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Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy)

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Abstract

There are reports that complex regional pain syndrome, type I (reflex sympathetic dystrophy; CRPS-I/RSD) can spread from the initial site of presentation, but there are no detailed descriptions of the pattern(s) of such spread. We describe a retrospective analysis of 27 CRPS-I/RSD patients who experienced a significant spread of pain. Three patterns of spread were identified. 'Contiguous spread (CS)' was noted in all 27 cases and was characterized by a gradual and significant enlargement of the area affected initially. 'Independent spread (IS)' was noted in 19 patients (70%) and was characterized by the appearance of CRPS-I in a location that was distant and non-contiguous with the initial site (e.g. CRPS-I/RSD appearing first in a foot, then in a hand). 'Mirror-image spread (MS)' was noted in four patients (15%) and was characterized by the appearance of symptoms on the opposite side in an area that closely matched in size and location the site of initial presentation. Only five patients (19%) suffered from CS alone; 70% also had IS, 11% also had MS, and one patient had all three kinds of spread. Our results suggest that CRPS-I/RSD spread may not be a unitary phenomenon. In some it may be due to a local spread of pathology (CS); in others it may be a consequence of a generalized susceptibility (IS). In the MS case, spread may be due to abnormal neural functioning spreading via commissural pathways. Alternatively, we discuss the possibility that all three kinds of spread may be due to aberrant CNS regulation of neurogenic inflammation. © 2000 Published by Elsevier Science B.V. on behalf of International Association for the Study of Pain.

Keywords: Complex regional pain syndrome type I; Reflex sympathetic dystrophy; Causalgia; Neurogenic inflammation

1. Introduction

Complex regional pain syndrome, type I (reflex sympathetic dystrophy; CRPS-I/RSD) is generally precipitated by trauma to an extremity, although a minority of cases are reported to follow CNS trauma, or to have no clear antecedent (Bonica, 1990). A diagnostic algorithm for CRPS-I/RSD has been proposed recently (Stanton-Hicks et al., 1995). The CRPS-I/RSD symptom complex is composed of the following five elements: (a) pain; (b) edema; (c) dysregulation of vasomotor, sudomotor and pilomotor control; (d) a movement disorder consisting of difficulty initiating movement, weakness, tremor, and dystonia; and (e) trophic changes in skin, nails and bone (Schwartzman and McLellan, 1987; Schwartzman, 1996). Edema and autonomic dysregulation dominate in the early stage of the disease, while the movement disorder and dystrophic changes are more apparent in the later stages. The pathogenesis of CRPS-I/RSD is not known.

There are several reports that CRPS-I/RSD can spread from the initial site of presentation, but this facet of the syndrome has not been considered in detail (DeTakats, 1937; DeTakats, 1943; Kozin et al., 1976a,b; Bentley and Hameroff, 1980; Bonica, 1990; Barrera et al., 1992; Bhatia et al., 1993; Schiffenbauer and Fagien, 1993; Veldman et al., 1993; Teasell et al., 1994; Veldman and Goris, 1996). The purpose of this study is to describe the patterns of spread. A preliminary report has appeared (Maleki et al., 1998).

2. Methods

This is an analysis of 27 consenting CRPS-I/RSD patients who were being treated in our pain clinic. Inclusion criteria were: (a) a diagnosis of CRPS-I/RSD at the initial site of involvement that met IASP criteria (Merskey and Bogduk, 1994) and (b) a history of spreading pain documented in the case record. Each patient was re-examined expressly for the purpose of this study.

The following historical data were obtained: (a) patient demographics; (b) the nature of the initial injury; (c) the interval between the initial injury and the onset of CRPS-I/RSD; and (d) the evolution of the symptoms from the time

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eported to be immediate by nine patients (33%), 5 days or less by six patients (22%), 1 month or less by five patients (19%), 3 months or less by four patients (15%), and between 10 months and 2.5 years by three patients (11%). The interval between CRPS-I/RSD onset and diagnosis averaged 7 months (range 1 week–3 years). On examination, the pain at the initial site was given a mean VAS of 6.7 (range 3–10).

