Dystonia in complex regional pain syndrome : clinical, pathophysiological and therapeutic aspects

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Spreading of Complex Regional Pain Syndrome: not a random process

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Abstract

Background: Complex Regional Pain Syndrome (CRPS) generally remains restricted to one limb but occasionally may spread to other limbs. Knowledge of the spreading pattern of CRPS may lead to hypotheses about underlying mechanisms but to date little is known about this process.
Objective: To study patterns of spread of CRPS from a first to a second limb and the factors associated with this process.
Methods: One hundred-eighty-five CRPS patients were retrospectively evaluated. Cox's proportional hazards model was used to evaluate factors that influenced spread of CRPS symptoms.
Results: Eighty-nine patients exhibited CRPS in multiple limbs. In 72 patients spread from a first to a second limb occurred showing a contralateral pattern in 49%, ipsilateral pattern in 30% and diagonal pattern in 14%. A trauma preceded the onset in the second limb in 37, 44 and 91%, respectively. The hazard of spread of CRPS increased with the number of limbs affected. Compared to patients with CRPS in one limb, patients with CRPS in multiple limbs were on average 7 years younger and more often had movement disorders.
Conclusions: In patients with CRPS in multiple limbs, spontaneous spread of symptoms generally follows a contralateral or ipsilateral pattern whereas diagonal spread is rare and generally preceded by a new trauma. Spread is associated with a younger age at onset and a more severely affected phenotype. We argue that both spinal and supraspinal processes may play a role in the spontaneous spread in CRPS.

Introduction

Complex regional pain syndrome (CRPS) is characterized by various combinations of sensory, autonomic and motor disturbances, and is usually preceded by a minor to severe trauma affecting a limb.[1-3] CRPS usually remains restricted to one limb, but it can spread to other body parts.[4,5] Although several small studies have reported spread of specific sensory, autonomic or motor features of the syndrome, the overall picture remains unclear.[4-7] CRPS in one limb may extend to another limb either as result of a new trauma to a previously unaffected limb, or because the syndrome spreads spontaneously. Although different causes of spontaneous spread have been proposed, including genetic predisposition, aberrant regulation of neurogenic inflammation and maladaptive neuronal plasticity, the underlying mechanisms have not been elucidated.[4,5,8]

We were able to characterize a large sample of patients in whom CRPS in one limb spread to involve another limb. We were particularly interested in patients in whom spreading occurred spontaneously, because this may reflect true spread of the disorder, which might provide important information about the mechanisms behind this process. For example, if systemic factors underpin spontaneous spread, then one would expect an indiscriminate pattern of spread; if cortical mechanisms underpin spontaneous spread, then one would expect an ipsilateral pattern, and if spinal mechanisms underpin spontaneous spread, then one would expect a contralateral pattern.

The present study aims to evaluate patterns of spread of CRPS from one to a second limb and consider potential mechanisms that could explain this process. In addition, factors that are associated with the occurrence of spread are studied.

Methods

Patients

All patients who visited the outpatient movement disorders clinic of the department of Neurology of the Leiden University Medical Center in the period from January 1998 to April 2004 were considered for inclusion in the study. Patients were eligible if they met the CRPS criteria of the International Association for the Study of Pain (IASP), either at the time of disease onset or at the time of presentation at the clinic. The IASP criteria include the combination of: 1) the presence of an initiating noxious event or a cause of immobilization, 2) continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event, 3) evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain

and 4) absence of a condition that would otherwise account for the degree of pain and dysfunction. Although only criteria 2-4 have to be satisfied[3], we only included patients who identified an initiating noxious event in the first affected limb. Patients consent was obtained according to the Declaration of Helsinki and the study was approved by the Ethical Committee of the Leiden University Medical Center

