Special Interest Group on Pain in Childhood
INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN

Pediatric Pain Letter
Commentaries on pain in infants, children, and adolescents

February 2021 **Vol. 23 No. 1** **www.childpain.org/ppl**

Editor: Deirdre E. Logan, PhD, deirdre.logan@childrens.harvard.edu

Associate Editor: Abbie L. Jordan, PhD, a.l.jordan@bath.ac.uk

© 2021, Special Interest Group on Pain in Childhood, International Association for the Study of Pain®

Commentary

Diagnostic delay in pediatric complex regional pain syndrome (CRPS): Current problem and potential solutions

Giulia Mesaroli, Geraldine Cullen-Dean, Catherine Munns, and Stephen Brown

Complex regional pain syndrome (CRPS) is a severely painful condition typically in the distal region of a limb. It commonly occurs after minor trauma, for which the pain is disproportionate to the extent of tissue damage (Nicholas et al., 2019). Further to pain, an array of symptoms are usually present including abnormalities in sensation, vasomotor, motor, and autonomic dysfunction (Marinus et al., 2011). The pathophysiology is complex with a number of purported contributing factors including neurogenic inflammation, maladaptive plasticity, sensitization of nociceptors and vasomotor dysfunction (Marinus et al., 2011).

In children, CRPS is a rare disease and affects predominately females (85%) with an average age of onset 12 years, and typically occurs in the lower extremity (Abu-Arafeh & Abu-Arafeh, 2017). Gold standard treatment is an interdisciplinary approach combining pharmacology, physical and psychological therapies (Ayling Campos et al., 2011; Borucki & Greco, 2015). Key outcomes of treatment are focused on function, rather than pain, with a specific focus on physical, sleep, social and emotional function (McGrath et al., 2008; Grieve et al., 2017). Early diagnosis and treatment of CRPS is thought to improve functional outcomes and prevent secondary complications, disability and psychological distress (Schürmann et al., 2007; de Mos et al., 2009; Lee & Nandi, 2011; Breivik & Stubhaug, 2016; Weissmann & Uziel, 2016). The International Association for the Study of Pain (IASP) recommends a 1-week wait-time for people referred to pain clinics with suspected CRPS, in an effort to expedite treatments (Collett et al., 2011). However, facilitating early diagnosis and treatment is challenging with long wait-times and limited resources in pain clinics.

Current problem

CRPS in children can be particularly challenging to diagnose for a number of reasons. First, CRPS manifests not only as severe pain, but an array of symptoms that can vary from child to child (Marinus et al., 2011). One child can present with sensitivity to touch and color changes, and another with predominant swelling and motor dysfunction. This presentation, although recognisable to a pediatric pain specialist, can be confusing for other clinicians (novice clinicians, primary care providers or other subspecialists). This may lead clinicians down a path of medical investigations instead of diagnosing CRPS and initiating appropriate referrals or treatments.

Second, there is no gold standard radiological, laboratory or genetic test for CRPS. A number of clinical criteria have been developed over time, with the Budapest Criteria endorsed as the superior tool for adults with CRPS (Harden et al., 2010). No diagnostic tools have been validated for use in pediatric CRPS, and is therefore often based on clinical judgment (Borucki & Greco, 2015; Mesaroli et al., in press). Given the subjective nature of diagnosis, CRPS is sometimes incorrectly thought to be a diagnosis of exclusion, leading to

diagnostic delay while other pathologies are investigated. Differential diagnoses of CRPS are broad and include orthopedic conditions (ligament sprains, fracture), neurological disorders (peripheral or central neuropathies), rheumatic (Raynaud's), infectious, vascular and psychiatric disorders (somatoform disorders; Borucki & Greco, 2015).

Third, pediatric CRPS seems to be distinct from adult CRPS. Some studies indicate that some symptoms of CRPS, particularly trophic changes, are relatively rare in children (Mesaroli et al., 2019). Other studies suggest pediatric CRPS is milder than adult CRPS, and the diagnostic threshold should be lowered in this population (Evans, 1946; Low et al., 2007; Friedrich et al., 2019). As a result, significant expertise is needed to evaluate the clinical features of CRPS in children.

Potential harms of diagnostic delay in children with CRPS

Treatment delays can result in secondary complications (e.g. muscle wasting and contractures) as well as psychological distress for the child and family. However, very few studies have examined this association between time-to-treatment and disease outcomes in adult (Bean et al., 2014; Lunden et al., 2016; Zych-Litwin & Litwin, 2019) or pediatric patients with CRPS (Kachko et al., 2008; Mesaroli et al., 2019). These studies are limited by small sample sizes, retrospective designs with a lack of standardized approach to defining outcomes. A 2014 systematic review (Bean et al., 2014) suggests many adults with CRPS experience symptom resolution between 6-13 months, and perhaps early diagnosis and treatment may be correlated with earlier symptom resolution. Qualitative research in children with a variety of chronic pain disorders has explored the impact of diagnostic uncertainty, citing families may feel something has been missed, seek alternative diagnoses and develop mistrust for the medical system (Neville et al., 2019).