In all cases but one, spread (of any of the three types described below) occurred when the initially affected site was still symptomatic. The exceptional case was a patient who experienced spread to the right foot approximately 12 years after CRPS-I/RSD in her left foot had been relieved by a lumbar sympathectomy.

Three distinct patterns of spread were found (Fig. 1).

3.2. Contiguous spread (CS)

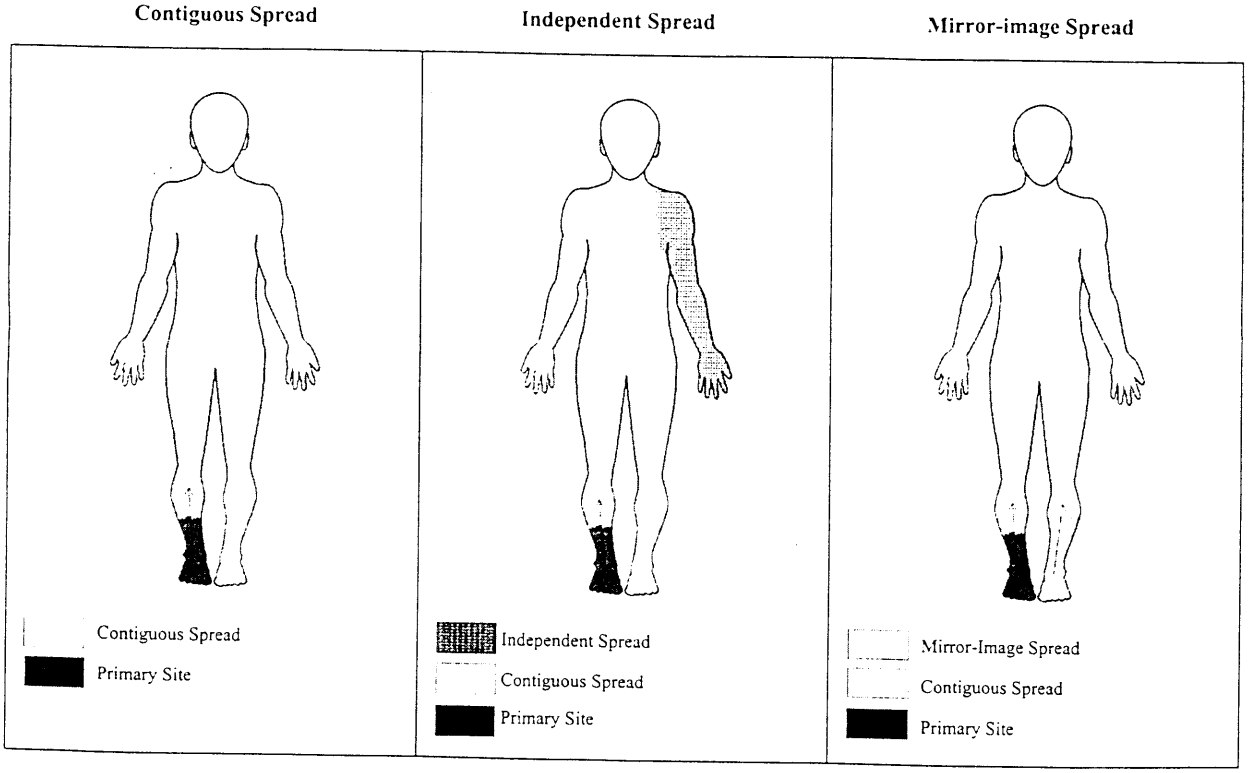
All twenty-seven patients reported significant spread of pain and other symptoms from the initial site to contiguous areas (Table 2). The average interval between the initial CRPS-I/RSD and the onset of spread was 78 days (range 2 days–13 months). As the initial site was usually a distal extremity, CS necessarily moved proximally. However, in the six cases where the initial site was the knee, spread was in both the proximal and distal directions. This proximo-distal expansion was always asymmetrical and began in the distal direction before spreading proximally. In four cases with a proximal location of the initial site (one hip, one lower back, and two shoulder cases), the spread occurred only distally.