Data Collection

Dates of onset of CRPS signs or symptoms for every involved limb were obtained from the patient's history. Medical records were reviewed to verify data wherever possible. Recorded sensory features included pain, hypoalgesia, hyperalgesia and allodynia. Recorded autonomic features involved oedema, temperature changes, colour changes, hyper- or hypohidrosis, and changes in nail and hair growth. Recorded movement disorders included dystonia, tremor and myoclonus. For all affected limbs we evaluated if the symptoms and signs fulfilled the IASP criteria for CRPS. Age at onset in the first limb and length of interval to onset of symptoms in subsequent limbs were calculated. The presence and type of traumas (soft tissue injury, fracture, surgery) preceding CRPS was registered. We categorized patients according to three criteria. First, if CRPS was present in one limb, patients were categorized as 'Single-CRPS'. If CRPS was present in more than one limb, they were categorized as 'Multiple-CRPS'. Second, Multiple-CRPS cases were categorized according to whether or not spread was associated with a separate trauma to the limb. If not, patients were categorized as 'Spontaneous spread'. If so, they were categorized as 'Separate trauma'. Third, Multiple-CRPS cases were categorized according to which limb was subsequently affected: 'Contralateral' (e.g. left hand to right hand), 'Ipsilateral' (e.g. left hand to left leg) or 'Diagonal' (e.g. left hand to right leg).

Statistical analysis

The independent-samples t-test was used to assess differences between groups in normally distributed continuous data, while non-parametric tests were used to assess differences in non-normally distributed continuous or categorical data. Baseline differences in disease duration were taken into account and analyzed with analysis of covariance. The time from onset of initial symptoms to extension to other limbs was calculated for each limb, where time to spread was censored at the time of last assessment. In patients who showed spontaneous spread of symptoms to subsequent limbs, a multivariate analysis of factors associated with spread of symptoms was carried out with Cox's proportional hazards model. At any point in time, an individual has an instantaneous risk ("hazard") to reach the endpoint (here: "spread to a second limb"). The Hazard ratio presents the increased or decreased risk on reaching the endpoint at any point in time (compared

to a reference value), adjusted for other potentially confounding variables in the model. Patients with simultaneous onset of symptoms in more than one limb or with simultaneous spread from one affected limb to more than one subsequent limb were excluded from this analysis. The hazard of spread was estimated while several variables were accounted for, including trauma characteristics, location of initial symptoms, presence of movement disorders and patient characteristics. The probabilities of spread to other limbs were calculated as cumulative incidences (competing risks).[9] For the analysis of rate of spread comparing the presence of one, two or three affected limbs, the variance of the estimated coefficients was adjusted by using a sandwich estimator, accounting for possible correlations of event times within patients.[10] P values £0.05 were considered significant. All statistical analyses were performed with SPSS (version 14.0), except for the survival analyses, which were performed with 'R' (version 2.0.1).

Results

One-hundred-eighty-five patients were included in the study (table 1, figure 1). At assessment, 96 patients (52%) had a single affected limb, whereas 89 (48%) had multiple affected limbs. Signs and symptoms are presented in Table 2. In the Multiple-CRPS group, the syndrome started in one limb in 78 patients (i.e. 88%), a simultaneous start in two limbs occurred in 10 patients (11%) and a simultaneous start in four limbs occurred in one patient (1%).