Implications for clinical practice

Given the various factors that may perpetuate diagnostic delay, and knowing some of the potential consequences for children, pediatric pain experts must find creative solutions to facilitate rapid access to specialists. This may include interventions at the clinic level (i.e. reducing clinic wait times), at the organization level (i.e. educating referring providers regarding the importance of early referrals alongside ongoing investigations) or community-outreach (i.e. educating primary care providers on CRPS so they can more easily identify and initiate front-line treatments). Below is a case study of a clinic-level intervention, a rapid access clinic for pediatric CRPS-1 aimed at reducing wait-times for children with suspected CRPS.

A potential solution? Case study of a novel rapid access clinic for CRPS

The Chronic Pain Clinic at The Hospital for Sick Children in Toronto, Canada, implemented the Rapid Access Clinic (RAC) for pediatric CRPS. This novel clinical model aimed to reduce wait-times for interprofessional assessment, diagnosis, physical and psychological therapy. Quality improvement evaluation also aimed to evaluate the feasibility and acceptability. Clinic description: Patients referred to our center with suspected CRPS underwent a rapid triage process, interprofessional assessment (including an anesthesiologist, clinical nurse specialist, physiotherapist and psychologist), and rapid access to treatments. Nursing and administrative staff adapted their workflows to identify electronic referrals early; this included modifications to the referral form and Epic (Epic Systems Software, Verona, WI) workflow. Interprofessional assessment mirrored that of the typical clinic assessment (90 minutes), and included patient interview, physical examination, diagnosis and treatment recommendations. Assessments were held on non-clinic days, or as an add-on to clinic days. Results: Between April 2019 and March 2020, 24 patients were referred to the RAC. Two patients were lost to follow-up (unable to contact the family), two patients declined an appointment (family preference to pursue further medical investigations), and three were deemed inappropriate after nursing triage, and instead were rerouted to the Chronic Pain Clinic. Reason for referrals deemed inappropriate include significant mental illness requiring psychiatric consultation, which was not available in the RAC. A total of 17 patients attended the RAC within this time-period. See Table 1 below

Table 1
Summary of mean wait-times* for patients referred (N=24) to the Rapid Access Clinic

Assessment or treatment	n	Wait time, mean (days)	Wait time, range (days)	Definition of wait-time
Nursing triage	24	4.3	0 - 21	Number of days between referral and triage decision (accept or decline)
Rapid access clinic	17	12.5	1 - 41	Number of days between referral and RAC appointment
Physiotherapy**	14	9.5	0 - 35	Number of days between RAC appointment and first physiotherapy visit
Psychology**	10	13.6	6 - 35	Number of days between RAC appointment and first psychology visit

*Wait-times include weekend days; clinical services were provided Monday-Friday.
**Services provided within the Chronic Pain Clinic; community-based services were not included.

for a summary of wait-times for nursing triage, assessment, and treatments. Data obtained from patient and family satisfaction surveys and staff focus groups yielded highly positive results. Staff reported challenges including administrative and scheduling barriers, in particular coordinating schedules of clinicians in a timely manner.

Implications for research

Further research is needed to understand whether there is a relationship between time-to-diagnosis and outcomes in pediatric CRPS. Prospective observational cohort studies are ideal given experimental designs are impossible to answer this question, as one cannot ethically randomize patients to long wait-times. Observational studies can analyze time-to-diagnosis as a continuous predictor variable and explore relationships with outcome variables such as pain or function. In addition to assessing this potential relationship, research is needed to evaluate the outcomes of any intervention aimed at facilitating early diagnosis. In the case where a change in practice is implemented, such as the Rapid Access Clinic described above, research studies can measure and analyze pre-post patient-related outcomes. Between-group comparisons (age and sex-matched) would be particularly valuable, for example, comparing outcomes between patients who were seen before and after the change in practice was implemented. Given CRPS is a rare disease in children, future research will need to harness multicenter partnerships to pool data using a core outcome set (McGrath et al., 2008); this partnership would be best facilitated through a formal research collaboration with international pediatric pain clinics. Future studies will inform pediatric pain clinics' existing models of care, support advocacy for financial resources to reduce wait-times and aid governmental and healthcare organizations in their decision-making.

Conclusion

Children with CRPS may be subject to diagnostic delay due to its rare prevalence, complexity of presentation, lack of standardized approach to diagnosis, and long wait-times in pain clinics. Clinical expertise suggests early intervention may lead to a more favorable outcome, although this remains largely unstudied. Future research is needed to evaluate the association between time-to-diagnosis and disease outcomes. In the meantime, clinicians are faced with implementing creative solutions to facilitate early diagnosis and meet the IASP standards for wait-times.

