of age after Legg-Calvé-Perthes disease [6]. However, DXA provides only two-dimensional measurements and fails to separate trabecular from cortical bone.

High-resolution peripheral quantitative computed tomography (HR-pQCT), in contrast, provides separate measurements of trabecular and cortical bone density, as well as measurement of a trabecular volume, from which the thicknesses of the trabecular and cortical bones can be determined. Although the information is less detailed compared to a histomorphometric assessment of a bone biopsy specimen, both the quantitative measurements and the appearance of the images are highly informative. Micro-CT has been used in a rat model of CRPS-I to investigate the response to antibodies against nerve growth factor (NGF) [7]. In an 11-year-old girl, HR-pQCT showed an improvement in bone mineralization after a few months of pamidronate therapy [8]. HR-pQCT may hold promise for monitoring the course of CRPS-I by providing local objective data. If this promise is to be fulfilled, reference values in the paediatric age group will first have to be collected.

For many years, bone scintigraphy has proved a useful contributor to the early diagnosis of paediatric CRPS-I. Uptake is decreased in the affected area, producing a cold spot (Fig. 2b). The three stages of disease progression described in adults have also been documented in a 12-year-old [9]. At the diagnosis of CRPS-I, blood flow is diminished compared to the unaffected side during phase 1 (1st minute after radionuclide injection) and phase 2 (next 4 minutes) of bone scintigraphy and uptake is low during phase 3 (after 2 hours). Marked differences may still be found several months later, with a cold extremity and livedo reticularis sign. When the clinical manifestations abate, the differences between the two sides tend to diminish or become reversed, with increased uptake in the affected extremity [9].

MRI abnormalities are far from uncommon and changes consistent with bone contusion or oedema may be visible [10] (Fig. 2c). In adults, soft-tissue alterations have been reported early in the course, including increased skin tissue thickness, subcutaneous oedema, and tissue enhancement, with a tendency to resolve as the condition improves [11]. Muscle changes at the early stage consist of high-intensity signal on T2-weighted images and postgadolinium enhancement on fat-suppressed T1-weighted images and are followed at the chronic stage by muscle wasting with absence of post-gadolinium enhancement [12].

5. Factors associated with greater severity of complex regional pain syndrome type 1 (CRPS-I)

A delayed diagnosis and inappropriate management are clearly associated with a longer disease course, improvements that fall short of a full recovery, and sequelae. Other factors of adverse
prognostic significance include parent denial of this serious condition and a history of personal events that adversely affect mood.

The severity of CRPS-I lies in the recovery rate of only about 50% after 3–6 months, with some additional patients recovering after more than 1 year [3]. Persistent abnormalities that impair quality of life are common. Even worse is the nonnegligible risk of recurrence, which raises major therapeutic challenges. Few tools for assessing outcomes have been published. The Paediatric Quality of Life Inventory version 4.0 (PedsQL 4.0) developed by Varni et al. has been validated in the various paediatric age groups for assessing the impact of acute and chronic pain [13]. In children with CRPS-I, PedsQL 4.0 scores were lower (worse) for physical, psychosocial, emotional and social items [3]. The only item with a high score was school performance.

Major psychological factors are reported in over half the cases of paediatric CRPS-I. They include family conflict, the death of a loved one, difficulties at school, sexual abuse and having witnessed disturbing events (e.g., a terrorist attack [2,3,14]). The combination of anxiety, atopic background, excellent school performance and difficulty falling asleep is particularly unfavourable. Other reported factors include abdominal pain, headaches and prior psychotherapy [11]. In contrast, one paediatric study found that patients with CRPS-I had no psychological differences compared to patients with migraine or controls [15].

6. Differences between paediatric and adult complex regional pain syndrome type I (CRPS-I)

Paediatric and adult CRPS-I differ regarding the aetiopathogenic factors, psychopathological profile, circumstances of onset, and clinical manifestations. These differences have major consequences. In particular, the treatments used in adults are not always optimal in children.