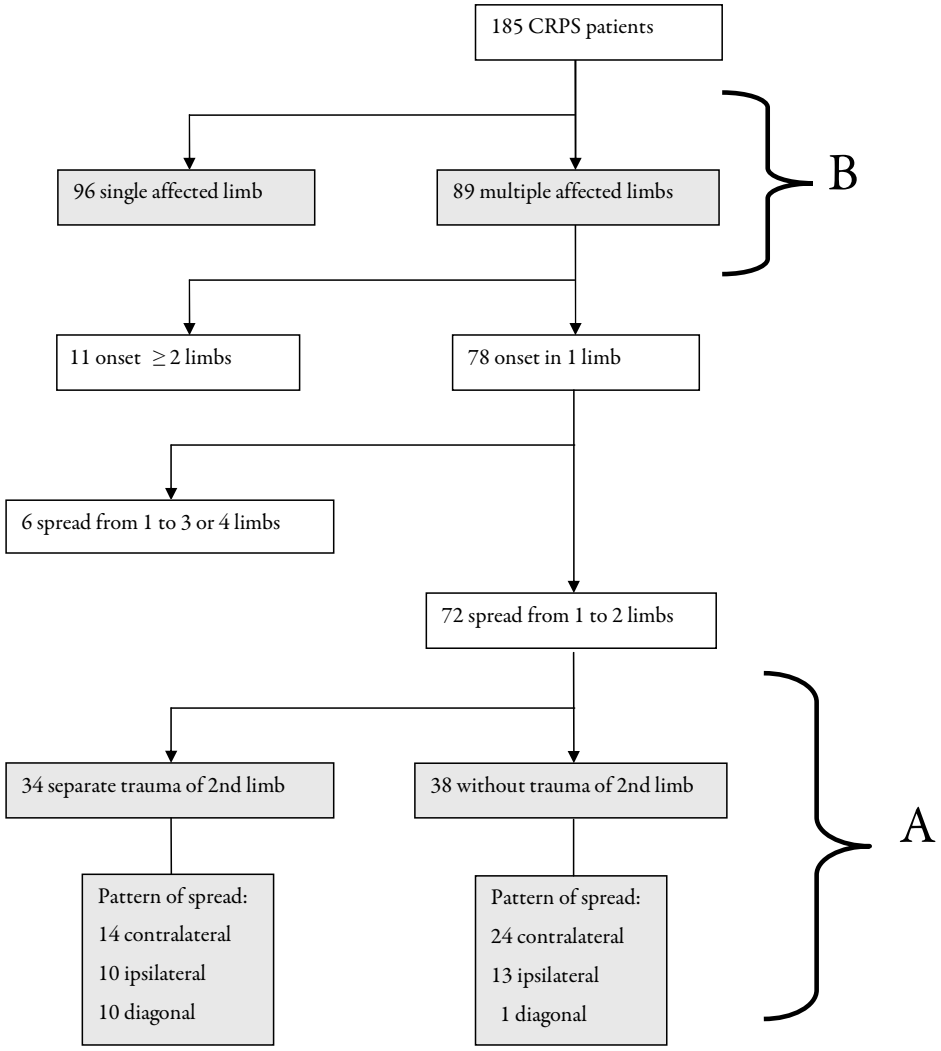
Spread of CRPS from one to two limbs

CRPS had spread to another limb in 78 patients. Spread occurred simultaneously from one to three limbs in 5 patients and from one to four limbs in one (figure 1). CRPS spread from one to two limbs in 72 patients according to the following patterns (table 3): contralateral pattern in 38 patients (53%; 22 arm to arm, 16 leg to leg); ipsilateral pattern in 23 patients (32%; 12 arm to leg, 11 leg to arm) and diagonal pattern in 11 patients (15%). New trauma preceded the onset of CRPS in the second limb in 37 % of the patients with contralateral spread, in 44% of the patients with ipsilateral spread and in 91 % of the patients with diagonal spread, which indicates that diagonal spreading is almost always associated with a new trauma. Patient characteristics did not differ between the three types of spread.

Table 1. Demographics of 185 patients with CRPS.

Characteristic	Value
females - no (%)	160 (86.5)
disease duration, mean (SD) - years	6.0 (6.0)
age at assessment, mean (SD) - years	43.5 (15.4)
age at onset of CRPS, mean (SD) - years	37.5 (15.4)
preceding trauma - no (%)	
soft tissue injury	92 (49.7)
fracture	48 (25.9)
surgery	45 (24.3)
CRPS involvement - no (%)	
- single limb	96 (51.9)
- multiple limbs	89 (48.1)
affected limbs at initial CRPS onset - no (%)	
1	78 (87.6)
2	10 (11.2)
3	0
4	1 (1.1)
affected limbs at assessment - no (%)	
2	45 (50.6)
3	18 (20.2)
4	26 (29.2)

Figure 1. Flow diagram of patients included in the study.



Section A shows the included patients in which CRPS symptoms spread from one to two limbs and who were evaluated for different patterns of spread. Section B shows the included patients with multiple and single affected limbs that were compared for differences in clinical characteristics.

