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The risk of pain syndrome affecting a previously non-painful limb following trauma or surgery in patients with a history of complex regional pain syndrome

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HIGHLIGHTS

- Chronic regional pain syndrome (CRPS) is a challenging complication after surgery or trauma.
- Among patients with a history of CRPS, rates of recurrent CRPS in a second extremity were evaluated.
- This rate was compared to general population incidence as reported in the literature.
- It was also compared to reported rates of CRPS after distal radius fracture.
- Patients with a history of CRPS may be at increased risk for CRPS in a second extremity.

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ABSTRACT

Background and purpose: Complex regional pain syndrome (CRPS) is a challenging complication after surgery or trauma. This study sought to determine the incidence of CRPS after a second inciting event in a previously unaffected extremity in patients with a history of an ongoing CRPS diagnosis in another extremity.
Methods: A retrospective review identified patients with CRPS seen in clinic over a 20-month period. The incidence of CRPS after subsequent surgery or injury in a previous unaffected extremity was determined and compared to an average incidence reported in the literature.
Results: Ninety-three patients had a diagnosis of primary CRPS. Nineteen (20.4%) developed CRPS in one or more additional extremity compared to the incidence of 23.4 per 100,000 (0.0234%) in the literature (odds ratio 1069.6, $p < 0.0001$, 95% CI 562.0–2035.7). Twenty patients had a documented secondary injury or surgery in a second extremity. Fifteen (75%) developed secondary CRPS compared to a CRPS incidence rate of 6.4% following distal radius fracture, as determined by literature review (odds ratio 11.7, $p < 0.001$, 95% CI 5.9–23.2).
Conclusions: These result suggest that patients with a history of CRPS are more likely to develop secondary CRPS compared to the rates reported in the literature among the general population.
Implications: Patients with a history of CRPS should be counselled that they may be at risk for developing secondary CRPS if they undergo surgery or sustain trauma to another extremity.

1. Introduction

Complex regional pain syndrome (CRPS) is a challenging condition, defined as pain, functional impairment, autonomic dysfunction and vasomotor abnormalities often occurring in the extremities. Initiated in the periphery, CRPS has functional and central nervous system implications. It is well known that CRPS frequently occurs as the sequelae of a trauma or surgical procedure. Knowledge of the symptoms and signs with which a patient with

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Table 1
IASP CRPS diagnostic criteria.

1. Continuing pain, which is disproportionate to any inciting event
2. 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 colour changes and/or skin colour asymmetry
• *Sudomotor/oedema*: reports of oedema 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)
3. 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 colour changes and/or asymmetry
• *Sudomotor/oedema*: evidence of oedema and/or sweating changes and/or sweating asymmetry
4. There is no other diagnosis that better explains the signs and symptoms.

CRPS may present is critical; CRPS is a clinical diagnosis with no pathognomonic test or examination finding. The most cited diagnostic criteria are the International Association of the Study of Pain (IASP) "Budapest criteria" (Table 1) [1]. This classification includes a spectrum of patient symptoms and physical exam findings which may lead to the diagnosis but requires that the pain be out of proportion to the inciting event with no other identifiable cause or diagnosis.

While the exact incidence and prevalence of CRPS remains unknown, several studies have sought to provide an estimate with a reported incidence ranging from 20.6 to 26.2 cases per 100,000 person years [2,3]. Further research has been focused on the incidence of CRPS following specific injuries and surgeries. An incidence rate of 1.1–34.6% has been reported following distal radius fracture [4,21] and 25–30% following tibial fractures [5,22,23]. Common injuries and elective surgeries, including carpal tunnel release, fasciectomy for Dupuytren's contracture and fractures of the distal radius are associated with subsequent CRPS [24,25].

It has been postulated that there is increased potential risk of CRPS spreading to a previously unaffected extremity after new traumatic insult such as a surgical procedure in a patient with a known history of CRPS. However, the exact risk of CRPS spreading remains unknown. The potential importance of this information to those treating patients with a history of CRPS is clear. Patients presenting with new extremity injuries or requiring surgery on another extremity may benefit from preventative therapy or early intervention if signs of secondary CRPS develop. When deciding whether to proceed with any elective extremity surgery, knowledge of and proper counselling about the possible increased risk of secondary CRPS would be beneficial. This retrospective study evaluates the hypothesis that patients with a history of CRPS are more likely to develop secondary CRPS in another extremity following subsequent surgery or injury. It also evaluates the potential importance of prophylactic care, increased vigilance and early sympatholytic intervention.

