Complex regional pain syndrome in children: Asking the right questions

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BACKGROUND: Complex regional pain syndrome (CRPS) is a painful disorder without a known unifying mechanism. There are little data on which to base evaluation and treatment decisions, and what data are available come from studies involving adults; however, even that literature is relatively sparse. Developing robust research for CRPS in children is essential for the progress toward optimal treatment.

OBJECTIVES: To determine potential avenues of research in pediatric CRPS based on a review of the literature. Areas of concern include diagnostic criteria, peripheral mechanisms, central nervous system mechanisms, the role of the autonomic nervous system, possible risk factors, options for prevention and potential avenues of treatment.

METHODS: A literature review was performed and the results applied to form the hypotheses posited in the form of research questions.

RESULTS AND CONCLUSIONS: CRPS is a complicated entity that is more than a painful sensory condition. There is evidence for peripheral inflammatory and neurological changes, and reorganization in both sensory and motor cortices. In addition, a significant motor component is frequently observed and there appear to be tangible risk factors. Many of these pieces of evidence suggest options for prevention, treatment and monitoring progress and outcome. Most of the data are derived from adult studies and need to be replicated in children. Furthermore, there may be factors unique to pediatrics due to developmental changes in neuroplasticity as well as somatic, endocrinological and emotional growth. Some of these developmental factors may shed light on the adult condition.

Key Words: Complex regional pain syndrome; Pain; Pediatric; Review

Le syndrome douloureux régional complexe chez les enfants : poser les bonnes questions

HISTORIQUE : Le syndrome douloureux régional complexe (SDRC) est un trouble douloureux sans mécanisme unificateur connu. Il existe peu de données sur lesquelles fonder l'évaluation et les décisions thérapeutiques, et celles qui existent proviennent d'études sur des adultes. Cependant, même ces publications sont relativement rares. Il est essentiel de planifier des recherches solides sur le SDRC chez les enfants pour évoluer vers un traitement optimal.

OBJECTIFS : Déterminer les voies potentielles de la recherche sur le SDRC en pédiatrie d'après une analyse bibliographique. Les secteurs de préoccupation incluent les critères diagnostiques, les mécanismes périphériques, les mécanismes du système nerveux central, le rôle du système nerveux autonome, les facteurs de risque possibles, les possibilités de prévention et les possibilités de traitement.

MÉTHODOLOGIE : Les chercheurs ont procédé à une analyse bibliographique et utilisé les résultats pour énoncer des hypothèses présentées sous forme de questions de recherche.

RÉSULTATS ET CONCLUSIONS : Le SDRC est une entité complexe qui ne se limite pas à un trouble sensoriel douloureux. On remarque des modifications inflammatoires et neurologiques périphériques et une réorganisation des cortex sensoriels et moteurs. De plus, on remarque souvent un élément moteur important, sans compter la possibilité de facteurs de risque tangibles. Bon nombre de ces éléments laissent supposer des possibilités de prévention, de traitement et de surveillance des progrès et des issues. La plupart des données proviennent d'études menées chez les adultes et doivent être répliquées chez les enfants. De plus, certains facteurs pourraient être uniques à la pédiatrie en raison des changements développementaux de la neuroplasticité et de la croissance somatique, endocrinologique et émotionnelle. Certains de ces facteurs de développement jetteront peut-être la lumière sur le syndrome chez les adultes.

A growing body of literature amassed over the past decade underscores the complexity of an entity known as complex regional pain syndrome (CRPS). As in most painful conditions, the bulk of the investigations have been performed in the adult population; however, pediatric health care workers are tasked with evaluating and treating adolescents with CRPS. How do data acquired from patients 40 to 80 years of age apply to the pediatric population? Multidisciplinary interventions have received the most study, and have shown success; however, relapse rates are high (1). Few of the interventional and medication treatments routinely used in adults have been formally studied in pediatric patients. Viewing the condition in children and adolescents may provide a window into the mechanisms of neuroplasticity, cortical reorganization and peripheral mechanisms that appear to function so prominently in adults with CRPS. Furthermore, the study of CRPS in pediatric patients may shed light on genetic and other risk factors for the development of CRPS.