Table 2. Signs and symptoms of CRPS in affected limbs

Variable	Affected limb 1st (n = 185)	2nd (n = 89)	3rd (n = 44)	4th (n = 26)
Pain				
Present/absent/unknown, no.	185/0/0	89/0/0	44/0/0	26/0/0
Hyperalgesia/allodynia				
Present/absent/unknown, no.	101/78/6	40/48/1	19/24/1	10/16/0
Hypoalgesia				
Present/absent/unknown, no.	152/30/3	72/17/0	39/5/0	23/3/0
Edema				
Present/absent/unknown, no.	168/9/8	67/20/2	27/13/4	17/8/1
Temperature changes				
Present/absent/unknown, no.	165/9/11	73/9/7	41/2/1	21/4/1
Color changes				
Present/absent/unknown, no.	176/3/6	82/5/2	33/7/4	24/2/0
Hyper/hypohidrosis				
Present/absent/unknown, no.	122/44/19	59/27/3	26/15/3	13/12/1
Hair and nail growth changes				
Present/absent/unknown, no.	134/42/9/	52/32/5	27/13/4	18/7/1
Movement disorders*				
Present/absent/unknown, no.	115/70/0	67/22/0	36/8/0	25/1/0

Variables were deemed to be present if a symptom, a sign or both were reported or observed.
* Recorded movement disorders were dystonia, tremor and myoclonus.

Table 3. Patterns of spread in 72 patients who spread from one to two limbs spontaneously or after a separate trauma of the second extremity

Pattern of spread*	Total N=72	Spontaneous spread N=38	Separate trauma N=34
Contralateral - no.(%)	38 (53)	24 (63)	14 (41)
Ipsilateral - no.(%)	23 (32)	13 (34)	10 (29)
Diagonal - no.(%)	11 (15)	1 (3)	10 (29)

* Patterns of spread were significantly different between patients with spontaneous spread and spread after a separate trauma; $\chi^2(2) = 10.2$; p=0.006.

Spontaneous spread versus spread after separate trauma

In thirty-eight patients who showed spontaneous spread of CRPS from a first to a second limb, contralateral spread occurred in 24 (63%, 11 arm to arm and 13 leg to leg) (table 3). Ipsilateral spread occurred in 13 patients (34%, 8 arm to leg and 5 leg to arm) and diagonal spread in 1 (3%). In 34 patients who showed spread after a separate trauma of the second limb, contralateral spread occurred in 14 (41%, 11 arm to arm and 3 leg to leg). Ipsilateral spread occurred in 10 patients (29%, 4 arm to leg and 6 leg to arm) and diagonal spread also occurred in 10 (29%, 4 arm to leg and 6 leg to arm). Patterns of spread differed significantly between patients with spontaneous spread and spread after a separate trauma ($\chi^2(2) = 10.2$; p=0.006). Patient characteristics did not differ significantly between patients who spread spontaneously and those who spread after a separate trauma. Patients in whom spreading occurred spontaneously showed a non-random pattern of spread, so further analysis were performed on data from this subgroup.

Characteristics of spontaneous spread

The median interval between occurrence in the first and second limb was 21 months (n=24, range 2-95) for contralateral spread, 19 months (n=13, range 3-58) for ipsilateral spread and 10 months (n=1) for diagonal spread. The difference in intervals between contralateral and ipsilateral pattern was not significant (Mann-Whitney U test; p =0.16).

Next, the hazard of the different types of spontaneous spread was calculated (table 4). Compared to patients with contralateral pattern (reference value of 1.00) the hazard of ipsilateral spread was 0.44 (95% CI: 0.22-0.89), whereas the hazard of diagonal spread was 0.04 (CI 0.005-0.30) (figure 2). Age at onset, sex, onset of symptoms in arm or leg, or in left or right sided limbs, did not affect the hazard. Compared to presence of CRPS in one limb, the presence in two limbs increased the hazard of spread of CRPS to a third limb with 2.19 (95% CI: 1.35-3.57). CRPS in three limbs increased the hazard of spread to a fourth limb to 3.75 (95% CI: 1.92-7.32). The hazard of spread in patients with onset of CRPS on the left side was 1.46 (95% CI: 1.00-2.11, P=0.047) compared to patients with right-sided onset, indicating a somewhat higher risk of spread in patients with left sided onset.