In two paediatric case-series studies, one in 73 patients in Toulouse, France, and the other in 20 patients in Australia [3,16], CRPS exhibited the following characteristics:

- predominance of girls, who accounted for about 90% of patients;
- mean age at onset of about 11–12 years with a range of 5 to 16 years;
- preference for the lower limb (80%–90% of cases) over the upper limb, with predominant involvement of the foot;
- minor inciting trauma in many, but not all, cases;
- mean time to diagnosis of 3–4 months;
- coolness to touch of the painful extremity in up to 81% of cases [3], in addition to two other objective clinical signs, i.e., oedema and cyanosis. These signs denote vasomotor disturbances, which also explain the decreased uptake by bone scintigraphy; thus, paediatric CRPS-I differs from Sudeck’s atrophy or reflex sympathetic dystrophy, which predominantly affects the hand in elderly patients and whose clinical and bone scintigraphy features at the early stage indicate increased blood flow (warm skin and hot spots by scintigraphy);
- psychological disorders, often with excellent school performance;
- functional MRI evidence of differences in central nervous system (CNS) processing between adults and children [17].

7. Aetiopathogenesis of complex regional pain syndrome type I (CRPS-I)

General agreement has developed that the multifactorial pathophysiology of CRPS-I reflects an inappropriate response to an insult [18]. The mechanisms recognised to date are neurogenic inflammation complicating small nerve-fibre degeneration, microcirculatory alterations and dysfunction of the ANS (sympathetic system) and CNS. These mechanisms are intertwined and exacerbate one another. Nevertheless, many unresolved issues remain, as each of these mechanisms can occur as either a cause or a consequence of CRPS-I.

7.1. Inflammation

In vivo, minor tissue damage is associated with elevated concentrations of cytokines and NGF, which stimulate the release of pro-inflammatory neuropeptides, substance P, and calcitonin gene-related peptide (CGRP) by peripheral neurons, inducing retrograde depolarisation of small-diameter fibres (C and Aβ). The result is peripheral sensitisation, with vasodilation and protein extravasation, which explain the acute symptoms (erythema, local warmth, oedema, allodynia, and hyperalgesia). Plasma levels of substance P and CGRP are higher in patients with CRPS-I than in controls [18]. Increased levels in plasma and skin biopsies are also found for other pro-inflammatory cytokines including tumor necrosis factor α, interleukin-1 and interleukin-6. However, the magnitude of the elevation is not proportional to the severity of the clinical manifestations.

In paediatric patients, CRPS-I may develop in the absence of an inciting tissue insult. Furthermore, the inefficacy of anti-inflammatory drugs on the inflammation remains unexplained.

7.2. Autonomic nervous system (ANS) dysfunction

The ANS makes a more modest contribution to CRPS-I than previously thought. There seems to be no increase in ANS activity. On the contrary, a decrease may occur at the early stage. Inhibition of the vasconstriction induced by the sympathetic system plays a role in the vasodilatation that develops later on. The ‘cold’ stage may be related to an increase in the density and/or sensitivity of the α-adrenergic receptors in the skin [19]. However, these alterations in ANS function fail to explain the occurrence of primarily ‘cold’ variants of CRPS-I.

7.3. Alterations in the microcirculation

The endothelial lesions identified in biopsy specimens from patients with CRPS-I resemble those found in animal models of ischaemia-reperfusion injury. Cellular oedema is seen, with an abundance of polymorphonuclear cells. Vessel lumen obstruction results in the development of arterio-venous shunts that diminish the downstream blood flow and cause metabolic acidosis. Hypoxic stress leads to the production of free oxygen radicals, which exacerbate the inflammation and microcirculatory lesions [19].