Several excellent reviews of the overall topic of CRPS have been published recently (2,3); therefore, the present review will focus on potential avenues of research in pediatric CRPS. Approaching the issue from the standpoint of potential mechanisms appears to be reasonable because there has only been speculation about a unifying pathophysiological mechanism. The following questions are addressed.

WHAT IS CRPS?

This is the obvious query. While CRPS is indeed complex, the regional aspect is less clear. Contributions to the symptom constellation come from the autonomic nervous system (ANS), the immune system, the central nervous system (CNS) and the peripheral nervous system, and involve motor as well as sensory system changes. These findings have been adequately summarized elsewhere (2,3). Collectively, these contributions speak to a more systemic disorder, although no unifying mechanism has yet been found. In fact, several pathophysiological syndromes with similar phenotypes may be in play and attempts at unification may, thus, be in vain. For practical purposes, it is useful to break down the mechanistic questions according to system or anatomical region. However, the bigger picture must be kept in mind as each of these pathways is dissected and analyzed.

How is CRPS diagnosed? Are the International Association for the Study of Pain criteria developed for adults useful in children? Do they

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have prognostic value? The lack of a unifying pathophysiology and means by which to measure it leave the criteria for diagnosis descriptive. The 1994 International Association for the Study of Pain criteria (4) and its updates (5) have become the most commonly used criteria for diagnosis. Attempts to validate the criteria have been made (6,7). However, such refinements and validation of criteria are of limited value, owing to the lack of a unifying mechanism to serve as a measurable 'gold standard'. For now, expert consensus and survey data are the best attempts to achieve uniformity of the patient population for both therapeutic and research purposes.

What are the relevant peripheral mechanisms?
Neurogenic inflammation has been speculated to play a role, at least in the earlier stages of CRPS development. Increased tissue levels of calcitonin gene-related peptide, substance P and tumour necrosis factor-alpha (TNF-α) have been found in several adult studies. Protein extravasation is observed to be increased under experimental conditions (8). Methodologies include creating blisters from which fluid is sampled and analyzed (9,10), and biopsies (11), with elevations in proinflammatory cytokines found for months to years after symptom onset (12). Furthermore, blood samples have shown elevations of a variety of cytokines and related inflammatory mediators (13-15). No similar studies have been performed in pediatric subjects, leaving open the question of the role of inflammation (neurogenic or otherwise) in pediatric CRPS.

Alterations in peripheral innervation have received some attention based on detailed, but very small, studies involving amputated limbs and biopsies (16,17). No data are available in children. Thus, do changes in peripheral innervation occur in children with CRPS, are they related to duration or severity of symptoms and are they permanent? As discussed below, reversal of CNS changes has been observed in correlation with clinical recovery, so a similar question can be asked for changes in the periphery (a question without answer in adults as well).

What role does the ANS play?
The phrase 'sympathetically maintained pain' has been used for many years, and is often considered to be synonymous with CRPS. Hence, sympathetic blocks have been a mainstay of treatment in adult CRPS for decades. However, not all patients with CRPS have prominent involvement of the ANS clinically, and many do not respond to interventions aimed at blockade of the sympathetic nervous system. The pain of these patients then is termed 'sympathetically independent pain'. However, there is evidence that the ANS is involved in ways beyond those related to direct sympathetic innervation. Circulating catecholamines are altered in adults with CRPS (18,19), although studies are limited in scope and interpretability. Enhanced peripheral adrenergic sensitivity has also been proposed based on studies in adults (20), but no studies exist in the pediatric population. Although pediatric patients often complain of ANS-related symptoms, such as dizziness and lightheadedness, tilt table testing has not confirmed autonomic dysfunction. Such symptoms appear to resolve with treatment (21). Adult CRPS presents with both warm and cold variants (22), whereas pediatric CRPS more commonly presents as a cool, cyanotic extremity (23,24). Questions centre on whether this relates to differences in ANS involvement (versus inflammatory factors) and how the answer to those questions then relates to treatment options. For example, although sympathetic nerve blocks have been used successfully in children on an anecdotal basis (25), current practice appears to rely more on multidisciplinary care with selective use of nerve blocks (26). A better understanding of the role of the ANS would allow evidence-based decisions to focus the use of the appropriate block (if any) for the appropriate patients.