The onset of CS (Table 2) did not appear to be associated with any precipitating factor in seven patients (26%). In ten patients (37%) a therapeutic intervention may have initiated or exacerbated CS: splinting or casting (five cases), neuroma resection (two cases), and one case each: carpal tunnel surgery, brachial plexus decompression, knee arthroscopy, surgical reduction of a foot fracture, lumbar nerve blocks, and physical therapy. In nine patients (33%), CS occurred while there was an ongoing pain problem that affected the area in which CS occurred: five cases with radicular pain, three cases with suspected brachial plexus injuries (none of the radiculopathy and plexopathy patients had radiological or electrodiagnostic evidence of a lesion). In one case persistent overuse of an involved knee and in another chronic hemorrhagic knee effusion requiring frequent joint punctures were possibly related to spread.

Only five of the 27 patients suffered from CS alone. Nineteen patients (70%) also experienced IS, three (11%) experienced CS followed by MS, and one patient experienced CS, IS, and MS. CS occurred first in all cases where one or both of the other types of spread occurred.

3.3. Case history of a patient experiencing CS

A 24-year-old man (Tables 1 and 2: patient 1) twisted his left knee in mid-June 1998. He was subsequently diagnosed with meniscus and ligament tears and underwent an arthro-



1. Schematic drawings showing the three types of spread found in patients with complex regional pain syndrome, type I (reflex sympathetic dystrophy). Arrows indicate the direction of spread.

of onset to the present. Spread of CRPS-I/RSD was documented as to: (a) latency of onset; (b) spatial location and extent of spread; (c) the symptoms present in the area of spread; (d) the evolution of the symptoms appearing in the area of spread; and (e) identification of possible initiating events for the spread.

The physical examination concentrated on the following in both the original and new areas of CRPS-I/RSD: (a) pain intensity as measured by a 10-cm visual analog scale (VAS); (b) the presence of hyperalgesia (supernormal pain to pin prick) and mechano-allodynia (pain evoked by gentle touch); and (c) identification of factors that alleviated or worsened the pain. Autonomic dysregulation was assessed by examination of skin color and temperature, hyper- or hypohydrosis and piloerection. Features of the movement disorder that were noted were difficulty in initiating movement, weakness, tremor and dystonia. The nails were examined for hypertrophy, and the skin for loss of soft tissue and abnormal hair growth.

3. Results

3.1. Demographics and initial CRPS-I/RSD presentation

Five men and 22 women (Table 1) were recruited to the study over a period of 2 years. The initial presentation of CRPS-I/RSD was due to trauma in all cases. The initial sites of CRPS-I/RSD were: hand (nine cases), foot (seven cases), knee (six cases), shoulder (two cases) and one case each for ankle, hip and lower back. The average duration of CRPS-I/RSD at the time of entry to the study was 4.5 years (range 7 months–14.5 years). The interval between the precipitating trauma and the initial presentation of CRPS-I/RSD was

Table 1
Patient demographics and CRPS-I history

Patient. no.	Sex	Age	Pain VAS	Latency initial trauma to onset	Latency onset to diagnosis	Latency onset to spread			Total time with CRPS-I
						Contiguous	Independent	Mirror	
1	M	24	8	3 months	21 days	21 days			9 months
2	F	45	8	1 month	1 month	1 month	3 months/5 months[a]		8 months
3	F	29	10	1 day	4 months	1 month	?[b]		3 years
4	F	33	6	1 day	35 days	1 month	3 months/9 months		15 months
5	F	29	8	Immediate	4 months	3 months	12 months/21 months		23 months
6	M	44	6	2 months	7 months	1 month	31 months		3 years
7	F	41	8	2 months	21 month	1 year	24 months		2.5 years
8	F	23	7	14 days	1 year	2 months	26 months		27 months
9	F	33	5	Immediate	6 months	2 months		2 years	13.2 years
10	F	42	6	7 days	15 months	4 months	8 years	7.6 years	8.5 years
11	F	38	10	2.5 years	17 months	3 months			21 month
12	F	52	10	Immediate	5 months	14 days			7 months
13	F	45	5	3 days	1 month	13 months	2 years		14.5 years
14	F	49	3	Immediate	10 months	3 days		1 month	8.5 years
15	M	48	7	1 day	4 months	14 days	1 month		14 months
16	F	49	7	Immediate	3 years	10 months	2 years		3.5 years
17	F	27	8	10 days	1 month	25 days	?[b]		7 months
18	F	39	5	Immediate	2 months	35 days		5 months	19 months
19	F	43	3	2 days	7 days	7 days			12.3 years
20	M	37	7	14 days	6 months	2 months	6 months		8.7 years
21	F	40	7	Immediate	1.6 months	7 days	1 month		15 months
22	F	22	7	Immediate	3 months	1.5 months	14 months		17 months
23	M	52	4	1 day	18 months	2 days	2 years		4.4 years
24	F	36	7	2 months	2 months	2 months	2 years/8 years		12.6 years
25	F	42	7	10 months	1 month	3 months			4.2 years
26	F	45	8	2 years	6 months	7 days	7 years		8.4 years
27	F	38	6	Immediate	8 months	6 months	12 years		11 months
Mean		38.7	6.7	3 months	7 months	2.6 months	2.6 years[c]		4.5 years
SD		8.7	1.8	7.5 months	8 months	3.5 months	3.3 years		4.5 years
Median		40	7	2 days	4 months	35 days	2 years		2.5 years
75%		45	8	1.5 months	9 months	3 months	2.1 years		8.5 years
25%		33	6	Immediate	1.5 months	14 days	6 months		15 months
Maximum		52	10	2.5 years	3 years	13 months	12 years		14.5 years
Minimum		22	3	Immediate	7 days	2 days	1 month		7 months