2. Methods

An Institutional Review Board-approved, retrospective review was conducted to identify patients presenting to our institution's Orthopaedic Surgery clinic with a diagnosis of CRPS over a 20-month period from September 2012 to June 2014. This included both patients who developed CRPS after an injury for which they were being treated at our institution and those referred specifically for management of already existing CRPS. Potential study patients were identified using the International Classification of Disease (ICD-9) codes for complex regional pain syndrome/causalgia (352.2 and 355.71), algoneurodystrophy (733.7) and reflex sympathetic dystrophy (337.20, 337.21 and 337.22). All available patient records were reviewed to determine whether patients had documented signs and symptoms consistent with a diagnosis of CRPS based on the IASP "Budapest criteria." Only patients meeting these criteria were included in the study.

Table 2
Patient demographics.

Characteristic	Value (*n*)
Sex	
Male	25.8% (24)
Female	74.2% (69)
Age (years)	41.4
Body mass index	29.3
Diabete mellitus	12.9% (12)
Current tobacco use	26.9% (25)

2.1. Demographics

Demographic characteristics of study patients were documented including: age, sex, body mass index, medical comorbidities, current tobacco use and hand-dominance. Details including the extremity involved, aetiology of the inciting incident and classification of Type I or II CRPS diagnosis were noted, as well as subsequent treatment modalities and length of follow-up. All notes available in our electronic medical record system were reviewed to determine if the patient incurred a documented subsequent surgery or traumatic injury to another extremity. Details regarding any subsequent diagnosis of CRPS were recorded, again utilizing the "Budapest criteria" to confirm this diagnosis. For the purpose of this study, patients were considered as having developed "secondary" CRPS if this subsequent diagnosis occurred in a second, previously unaffected extremity.

2.2. General population incidence of CRPS

Based on PubMed search, a reported range of CRPS incidence rates in population-based studies was identified. An average incidence rate was utilized to compare to that seen in our study population. A second literature review was conducted to identify articles reporting the incidence of CRPS following distal radius fracture, a common and well-researched orthopaedic diagnosis. All available English language articles identified using a PubMed search of the terms "distal radius fracture" and "CRPS". Those with a reported incidence per number of included patients were included, regardless of treatment modality utilized. The combined incidence rate from these articles was compared to the rate of secondary CRPS following a documented injury in this study group. An odds ratio was calculated in each comparison with a p-value of <0.05 and 95% confidence interval (CI) not including 1 considered statistically significant.

One-hundred and thirty-three patients seen during the study period had a documented CRPS-related diagnosis were identified. Of these patients, 93 patients meet the IASP diagnostic criteria for CRPS in one upper or lower extremity. All available records from before and after the study period were reviewed. Patients ranged from 8 to 72 years of age with a notable female predominance (74.2%). Some patients developed CRPS while already under our institutions care. Duration of symptoms at presentation among those referred with an already existing CRPS diagnosis ranged from a few weeks to several years. Other demographic characteristics are detailed in Table 2.

Table 3
Characteristics of primary CRPS diagnosis.

	Percent (*n*)
Extremity	
Upper	52.7 (49)
Lower	47.3 (44)
Inciting event	
Trauma	39.8 (37)
Surgery	26.9 (25)
Both	26.9 (25)
Unknown	6.5 (6)
Treatment modality	
Therapy	51.6 (48)
Nerve block	29.0 (27)
Peripheral nerve surgery	22.6 (21)
Nerve stimulator	9.7 (9)

Table 4
Rates of secondary CRPS diagnosis.

	Percent (*n*)
Secondary CRPS with inciting event	16.1 (15)
Secondary CRPS with no inciting event	4.3 (4)
No secondary CRPS with inciting event	5.4 (5)
No secondary CRPS with no inciting event	74.2 (69)

On review of the characteristics of the initial, primary CRPS diagnosis, there was a roughly equal distribution of upper and lower extremity involvement. Among those patients with a documented inciting event (94%), 39.8% of CRPS diagnoses occurred following trauma, 26.9% following surgery and 26.9% following trauma which required surgery. The most commonly cited treatment modalities included physical and/or occupational therapy, nerve blocks, peripheral nerve surgery and nerve stimulators (Table 3).