What are the CNS mechanisms?
Myriad observations have been made in patients with CRPS that point toward a prominent CNS role. One of the most fascinating findings in CRPS research has been the description of cortical reorganization (27,28). This phenomenon is also observed in patients

with phantom limb pain (29), and is found in both adult and pediatric (30) CRPS patients. The reorganization occurs in both sensory and motor cortexes. The CNS response to peripheral stimulation can be measured by electroencephalography, electromagnetoencephalography and functional magnetic resonance imaging. These tools have been used to demonstrate that the sensory cortexes, both primary and secondary, functionally 'shrink' in CRPS. Notably, the reorganization largely reverses after treatment and alleviation of symptoms in adults (31). This finding correlates with similar findings in phantom limb pain (32). Of interest, the motor cortexes functionally enlarge in the presence of CRPS, and actually show bilateral changes (33). While the significance is not entirely clear, it is important that any unifying hypothesis accounts for changes in both sensory and motor systems. The question for pediatric investigators is: what is the relation between cortical reorganization – both motor and sensory – to the patients' sensory and motor symptoms, and what are the changes observed with therapy and resolution? Secondary questions relate to the CNS findings in patients who do not improve and the mechanisms for both initiation and resolution of the reorganization. What is the role and strength of neuroplasticity in children and can it be enhanced to improve outcomes? Furthermore, one could speculate about why CRPS is so rarely observed in prepubertal patients and whether there are hormonal or other influences in addition to those noted above.

Many adult patients appear to have decreased sensory discrimination capacity. For example, spatial targeting during reach and grasp tasks are impaired (34), as is two-point discrimination in the affected limb (35). The tactile impairment may correlate with central cortical changes as described above. Studies have shown a decreased ability to relearn two-point discrimination (36). Visual input appears to be important in modifying sensory perceptions, as demonstrated with mirror box experiments (37). What is fascinating is the ability to modify both normal (38) as well as abnormal sensations by use of visual feedback, leading to the use of mirror box therapy for CRPS (38,39), as has been used in phantom limb pain. The conceptual and physical challenges of this therapy to patients are minimal. In simplified form: patients place the affected extremity behind a mirror, so that all they see is their normal extremity and its reflection. They then move the normal limb while watching the reflection (providing visual symmetry) while mentally envisioning the painful limb moving the same way. Sessions are short and repeated daily over a period of weeks. If the neurophysiology of CRPS in children is similar to that in adults with CRPS and phantom limb pain, it is possible that mirror box therapy will help improve the rate of recovery in children.

Movement disorders occur with some frequency in both adult (40) and pediatric CRPS (41). In adults, there is a correlation between movement disorders and severity and younger age of onset which, interestingly, does not extrapolate to pediatric CRPS. That is, if movement disorders occur more frequently in younger adult patients, then logically children should experience a higher frequency than adults. However, there is no evidence of such a pattern; this lack of evidence could represent a true finding or may result from a difference in defining or documenting motor symptoms in children with CRPS. If a true observation, then one could ponder developmental differences in neuroplasticity, or inter-relationships between sensory and motor cortexes that may explain why motor symptoms are not seen more often.