Giulia Mesaroli, MScPT
Department of Rehabilitation, The Hospital for Sick Children and Department of Physical Therapy, University of Toronto, Toronto, ON, Canada
email: giulia.mesaroli@sickkids.ca

Geraldine Cullen-Dean, RN, MN
Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada

Catherine Munns, PsyD, CPsych
Department of Anesthesia and Pain Medicine and Department of Psychology, The Hospital for Sick Children, Toronto, ON, Canada

Stephen Brown, MD, FRCPC
Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada

Acknowledgement

We would like to acknowledge Susan Lawless and Kara Manning for their administrative assistance with the Rapid Access Clinic. Mesaroli was supported by a Frederick Banting and Charles Best Canada Graduate Scholarship (CGS-M) from CIHR and a Clinician Scientist Training Program Scholarship from The Hospital for Sick Children.

References

Abu-Arafeh H, Abu-Arafeh I. Complex regional pain syndrome in children: a systematic review of clinical features and movement disorders. Pain Manag 2017;7:133-140. www.pubmed.gov/28142335

Ayling Campos A, Amaria K, Campbell F, McGrath PA. Clinical impact and evidence base for physiotherapy in treating childhood chronic pain. Physiother Can 2011;63:21-33. www.pubmed.gov/22210976

Bean DJ, Johnson MH, Kydd RR. The outcome of complex regional pain syndrome type 1: a systematic review. J Pain 2014;15:677-690. www.pubmed.gov/24530407

Borucki AN, Greco CD. An update on complex regional pain syndromes in children and adolescents. Curr Opin Pediatr 2015;27:448-452. www.pubmed.gov/26087424

Breivik H, Stubhaug A. Importance of early diagnosis of complex regional pain syndrome (CRPS-1 and CRPS-2): delayed diagnosis of CRPS is a major problem. Scand J Pain 2016;11:49-51. www.pubmed.gov/28850469

Collett B, Haanpää M, Kamel C, Lynch M, Rajagopal R, Sessle B, et al. International Association for the Study of Pain Task Force on Wait-Times: summary and recommendations, 2011. www.iasp-pain.org/files/Content/NavigationMenu/EducationalResources/IASP_Wait_Times.pdf

de Mos M, Huygen FJPM, van der Hoeven-Borgman M, Dieleman JP, Ch Stricker BH, Sturkenboom MCJM. Outcome of the complex regional pain syndrome. Clin J Pain 2009;25:590-597. www.pubmed.gov/19692800

Evans JA. Reflex sympathetic dystrophy. Surg Clin North Am 1946;26:780-790.

Friedrich Y, Zurakowski D, Sieberg CB, Logan DE, Sethna N. Evaluation of the Budapest Criteria. Poster presented at the International Symposium on Pediatric Pain, Basel, Switzerland, June 2019.

Grieve S, Perez RSGM, Birklein F, Brunner F, Bruehl S, Harden, RN, et al. Recommendations for a first Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies (COMPACT). Pain 2017;158:1083-1090. www.pubmed.gov/28178071

Harden RN, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. Pain 2010;150:268-274. www.pubmed.gov/20493633

Kachko L, Efrat R, Ben Ami S, Mukamel M, Katz J. Complex regional pain syndromes in children and adolescents. Pediatr Int 2008;50:523-527. www.pubmed.gov/19143976

Lee J, Nandi P. Early aggressive treatment improves prognosis in complex regional pain syndrome. Practitioner 2011;255:23-26. www.pubmed.gov/21370711

Low AK, Ward K, Wines AP. Pediatric complex regional pain syndrome. J Pediatr Orthop 2007;27:567-572. www.pubmed.gov/17585269

Lunden LK, Kleggetveit IP, Jørum E. Delayed diagnosis and worsening of pain following orthopedic surgery in patients with complex regional pain syndrome (CRPS). Scand J Pain 2016;11:27-33. www.pubmed.gov/28850465

Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery WS, et al. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10:637-648. www.pubmed.gov/21683929

McGrath PJ, Walco GA, Turk DC, Dworkin RH, Brown MT, Davidson K, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 2008;9:771-783. www.pubmed.gov/18562251

Mesaroli G, Hundert A, Birnie KA, Campbell F, Stinson JN. Screening and diagnostic tools for complex regional pain syndrome: a systematic review. Pain, in press. www.pubmed.gov/33230004

Mesaroli G, Ruskin D, Campbell F, Kronenberg S, Klein S, Hundert A, et al. Clinical features of pediatric complex regional pain syndrome: a 5-year retrospective chart review. Clin J Pain 2019;35:933-940. www.pubmed.gov/31490205

Neville A, Jordan A, Beveridge JK, Pincus T, Noel M. Diagnostic uncertainty in youth with chronic pain and their parents. J Pain 2019;20:1080-1090. www.pubmed.gov/30904516

Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain 2019;160:28-37. www.pubmed.gov/30586068

Schürmann M, Gradl G, Rommel O. Early diagnosis in post-traumatic complex regional pain syndrome. Orthopedics 2007;30:450-456. www.pubmed.gov/17598489

Weissmann R, Uziel Y. Pediatric complex regional pain syndrome: a review. Pediatr Rheumatol Online J 2016;14:29. www.pubmed.gov/27130211

Zych-Litwin C, Litwin JA. Complex regional pain syndrome: diagnosis and treatment at the very onset as the key to success? A case report with implications for first contact doctors. Reumatologia 2019;57:117-119. www.pubmed.gov/31130751