[a] First/second occurrence.
[b] Not determined.
[c] For first occurrence only.

scopic repair 3 weeks later. The knee was swollen and painful postoperatively, and almost weekly joint punctures were needed to drain hemorrhagic effusions. The onset of his CRPS-I/RSD occurred in early October 1998, when the intensity of his burning knee pain intensified and he developed mechano-allodynia, and changes of skin color and temperature in the region around the knee. Over the following 3–4 weeks his symptoms spread distally to the rest of his lower leg and foot, and then spread proximally to his mid and upper thigh. At the end of October his entire left lower extremity was almost completely involved.

3.4. Independent spread (IS)

Nineteen of the 27 patients (70%) experienced the appearance of CRPS-I/RSD in a location that was distant and non-contiguous with the initial site (Table 2). The average interval between the initial CRPS-I/RSD and the onset of IS (the initial IS when there were two) was 2.6 years (range 1 month–12 years). There were six patients who had two separate (in time and location) instances of IS.

The onset of IS (Table 2) did not appear to be associated with any precipitating factor in five of 19 patients (26%). In six patients (32%), a second trauma may have been responsible for IS onset (one of these was very probably a brachial plexus injury due to the improper use of crutches). In three patients (16%) a therapeutic intervention was closely associated in time with the appearance of IS (two epidural blocks and one lumbar sympathetic block). In five patients (26%), compensatory overuse of the arm (two cases) or opposite leg (three cases) was suspected to be responsible for IS.

For the six cases that experienced two instances of IS (Table 2), the second instance may have been due to brachial plexus injury from improper use of crutches in one case, to a fall in another, and to ongoing pathology in two cases (one lumbosacral radiculopathy and one bilateral brachial plexopathy, both conditions were present before the initial appearance of CRPS-I/RSD). In two cases there were no contributing factors identified. For four of the six patients, the average interval separating the first and second instances of IS was 5.7 months (range 2–9 months). The average excludes two patients (patients 3 and 17) who could only recall that the interval separating the first and second instances of IS was less than a few months in one case, and in less than a year in the other.

3.5. Case history of a patient who experienced two instances of IS

A 29-year-old woman (patient 5) received a stretch injury to her arm in March 1997 while trying to catch a person who was falling. Immediately following the accident, she developed burning pain, mechano-allodynia, and changes in skin color and temperature in her right hand, in addition to persistent pain in her right shoulder. Within the next 3 months the symptoms spread upwards from the hand to include the entire right arm. CRPS-I/RSD was diagnosed in our clinic in July 1997 and we have followed the patient regularly since then. In March 1998 identical symptoms appeared in her left shoulder, perhaps due to compensatory overuse of her left arm. The patient elected to have a brachial plexus decompression (with sympathectomy) on the right side in May 1998, and the same procedure was done on the left in August 1998. Both sides received only transient relief. By November 1998 the symptoms in her left shoulder progressed to encompass her entire left upper extremity. In December 1998 she presented with the apparently unprovoked appearance of CRPS-I/RSD in her right foot. At the time of examination 3 weeks later, the symptoms in her right foot had spread to her right ankle and lower leg.