Can we identify risk factors?
A number of potential risk factors have been explored in adults, although without conclusive evidence for any individual or group. Certain human lymphocyte antigen groups have been associated with CRPS (42-44); in addition, CRPS has been identified in familial clusters (45). A history of migraine headaches has also been associated with CRPS (46,47); given the relative frequency of migraines in adolescents (48) it would appear straightforward to assess this association in pediatric patients. Furthermore, the simple observation that CRPS is observed overwhelmingly in Caucasian children (49) suggests

genetic factors on a broad level. Careful family histories could identify familial clustering, with the potential for blood or tissue samples to be gathered for genetic analysis, which may lead to greater understanding of the role of genetic predispositions in the development of CRPS.

What are the best treatments in pediatric CRPS patients?
Interdisciplinary treatment programs are believed to be the ideal treatment for CRPS. However, the recurrence rate is high and a significant number of patients do not achieve full resolution of their symptoms (1,24,50,51). While data are being generated to form a unifying hypothesis that could guide diagnosis and treatment, it would be unethical not to treat patients in the meantime. Unfortunately, many CRPS treatments are based on scant evidence or on anecdotal evidence (even if dressed up as 'expert consensus'). Because there are data that suggest that pediatric and adult CRPS are more similar than once believed (51), extrapolation from adult findings may yield evidence to guide therapy in children. Therapeutic questions focus on five major areas.

What is the ideal medication treatment?: Medication use has been based on extrapolation from adult literature and from application of theory. Assuming CRPS to be a neuropathic pain condition, practitioners gravitate toward use of medications such as amitriptyline, gabapentin and oxcarbazepine. However, as more is learned about the role of cytokines, neuropeptides and the CNS, it is time to consider whether other medications, such as immunomodulatory agents and N-methyl-D-aspartate antagonists, may have a role. Furthermore, as more is learned about the physiological progression of CRPS (1,24,52), it will be important to study the use of agents that may act at specific steps in that progression, so that patients who present at varying points in the evolution of their CRPS can undergo targeted therapy.

What psychological therapies are appropriate?: Early suggestions of a psychological profile that is typical of CRPS patients have not been supported by more recent literature (53,54). There appears to be no association between a diagnosis of CRPS and depression, anxiety, obsessive-compulsive traits or a variety of other psychological characteristics. However, it is clear that cognitive-behavioural therapies have a role. Certainly, the literature is reasonably robust for other pediatric pain conditions such as abdominal pain, headaches and fibromyalgia (55-57), with reductions in pain and improvement in coping and level of function. The optimal psychological approach is a fertile area for study.

What should the role of physical therapy be, including the role for mirror box therapy?: Of the therapies that have been studied, physical therapy (PT) appears to have as much supportive evidence for efficacy as anything presently offered (1,24,52). Unfortunately for scientific purity, PT has not been studied in isolation, but as part of interdisciplinary care (which is the standard practice for pediatric CRPS). As mentioned above, mirror visual feedback (also known as mirror box therapy) has mounting evidence to support its use in adults. Can this therapy help children? If so, it would represent a much less distressing therapy than the current PT regimen that focuses on intensive desensitization and motor activities. The current PT interventions are not standardized due to lack of evidence, and how to refine this group of therapies continues to be an open question.

Does interventional therapy have a role and, if so, for which subset of patients?: Certainly, the cornerstone of CRPS therapy in adults has been neural blockade, especially that of the sympathetic nervous system. As has been shown, CRPS is a pain disorder that involves much more than the ANS. On the other hand, there is evidence in both adults and children that both somatic blocks and sympathetic blocks may be helpful in pediatric CRPS (25,58). It would be useful to derive criteria to determine which patients would benefit from which type of block, and combination with which therapeutic regimen. Limited data suggest that hypoesthesia and allodynia are negative predictors of success with sympathetic blockade (59), but positive predictors will also be needed. The data would then determine the role for these interventions in pediatric patients.