Table 4. Hazard on spread of CRPS - Multivariate Cox regression model

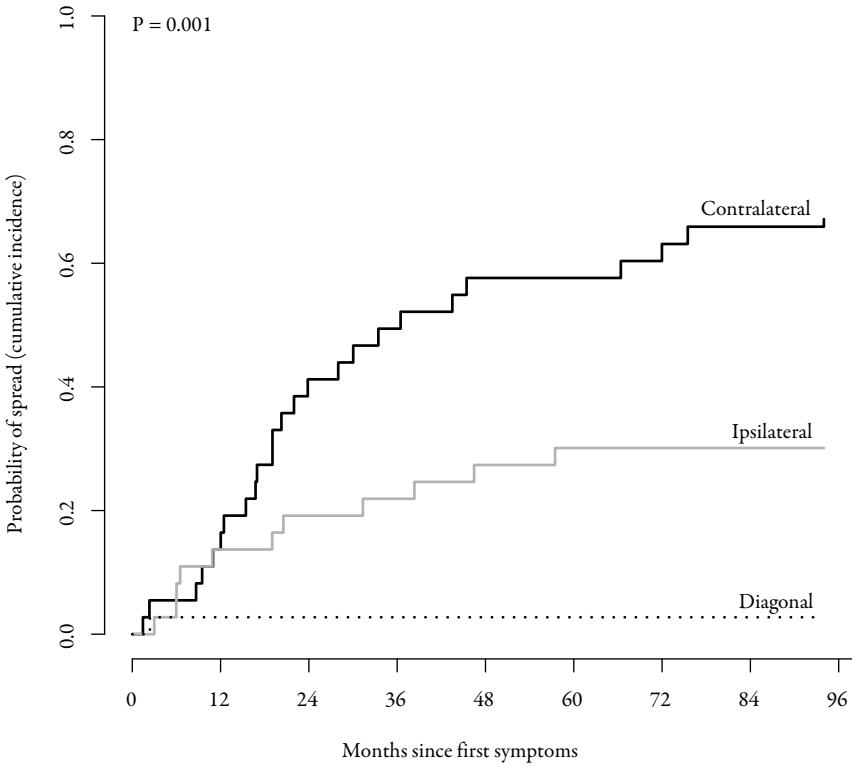
Variable	Hazard ratio	95%-CI
Pattern of spread to second affected limb		
Mirror-image	1	
Ipsilateral	0.44	0.22-0.89
Diagonal	0.04	0.005-0.30
Onset in limb		
Right sided	1	
Left sided	1.46	1.00- 2.11
Number of limbs already affected by CRPS		
1	1	
2	2.19	1.35- 3,57
3	3.75	1.92- 7.32

* Regression coefficient with 95%-CI

Comparison of Single and Multiple CRPS patients

Ninety-six patients with Single-CRPS were compared with 89 patients with Multiple-CRPS (figure 1, section B). Patients with Multiple-CRPS had longer disease duration, and were significantly younger at onset, than patients with Single-CRPS (table 5). Additional analyses with adjustment for differences in disease duration showed that patients with Multiple-CRPS were 6.7 years younger (95% CI: 6.3-7.1). There was no significant difference in type of trauma ($\chi^2(2) = 5.67$; p=0.06) between groups. Movement disorder was more common in those with Multiple-CRPS than it was in those with Single-CRPS (78% versus 54%, mean (95% CI) difference = 23% (10-37)). No difference between groups was found in the type of sensory symptoms ($\chi^2(2) = 0.73$; p=0.69). Patients with spontaneous spread had a shorter disease duration than those with secondary trauma-related spread (6.4 versus 9.6 years, mean difference 3.2 years, 95% CI: 0.4-5.8) but there were no other differences between these two groups.

Figure 2. The probability of spread of CRPS.



The probability on the occurrence of different types of spread in CRPS patients since the onset of symptoms in the first limb. In this multivariate model differences in patient characteristics were accounted for.