7.4. Role for the central nervous system (CNS)

As with all chronic pain syndromes, CRPS-I is characterized by central sensitisation at the dorsal horn of the spinal cord, which contributes to the allodynia and hyperalgesia. The cerebral cortex probably also plays a role in the pathophysiology of CRPS-I [20]. The abnormalities resemble those seen in stroke-induced unilateral neglect. The patients feel that the involved limb no longer belongs to them, is not in its actual position, or is larger than its actual size. Functional MRI studies have shown changes in the somatotopic map of the cortex contralateral to the affected limb. In response to touch, the representation of the affected limb is smaller than that of the contralateral limb [20]. Other studies demonstrated excitation of the oedema and pain when the patient viewed the affected limb in a mirror. Similarly, the skin temperature of the affected hand, which was spontaneously cooler, increased when
patients crossed their arms [21]. All these alterations resolve with the symptoms.

Scientific research has been confined to the superficial tissues of the affected limb. No studies have assessed the muscles, joints, or bone. Thus, no high-quality studies of the bone in CRPS-I are available. The reported efficacy of bisphosphonates should prompt research into the pathophysiological mechanisms that underlie the bone abnormalities seen in CRPS-I [8]. It is worth noting that all the pathophysiological studies of CRPS-I conducted so far were done in adults.

8. Treatment options

The optimal management strategy may consist in a multidisciplinary programme of noninvasive interventions including physiotherapy, occupational therapy, analgesics and psychotherapy. As with all chronic pain syndromes, CRPS-I should be managed according to the biopsychosocial model, either on an outpatient basis or more intensively during a brief hospital stay.

At present, the treatments used in children with CRPS-I are those previously found useful in adults. Noninvasive methods consist of medications, physiotherapy and psychotherapy. Invasive treatments include intravenous administration of adrenergic inhibitors, peripheral nerve blocks, epidural analgesia, sympathetic nerve blocks and surgical sympathectomy.

8.1. Functional rehabilitation therapy

Functional rehabilitation therapy includes physiotherapy in and out of a pool, occupational therapy, sensory rehabilitation, Scottish baths and elastic taping (which is better tolerated than adhesive strapping). Although no studies have compared management with versus without rehabilitation (as this design would be ethically unacceptable), these methods are the most widely used treatments for CRPS-I and provide good results. They constitute the cornerstone of the management strategy.

The goal of physiotherapy is to restore normal function of the affected limb by increasing the joint motion range, during passive then active movements, while also increasing loads and strength. Success rates of up to 90% have been reported, sometimes at the expense of 6 hours of physiotherapy every day [14,22]. A randomized single-blind trial that included only 28 patients compared physiotherapy once versus three times a week, combined with CBT [23]. Satisfactory outcomes were achieved in both groups, with no statistically significant differences.

Sensory rehabilitation, used in combination with physiotherapy, aims to gradually alleviate the allodynia.

In adults, Bowering et al. established that a graded series of movements performed with the unaffected limb viewed in a mirror alleviated the manifestations of CRPS-I [21]. The goal of this method is to correct the alterations in cortical somatotopic mapping seen in CRPS-I.

None of these techniques, including Scottish baths and taping, have been assessed for efficacy or other characteristics in paediatric patients.

8.2. Medications

Standard treatments for nociceptive pain (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs] and opiates) or neuropathic pain (antidepressants, anticonvulsants, topical analgesic patches) have been used to treat CRPS-I. In a retrospective study of 70 patients reported in 1992, 60% of patients reported no pain relief with NSAIDs, opiates or anticonvulsants; furthermore, glucocorticoid therapy was never effective [24]. Tricyclic antidepressants alleviated both the pain and the sleep disturbances in 50% of patients.

No high-quality efficacy data on these drugs are available for children. Only small case-series studies have been reported. Criticisms of these drugs in children include limited efficacy, the risk of adverse effects and the lack of information on potential long-term effects after exposure during brain development [14,22]. Thus, some authors feel that these drugs should not be recommended or even that they should be discontinued if already in use.