Is there need for preventive measures?
Vitamin C has been used to reduce the incidence of CRPS in adults with fracture and orthopedic surgeries (60-62). Without solid data regarding the incidence of CRPS in children, judging the need for routine use of vitamin C or other pre-emptive treatments is not feasible. Interestingly, differences in tissue TNF-α levels have been observed in skin biopsies from adults who have CRPS and patients with acute fractures compared with osteoarthritis patients; however, serum levels were higher in CRPS and osteoarthritis patients than patients with acute fractures (11). The authors suggest that biopsies may be useful in determining whether immunological interventions could be targeted to patients with elevations of TNF-α. The concept of determining risk factors and measurable guides to therapy is important. So, the two questions suggested are: is the rate of CRPS high enough to warrant preventive measures after fractures or orthopedic surgery and, if so, are there risk markers that can be used to guide pre-emptive interventions?

What are the long-term outcomes?
As mentioned, there is a substantial relapse rate and an incomplete cure rate for pediatric CRPS. Outcomes have included pain levels, functional capacity and ANS symptoms and signs. There have been no methodologically sound, long-term studies of outcome in children. Do children with a history of CRPS have a higher risk for repeat occurrence as adults? What happens to children whose symptoms do not resolve? Many of these patients are 'lost to follow-up' because frustration with failed therapies leads patients and families to look elsewhere for a cure. An early observation was that younger patients tended to have better resolution (24). Future research should include observation of age or developmental effects prognosis.

What are the challenges in pediatric CRPS research?
This key question underlies all others. The issues are multiple. There appear to be many fewer patients in the pediatric population from which to draw subjects, leading to issues of sample size, study design and recruitment. The length of time needed to follow patients before drawing conclusions regarding rates of resolution and recurrence is unknown. General concepts within pediatric research include those of consent and assent. A uniquely pediatric question is, 'What are the effects of long-term medication use on developing nervous systems?' From an ontological perspective, one must ask, 'Are there diagnostic changes that occur over time? Are the criteria for diagnosis truly the same as for adults, or are there factors and criteria that should change with physical, endocrinological, neurodevelopmental and social growth?'

CRPS is certainly complex, and is much more than a regional disorder. The past decade featured a number of fascinating and illuminating studies, predominantly involving adults. There are many similarities between adult and pediatric CRPS; however, there is potentially much to learn from ontological and neuroplasticity differences. Pediatric researchers and clinicians have benefited from the study of adult patients. The question is now, 'Can we return the favour?'

REFERENCES
1. Lee BH, Scharff L, Sethna NF, et al. Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. J Pediatr 2002;141:135-40.
2. Bruehl S. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology 2010;113:713-25.
3. Marinus J, Moseley GL, Birklein F, et al. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10:637-48.
4. Merskey H, Bogduk N, International Association for the Study of Pain. Task Force on Taxonomy. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms, 2nd edn. Seattle: IASP Press; 1994.
5. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8:326-31.

6. Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain 1999;81:147-54.

7. Harden RN, Bruehl S, Perez RS, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. Pain 2010;150:268-74.

8. Weber M, Birklein F, Neundorfer B, Schmelz M. Facilitated neurogenic inflammation in complex regional pain syndrome. Pain 2001;91:251-7.

9. Huygen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm 2002;11:47-51.

10. Huygen FJ, Ramdhani N, van Toorenenbergen A, Klein J, Zijlstra FJ. Mast cells are involved in inflammatory reactions during complex regional pain syndrome type 1. Immunol Lett 2004;91:147-54.

11. Kramer HH, Eberle T, Uceyler N, et al. TNF-alpha in CRPS and 'normal' trauma: Significant differences between tissue and serum. Pain 2011;152:285-90.

12. Munnikes RJ, Muis C, Boersma M, Heijmans-Antonissen C, Zijlstra FJ, Huygen FJ. Intermediate stage complex regional pain syndrome type 1 is unrelated to proinflammatory cytokines. Mediators Inflamm 2005;2005:366-72.

13. Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. Neurology 2001;57:2179-84.

14. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Mechanical hyperalgesia in complex regional pain syndrome: A role for TNF-alpha? Neurology 2005;65:311-3.