3. Results

Of the 93 patients who met the IASP criteria for CRPS, 19 patients (20.4%) developed CRPS in a second extremity (Table 4). Of these patients with secondary CRPS, fifteen had a documented inciting event in the available clinic notes while four did not. Among the 74 patients who did not have a documented secondary CRPS diagnosis, five patients (5.4%) had a documented secondary injury or potential inciting event in another extremity with no subsequent development of CRPS. The remaining 69 patients had no documented secondary inciting event and no secondary CRPS diagnosis. Of the total 20 patients who had a documented secondary inciting event in a non-index limb, 15 patients (75%) had a subsequent diagnosis of associated CRPS. A total of 6 patients (6.5%) developed CRPS in all 4 extremities. Five of these patients had a documented inciting event for each extremity.

3.1. General population incidence of CRPS

The literature review identified two studies reporting population-based CRPS incidence rates. A Dutch population study, which examined medical records of 600,000 patients, found an incidence rate of 26.2 cases per 100,000 person years [2]. A similar United States-based study evaluated the records for 106,470 patients in Olmsted County, Minnesota a CRPS rate of 20.6, respectively [3]. Therefore, an average incidence of 23.4 per 100,000 (0.0234%) was utilized for comparison.

Eighteen articles including CRPS incidence rates following distal radius fracture were identified [4–21]. Of the combined 3613 reported distal radius fractures, 231 patients (6.4%) developed CRPS. This rate was used to represent a CRPS incidence following an inciting event in the general population.

Table 5
Statistical analysis.

	Odds ratio	95% CI	*p*-Value
Secondary CRPS incidence v. general population incidence	1069.6	562.0–2035.7	<0.0001
Secondary CRPS incidence with inciting event v. general population following distal radius fracture	11.7	5.9–23.2	0.001

3.2. Study incidence of subsequent CRPS

The study incidence of CRPS in a second limb of 20.4% (19 out of 93 patients) was compared to the average population incidence of 0.0236% calculated based on literature review. The calculated odds ratio was 1069.6 ($p < 0.0001$, 95% CI 562.0–2035.7), a statistically significant difference (Table 5).

The reported 6.4% rate of CRPS following distal radius fracture on literature review was compared to the 75% incidence rate of secondary CRPS seen among study patients following a secondary inciting event. The calculated odds ratio was 11.7 (p, 0.001, 95% CI 5.9–23.2), a statistically significant difference (Table 5).

4. Discussion

While CRPS is a rare condition among the general population, it has been reported to occur in up to 30% of patients following common upper and lower extremity fractures [15,22]. Therefore, surgeons must be familiar with this condition in order to properly diagnose and treat CRPS following injury or surgery. Once the initial diagnosis and treatment are complete, there is little available literature regarding the possible long-term implications of this diagnosis on the development of recurrent or secondary CRPS in the future. A lack of understanding regarding the exact mechanism by which CPRS develops and possible predisposing genetic or injury mechanism-related factors further complicates this picture.

One study evaluating patients with a history of Type I CRPS following carpal tunnel release (CTR) sought to determine if such patients were at increased risk of developing recurrent CRPS in the same hand following repeat CTR [26]. They found that 11 of 34 patients (32.4%) did develop recurrent CRPS. Compared to the 5% CRPS incidence rate reported in the literature following primary CTR [24], this seems to suggest that patients with a history of CRPS in an extremity may be prone to develop recurrent CRPS following additional surgical intervention on the same extremity. Furthermore, they found that patients with abnormal laser Doppler imaging prior to repeat CTR were more likely to develop recurrent CRPS post-operatively compared to those with normal pre-operative imaging [26].

A similar study evaluated 47 patients with a previous diagnosis of CRPS Type I in an extremity who required subsequent surgery in that same extremity. However, in this case, perioperative measures were taken to prevent recurrent CRPS, including avoidance of tourniquet use and intravenous mannitol infusion. With such measures, only 6 patients (1.3%) developed recurrent CRPS, suggesting that prophylactic perioperative treatment may reduce the risk of recurrent CRPS in the same extremity if surgery is required [27].