Two case-reports, however, suggest that gabapentin may be effective [25]. Anecdotal case-reports describe the use of many other drugs, based on pathophysiological hypotheses, including immunoglobulins, ketamine, baclofen, botulinum toxin and angiotensin-converting enzyme inhibitors. Hyperbaric oxygen therapy has also been tried. To date, there is no evidence to support the use of these treatments.

No studies have compared the efficacy of intensive physiotherapy with versus without concomitant pharmacotherapy. In the study by Low et al., 70% of children required adjuvant treatment against neuropathic pain (gabapentin or tricyclic antidepressants) to perform their physiotherapy sessions [16]. Low et al. felt that pharmacotherapy was not curative but was sometimes useful to facilitate mobilisation during physiotherapy sessions.

8.3. Psychological counselling

As stated above, a contribution of psychological factors to the pathogenesis of CRPS-I cannot be ruled out. Sherry et al. reported that a fusional relationship between the child and one of the parents was a consistent finding [14]. Although the parents described their children as unusually bright, only 4 of 21 had above-average intelligence scores [26]. Whether these distinctive psychological features antedate or occur as a consequence of CRPS-I is unclear. Psychological counselling seeks to improve the patient’s pain management skills in order to expedite the return to normal activities. Since the 1980s, cognitive-behavioral methods have gained widespread acceptance and become the only psychological tools described in published studies. These methods include psychoeducation, relaxation, biofeedback, distraction and hypnosis. Their goal is to assist the child in accepting and managing the pain. No studies have compared treatment with versus without CBT. Nevertheless, CBT is widely used and is a component of most multidisciplinary management programmes [23,27].

8.4. Other treatments

Acupuncture was successful in some reported cases. Transcutaneous electrical nerve stimulation (TENS) is often beneficial in children with CRPS-I and induces no adverse effects. Transcranial magnetic stimulation is a recently introduced tool available only in a few specialised centres and used chiefly to treat depression, hallucinations and chronic pain. CRPS-I is not among the diagnoses currently recognised by experts as warranting transcranial magnetic stimulation. Two randomized controlled trials have established the efficacy of this method in adults. A meta-analysis of randomized controlled trials, done by Cossins et al., showed that high-level evidence was available to support the efficacy of transcranial magnetic stimulation [28].

No paediatric studies have demonstrated the efficacy of acupuncture, TENS, or transcranial magnetic stimulation.

9. The debate about calcitonin therapy

Calcitonin inhibits osteoclastic activity, diminishing bone resorption and thereby alleviating the pain and functional
impairment. Calcitonin is not licensed for use in CRPS-I in children. No paediatric studies of the efficacy of calcitonin are available. In adults, results obtained with calcitonin have been conflicting. However, a recent meta-analysis of randomized controlled trials indicated that calcitonin was effective in patients with a disease duration longer than 1 year [29].

10. Potential role for bisphosphonate therapy

In four randomized controlled trials in adults, bisphosphonate therapy significantly improved pain and functional impairments in the affected limb. The results of meta-analyses indicate that bisphosphonates are the most effective treatment options for CRPS-I in adults provided they are started within 12 months after symptom onset [28,29]. However, the best indications remain unclear; thus, the potential influence of symptom duration and bone involvement on the likelihood of a response is unknown.

The only paediatric data comes from a case-report describing a good response of an 11-year-old girl to pamidronate, with no recurrence 2 years later [8].

11. Potential role for invasive treatments

A few paediatric cases treated with sympathetic blockade have been reported. Regional nerve blockade or epidural analgesia (when both lower limbs are involved) proved effective over a short follow-up of 2 months [30]. However, no controlled or blinded trials of invasive treatments are available. In 2012, Zernikow et al. made a vigorous plea for the discontinuation of invasive treatments in children, arguing that these methods are aggressive yet unsupported by long-term evidence of efficacy and often followed by recurrences [2].