15. Schinkel C, Gaertner A, Zaspel J, Zedler S, Faist E, Schuermann M. Inflammatory mediators are altered in the acute phase of posttraumatic complex regional pain syndrome. Clin J Pain 2006;22:235-9.

16. Albrecht PJ, Hines S, Eisenberg E, et al. Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. Pain 2006;120:244-66.

17. Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). Pain 2006;120:235-43.

18. Harden RN, Duc TA, Williams TR, Coley D, Cate JC, Gracely RH. Norepinephrine and epinephrine levels in affected versus unaffected limbs in sympathetically maintained pain. Clin J Pain 1994;10:324-30.

19. Harden RN, Rudin NJ, Bruehl S, et al. Increased systemic catecholamines in complex regional pain syndrome and relationship to psychological factors: A pilot study. Anesth Analg 2004;99:1478-85.

20. Arnold JM, Teasell RW, MacLeod AP, Brown JE, Carruthers SG. Increased venous alpha-adrenoceptor responsiveness in patients with reflex sympathetic dystrophy. Ann Intern Med 1993;118:619-21.

21. Meier PM, Alexander ME, Sethna NF, De Jong-De Vos Van Steenwijk CC, Zurakowski D, Berde CB. Complex regional pain syndromes in children and adolescents: Regional and systemic signs and symptoms and hemodynamic response to tilt table testing. Clin J Pain 2006;22:399-406.

22. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. Lancet 1993;342:1012-6.

23. Tan EC, Zijlstra B, Essink ML, Goris RJ, Severijnen RS. Complex regional pain syndrome type I in children. Acta Paediatr 2008;97:875-9.

24. Wilder RT, Berde CB, Wolohan M, Vieyra MA, Masek BJ, Micheli LJ. Reflex sympathetic dystrophy in children. Clinical characteristics and follow-up of seventy patients. J Bone Joint Surg Am 1992;74:910-9.

25. Meier PM, Zurakowski D, Berde CB, Sethna NF. Lumbar sympathetic blockade in children with complex regional pain syndromes: A double blind placebo-controlled crossover trial. Anesthesiology 2009;111:372-80.

26. Berde CB, Lebel A. Complex regional pain syndromes in children and adolescents. Anesthesiology 2005;102:252-5.

27. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology 2003;61:1707-15.

28. Vartiainen NV, Kirveskari E, Forss N. Central processing of tactile and nociceptive stimuli in complex regional pain syndrome. Clin Neurophysiol 2008;119:2380-8.

29. Flor H, Nikolajsen L, Staehelin Jensen T. Phantom limb pain: A case of maladaptive CNS plasticity? Nat Rev Neurosci 2006;7:873-81.

30. Lebel A, Becerra L, Wallin D, et al. fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children. Brain 2008;131:1854-79.

31. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. Neurology 2004;63:693-701.

32. Birbaumer N, Lutzenberger W, Montoya P, et al. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci 1997;17:5503-8.

33. Schwenkreis P, Janssen F, Rommel O, et al. Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. Neurology 2003;61:515-9.

34. Maihofner C, Baron R, DeCol R, et al. The motor system shows adaptive changes in complex regional pain syndrome. Brain 2007;130:2671-87.

35. Pleger B, Ragert P, Schwenkreis P, et al. Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome. Neuroimage 2006;32:503-10.

36. Maihöfner C, DeCol R. Decreased perceptual learning ability in complex regional pain syndrome. Eur J Pain 2007;11:903-9.

37. Acerra NE, Moseley GL. Dysynchiria: Watching the mirror image of the unaffected limb elicits pain on the affected side. Neurology 2005;65:751-3.

38. McCabe CS, Haigh RC, Halligan PW, Blake DR. Simulating sensory-motor incongruence in healthy volunteers: Implications for a cortical model of pain. Rheumatology (Oxford) 2005;44:509-16.

39. Moseley GL. Graded motor imagery for pathologic pain: A randomized controlled trial. Neurology 2006;67:2129-34.

40. van Hilten JJ. Movement disorders in complex regional pain syndrome. Pain Med. 2010;11:1274-7.