In a review of 1183 consecutive patients diagnosed with reflex sympathetic dystrophy (RSD), 10% of patients developed recurrent RSD in the same limb or a new occurrence in a second limb. No significant difference was seen in the gender or initially involved limb between those who had a second case of RSD and those who did not. A much higher rate (53%) of "spontaneous" RSD, however, was seen

among those with a second case of RSD compared to those who did not develop recurrent or secondary case (10%). This is higher than the 21% (4 of 19 patients) seen in our study [28].

While research evaluating the risk for recurrent CRPS in the same extremity is limited, even less information is available regarding the possible increased risk for secondary CRPS in another extremity. In our review of the literature, only case reports of individuals developing CRPS in multiple extremities were found.

In one such report, a 50-year-old male was diagnosed with CRPS, based on clinical findings supported by plain film radiography and triple-phase bone scan, on four separate occasions in four different anatomic sites—the right foot, right knee, left knee and left foot. No clear inciting event was identified for any of the four sites [29]. Another case reported the spontaneous development of CRPS on three separate occasions in the right leg, right arm and left arm in an 11-year-old girl [30]. While these isolated cases occurred in the absence of a known inciting event required for the diagnosis of CRPS by the IASP "Budapest criteria," they may hint at an underlying physiological finding that might make certain individuals more likely to develop CRPS than others.

A predisposing physiologic or genetic milieu for CRPS is not a new theory. In fact, Philipp et al. identified a single nucleotide polymorphism within the α_{1a}-adrenoreceptor which was significantly associated with the development of CRPS in 15 patients out of 163 who were diagnosed following distal radius fracture [9]. While no one genetic or clinical test is available to diagnose or identify a predisposition for developing CRPS, ongoing research in this area is working towards developing such testing options.

We sought to determine whether individuals in our practice with a diagnosis of CRPS were more likely to develop a secondary CRPS diagnosis in another extremity with or without a documented secondary inciting event. Such information might support the theory that certain patients have an underlying predisposition to develop CRPS. This information would be of clinical importance in counselling patients with a history of CRPS on their risk for developing CRPS in a second limb following a new injury or surgery or when discussing possible elective extremity surgery.

Admittedly, this study is limited by several factors. Its retrospective nature and reliance on documentation from only one institution, which might not include all subsequent extremity injuries and secondary CRPS diagnoses, subjects it to bias. Patients may not recall inciting events or may falsely attribute the development of secondary CRPS to an insignificant, non-causal event. Furthermore, as a regional referral centre for CRPS, patients presenting to our clinic may have more severe or refractory variations of the condition, which may be more likely to be associated with an underlying predisposition to develop CRPS. Finally, the exact prevalence of CRPS in the general population and incidence of CRPS following all extremity injuries and surgeries is not known. Therefore, the control values utilized for comparison in this study are imperfect. Based on the literature available, efforts were made to determine evidence-based control rates for comparison.

Despite these limitations, an odds ratio of over 1000 when comparing the reported population incidence of CRPS to the rate of secondary CRPS documented in this study strongly suggests that patients with a history of CRPS may be at considerable risk of developing secondary CRPS. This finding is further supported by the more than 11-fold increased rate of secondary CRPS following a secondary inciting event seen in this study when compared to the reported rates of CRPS following distal radius fracture. This only supports a general predisposition for the development of secondary CRPS in those with a history rather than providing a precise prediction of secondary occurrence rates. Additional, prospective study with standardized follow-up to assess for subsequent injuries and secondary CRPS, however, at needed to better elucidate the significance of this risk.

5. Conclusions

We believe that these findings are useful for counselling patients who have had a diagnosis of CRPS and are considering undergoing an elective extremity procedure. While CRPS should not be considered a contraindication to surgery, knowledge of such predisposition may impact the risk-to-benefit ratio for a particular patient considering a procedure such as peripheral nerve decompression or hardware removal for symptomatic relief. Similarly, patients presenting with a new extremity injury or requiring non-elective surgery, should be advised of their increased risk of secondary CRPS and monitored closely for signs and symptoms that it may be developing.

Our findings also may support a change in clinical management of previous CRPS patients compared to those with no previous history. Should a patient with a history of CRPS decide to proceed with elective orthopaedic surgery or present with a new injury, appropriate counselling should be performed.

Ethical issues

This study was approved by our Institutional Review Board. No written consent was obtained from included patients as the risk of harm or discomfort that may occur as a result of taking part in this research study is not expected to be more than in daily life and because no identifying information was included.

Conflicts of interest

The authors have no conflicts of interest to report.

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