Table 5. Comparison of characteristics of CRPS patients with single and multiple affected limbs

Parameter	Total N=185	single N= 96	multiple N=89	Difference in % (95% CI)
Female - no. (%)	160 (86.5)	84 (87.5)	76 (85.4)	2.1 (-10.6;14.8)
First aff. limb arm - no. (%) n=174	91 (52.3)	50 (52.1)	41 (52.6)	0.5 (-14.4;15.4)
Disease duration - mean (SD) yr	6.0 (6.0)	4.1(4.7)	8.1 (6.6)	4.0 (2.3;5.7)
Age at onset CRPS - mean (SD) yr	37.5 (15.4)	40.7 (14.7)	34.0 (14.7)	6.7 (6.3;7.1)
Kind of trauma - no. (%)				
soft tissue injury	92 (49.7)	43 (44.8)	49 (55.1)	χ^2 (df=2) = 5.67
fracture limb/other	48 (25.9)	32 (33.3)	16 (18.0)	P= 0.06
operation limb/other	45 (24.3)	21 (21.9)	24 (27.0)	
Movement disorders - no. (%)	121 (65.4)	52 (54.2)	69 (77.5)	23.3 (10.1;36.5) [a]
Type sensory symptoms - no. (%) n=165				
hypaesthesia/hypalgesia	81 (49.1)	43 (52.4)	38 (45.8)	χ^2 (df=2) = 0.73
hyperaesthesia/hyperalgesia/ allodynia	41 (24.8)	19 (23.2)	22 (26.5)	P= 0.69
both	43 (26.1)	20 (24.4)	23 (27.7)	

[a] Adjusted for disease duration

Discussion

We set out to determine patterns of spread of CRPS and the factors that are associated with spread. Our results show that CRPS usually affects one limb but in some cases it spreads to another limb, most often in a contralateral (53%) or ipsilateral (32%) pattern and usually without secondary trauma. A diagonal pattern of spread was nearly always triggered by a new trauma. Spontaneous spread and spread after a separate trauma followed different patterns.

The mechanism underlying spontaneous spread of CRPS to other limbs is unclear. Common patterns of spontaneous spread of CRPS may hint at the origin of the pattern. Spread after a separate trauma followed no particular pattern, which strongly suggests that CRPS in one limb does not specifically predispose a particular other limb to CRPS and supports the idea that these patients have multiple CRPS rather than CRPS of multiple limbs. In contrast, spontaneous spread to the contralateral limb was 2.3 times more likely than spread to the ipsilateral limb and 25 times more likely than

diagonal spread. This result casts light on previous reports of similar rates of ipsilateral and diagonal spread[5] because that work did not differentiate between spontaneous and second trauma-related spread.

Patients with a spontaneous onset or who have a familial form of CRPS develop the syndrome at a younger age and are more likely to have a more severe phenotype.[11] Additionally, CRPS patients younger than 50 have an increased risk of having siblings with CRPS.[12] In line with these studies, patients with Multiple-CRPS more often exhibited movement disorders and also had a significantly younger age at onset of CRPS than patients with Single-CRPS. Collectively, these findings indicate that in patients with a younger onset of CRPS, genetic factors may play a role in the onset or chronicity of the syndrome. A genetic predisposition is also suggested by associations that were found with different human leukocyte antigen (HLA) class I and II factors.[13-16] Interestingly, HLA class I molecules have been implicated in non-immune roles including neuroplasticity.[17,18]

The dominant patterns of spontaneous spread observed here strongly suggest that CRPS does not spread according to some systemic vulnerability, but is more likely to spread via spinal or cortically mediated mechanisms.

Pain that spreads contralaterally has been reported in CRPS and other chronic pain conditions, such as atypical facial pain[19], phantom limb pain[20] and repetitive strain injury.[21] Several animal models of neuropathic pain and CRPS have reported contralateral spread of symptoms after nerve lesions or inflammation.[22-24] In a recent rat model of CRPS, 57% of the animals exhibited contralateral hindpaw mechanical hypersensitivity after unilateral needle stick distal nerve injury.[25] Following an intradermal injection of capsaicin, human subjects developed contralateral hyperalgesia and allodynia.[26] The etiology behind the contralateral spread of pain is largely unknown; however, increasing evidence from experimental studies on neuropathic pain suggests that contralateral changes arise via altered spinal processing of incoming sensory information.[22,27] This may be mediated by growth factors via commissural interneurons in the spinal cord and brainstem. In addition, spinal glia cells and pro-inflammatory cytokines have been documented as important factors behind the contralateral spread of symptoms.[28,29]