Two opposing attitudes can be found today. Noninvasive treatments are often recommended, even in recurrent forms, by authors from English-speaking countries, many of whom work in large paediatric pain clinics that offer specific programmes. On the other hand, there have been reports of favourable outcomes after regional nerve blockade, sympathetic blockade or even transient implantation of spinal cord stimulators.

12. Potential usefulness of multidisciplinary assessments

Clearly, some mild forms of CRPS-I that are diagnosed very early can be treated effectively with physiotherapy and appropriate medications. Not unfrequently, however, the outcome is less favourable than hoped. A common adverse factor is an often noxious influence of those caring for the child, particularly the parents, who may go from one physician to another, thus often triggering changes in the treatment strategy.

The first point is that the diagnosis of CRPS-I must be made as early as possible based on the physical examination and radiographs. If needed, MRI may be performed to rule out another cause to the symptoms.

The patient should be referred to a pain clinic for an assessment. If the results confirm the diagnosis of CRPS-I, a multidisciplinary management programme can be instituted immediately (Fig. 3). A paediatric psychiatrist and a physical therapist should participate in this programme from the outset. A moral contract should be established, as a prompt improvement must be achieved. If the treatment fails, hospital admission is offered to allow a comprehensive management strategy combining medications, psychological counselling and physiotherapy, as well as academic activities, music and even appropriate sporting activities (Fig. 4). The hospital stay lasts 1–2 weeks, during which the parents are asked to respect strict visiting hours.

CRPS-I is too complex to be managed effectively by a single person. This condition is devastating not only physically, but also psychologically and for the family. Every difficult case must be discussed by a panel including a pain specialist, a neurologist, a paediatric psychiatrist, a physical medicine and rehabilitation physician, a bone disease specialist, a rheumatologist, a radiologist, a psychologist, a physical therapist, an occupational therapist, a nurse and a paediatric orthopaedic surgeon (Fig. 3). The surgeon plays a pivotal role in establishing the diagnosis and selecting treatment options [1–3].
13. Research priorities

As stated above, paediatric CRPS–I has been the focus of only very few high-quality studies. Randomized controlled trials are particularly scarce. Most of the available data come from case-reports or case-series, with a risk of publication bias and short follow-ups. Thus, researchers now face a blank slate.

Given the complexity of CRPS–I, multicentre recruitment to randomized controlled trials is crucial in order to achieve sufficient statistical power:

- studies in growing animals may provide insights into the mechanisms underlying paediatric CRPS–I;
- having the patient perform movements in front of a mirror has produced good results in adults. This technique deserves to be tested in paediatric patients, comparatively with conventional physiotherapy [21];
- randomized controlled trials of bisphosphonate therapy are important to perform, given the prompt efficacy of this approach in adults.

14. Conclusions

Published data on the management of CRPS–I are scarce and often of mediocre quality. Despite recent insights into possible pathophysiological mechanisms, the differences between paediatric and adult CRPS–I remain ill-defined. Furthermore, treatments that benefit adults are not necessarily effective in children.

A key point is establishing the diagnosis of CRPS–I early on. There is universal agreement that earlier treatment initiation is associated with a higher success rate and shorter treatment duration. Another favourable factor is multidisciplinary management at a referral centre that has a special interest in CRPS–I. Information campaigns are needed to raise awareness of these facts among paediatricians and general practitioners.

Current treatment recommendations are not supported by scientific evidence. Most centres advocate physical therapy and intensive CBT in combination with medications. TENS can also be extremely helpful. There is insufficient data to conclude about calcitonin and bisphosphonate treatment in paediatric CRPS–I. Studies of these drugs are urgently needed, as rapid and long-lasting benefits have been documented in adults. Decisions to use invasive treatments must be taken by a multidisciplinary panel and not by a single physician.

Disclosure of interest

The authors declare that they have no competing interest.

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