41. Agrawal SK, Rittey CD, Harrower NA, Goddard JM, Mordekar SR. Movement disorders associated with complex regional pain syndrome in children. Dev Med Child Neurol 2009;51:557-62.

42. de Rooij AM, Florencia Gosso M, Haasnoot GW, et al. HLA-B62 and HLA-DQ8 are associated with complex regional pain syndrome with fixed dystonia. Pain 2009;145:82-5.

43. van de Beek WJ, Roep BO, van der Slik AR, Giphart MJ, van Hilten BJ. Susceptibility loci for complex regional pain syndrome. Pain 2003;103:93-7.

44. van Hilten JJ, van de Beek WJ, Roep BO. Multifocal or generalized tonic dystonia of complex regional pain syndrome: A distinct clinical entity associated with HLA-DR13. Ann Neurol 2000;48:113-6.

45. de Rooij AM, de Mos M, Sturkenboom MC, Marinus J, van den Maagdenberg AM, van Hilten JJ. Familial occurrence of complex regional pain syndrome. Eur J Pain 2009;13:171-7.

46. de Mos M, Huygen FJ, Dieleman JP, Koopman JS, Stricker BH, Sturkenboom MC. Medical history and the onset of complex regional pain syndrome (CRPS). Pain 2008;139:458-66.

47. Peterlin BL, Rosso AL, Nair S, Young WB, Schwartzman RJ. Migraine may be a risk factor for the development of complex regional pain syndrome. Cephalalgia 2010;30:214-23.

48. Hershey AD. Pediatric headache: Update on recent research. Headache 2012;52:327-32.

49. Wilder RT. Management of pediatric patients with complex regional pain syndrome. Clin J Pain 2006;22:443-8.

50. Logan DE, Carpino EA, Chiang G,et al. A day-hospital approach to treatment of pediatric complex regional pain syndrome: Initial functional outcomes. Clin J Pain 2012. Epub online ahead of print.

51. Stanton-Hicks M. Plasticity of complex regional pain syndrome (CRPS) in children. Pain Med 2010;11:1216-23.

52. Perez RS, Zollinger PE, Dijkstra PU, et al. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol 2010;10:20.

53. Beerthuizen A, Stronks DL, Huygen FJ, Passchier J, Klein J, Spijker AV. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1): A prospective multicenter study. Eur J Pain 2011;15:971-5.

54. de Mos M, Sturkenboom MC, Huygen FJ. Current understandings on complex regional pain syndrome. Pain Pract 2009;9:86-99.

55. Kashikar-Zuck S, Ting TV, Arnold LM, et al. A randomized clinical trial of cognitive behavioral therapy for the treatment of juvenile fibromyalgia. Arthritis Rheum 2012;64:297-305.

56. Palermo TM, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. Pain 2010;148:387-97.

57. Robins PM, Smith SM, Glutting JJ, Bishop CT. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. J Pediatr Psychol 2005;30:397-408.

58. Dadure C, Motais F, Ricard C, Raux O, Troncin R, Capdevila X. Continuous peripheral nerve blocks at home for treatment of recurrent complex regional pain syndrome I in children. Anesthesiology 2005;102:387-91.

59. van Eijs F, Geurts J, van Kleef M, et al. Predictors of pain relieving response to sympathetic blockade in complex regional pain syndrome type 1. Anesthesiology 2012;116:113-21.

60. Besse JL, Gadeyne S, Galand-Desme S, Lerat JL, Moyen B. Effect of vitamin C on prevention of complex regional pain syndrome type I in foot and ankle surgery. Foot Ankle Surg 2009;15:179-82.

61. Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: A randomised trial. Lancet 1999;354:2025-8.

62. Zollinger PE, Unal H, Ellis ML, Tuinebreijer WE. Clinical results of 40 consecutive basal thumb prostheses and no CRPS type I after vitamin C prophylaxis. Open Orthop J 2010;4:62-6.