In contrast to the number of studies on contralateral spread, data on mechanisms underlying spread of symptoms to the ipsilateral limb are scarce. Axial spread of disease along the spinal cord is well documented for degenerative diseases such as amyotrophic lateral sclerosis and infectious agents such as the poliovirus.[30] It is conceivable that glial mediated changes at one segment of the spinal cord can reach remote segments by axonal transport via descending or ascending fibre tracts. This is also suggested by a recent autopsy paper on a patient with longstanding CRPS that started in the left leg,

but eventually spread to all limbs.[31] The researchers demonstrated a significant loss of posterior horn cells and activation of both microglia and astrocytes not only at the site of the initial injury, but extending throughout the entire length of the spinal cord. These diffuse alterations may support the hypothesis that segmental changes in the spinal cord induced by CRPS in one limb, may not only spread to the contralateral side but can extend more rostrally and caudally from the initially affected segment. Interestingly, this latter study[31] also reported that the greatest degree of microglial cell activation in the spinal cord was seen in the left lumbar segments and the least in the right cervical cord, which suggests that ispilateral changes are induced more easily than diagonal changes.

Another explanation for spread of symptoms may be found at the supraspinal level. Rommel et al[32] showed hemisensory impairment in CRPS patients with only one affected limb, and that this was more commonly found in those with left-sided CRPS. They proposed that the results may reflect functional alterations in the thalamus. Relevant to this is the recent discovery of space-based, but not arm-based shift in tactile processing in people with CRPS of one arm.[33] Of further relevance here is the observation that left-sided CRPS is associated with a higher hazard of spontaneous spread – space-based tactile neglect after stroke commonly involves the left side of the body, consequent to right sided brain damage.[34]

Contralateral spread probably involves different supraspinal mechanisms. Noxious stimuli activate bilateral regions of the brain associated with descending control pathways including the thalamus and rostral ventral medulla, which suggests one putative mechanism for mediating altered spinal gating contralaterally.[35,36] Additionally, the growing body of data implicating cortical changes in CRPS (see[37] for review), offers potential mechanisms. For example, watching the mirror-image of the unaffected limb being touched elicits pain on the affected side[38] and referred sensations of a tactile or painful stimulus were also experienced outside its expected somatic territory.[39] Forss et al.[40] describe a patient with chronic CRPS type-1 in whom pain and motor symptoms spread to the contralateral arm, and whole-head-magnetoencephalography demonstrated abnormal bilateral activation in the primary somatosensory cortices to unilateral tactile stimuli, which suggests that interhemispheric spread of cortical activation may contribute to contralateral spread. Furthermore, supraspinal glia and glial-derived proinflammatory cytokines may play a role in spread of symptoms as well as their major influence on pain modulation.[27] Whether these supraspinal changes can initiate spread of CRPS symptoms or if they are secondary to peripheral or spinal processes remains to be elucidated.

Our study demonstrates that if CRPS develops spontaneously in more than one limb, there is a greater risk of spread to subsequent limbs without the requirement of a new

trauma. This accelerated occurrence has been documented for clinical manifestations of other diseases and probably reflect changes in the central nervous system, perhaps in an attempt to adapt to the altered condition by remodelling of neuronal contacts and circuits, a process also known as neuronal plasticity.[41-44]

Interpretation of our results should consider some methodological issues. A retrospective design is less accurate than prospective designs and may result in incomplete data, although such issues would seem unlikely to bias the results in one direction over another. Furthermore, follow-up data were not available and Single-CRPS patients had shorter disease duration than patients with Multiple-CRPS, which raises the possibility that some Single-CRPS patients would have ultimately developed Multiple-CRPS if we left it longer to find out. We addressed this issue by controlling for disease duration in the analysis.

In conclusion, this study shows that spread of CRPS symptoms often occurs spontaneously and contralateral spread is twice as likely as ipsilateral spread, but diagonal spread is rare. We contend that these patterns of spread implicate spinal cord and/or supraspinal mechanisms rather than systemic mechanisms, although further work is required to elucidate them in detail.

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