3.6. Mirror-image spread (MS)

In four of 27 patients (15%), CRPS-I/RSD appeared on the opposite side in an area that closely matched in size and location the site of initial presentation, i.e. a mirror-image of the initial site (Table 2). The average interval between the initial CRPS-I and the onset of MS was 2.5 years (range 1 month–7.6 years). The onset of MS may have been associated with surgery in one case. In two cases compensatory overuse of the opposite extremity was suspected. One case developed MS following an epidural block given to relieve a pre-existing lumbosacral radiculopathy.

3.7. Case history of a patient who experienced both MS and IS

A 42-year-old woman (patient 10) suffered bilateral knee injuries in a motor vehicle accident in November 1991. One week later she developed CRPS-I/RSD on the medial aspect of her left knee (the worse injured side). Concurrently, she experienced pain (but no mechano-allodynia or vasomotor symptoms) in her right knee, but she insisted that this pain was of a distinctly different quality from that on the left. Four months later (February 1992), following an arthroscopic surgery on the left knee, she experienced worsening and spread of symptoms to her distal left leg. Nearly 7 years later (July 1998), and 1 week following arthroscopic surgery on her right knee (which found cartilage damage and a meniscus tear), she developed burning pain, mechano-allodynia, hyperalgesia, and changes in skin color, temperature and edema on the medial aspect of her right knee with subsequent distal spread, exactly mirroring the phenomena first seen on the left. About 6 months later she presented with IS – the same symptoms had appeared in her right hand and distal forearm. The patient related this to a recent overuse of the right hand; no other potential cause was recalled.

3.8. Dissociated spread (DS)

In nine cases of IS and MS (patients 3, 5, 8, 10, 17, 18, 21, 22 and 26) we noted a dissociation of spreading symptoms,

Table 2
Types of CRPS-I spread and possible precipitating events[a]

Patient no.	Initial CRPS-I site; time to initial spread	Type of spread			Possible precipitating events
		Contiguous	Independent	Mirror	
1	L knee; 21 days	+			Ongoing hemorrhagic knee effusion
2	R hand; 1 month	+[1]	+[2]	+[3]	1. Ongoing plexus injury 2. R foot/leg: none 3. L foot/leg: none
3	L knee; 1 month	+[1]	+[2] +[3]		1. Splint placement 2. R leg: compensatory overuse 3. R arm: Plexus injury from crutches
4	R foot; 1 month	+[1]	+[2] +[3]		1. None 2. L foot: after blunt trauma 3. Both hands/forearms: preexisting plexus injury
5	R hand; 3 months	+[1]	+[2] +[3]		1. Ongoing brachial plexus injury 2. L shoulder: compensatory overuse 3. R foot/leg: none
6	L hand; 1 month	+[1]	+[2]		1. Ongoing brachial plexus injury 2. L foot: none
7	R foot; 1 year	+[1]	+[2]		1. Persisting R foot fracture and surgical repair 2. R arm/face/neck one day post successful lumbar sympathetic block
8	R knee; 2 months	+[1]	+[2]		1. None 2. L foot: none
9	R ankle; 2 months	+[1]		+[2]	1. Casting 2. Epidural block for L/S radiculopathy
10	L knee; 4 months	+[1]	+[2]	+[3]	1. Arthroscopic surgery 2. R hand: possible overuse 3. R knee: arthroscopic surgery
11	R hip; 3 months	+			Lumbar nerve blocks for ongoing radicular pain
12	R hand; 14 days	+[1]			Physical therapy
13	R foot; 13 months	+[1]	+[2]		1. Casting, neuroma resection 2. L plexus injury due to crutches
14	R knee; 3 days	+[1]		+[2]	1. Continued excessive flexion/extension of R knee 2. Excessive flexion/extension of L knee (job related)
15	R foot; 14 days	+[1]	+[2]		1. Ongoing L/S radicular pain 2. Epidural block
16	L hand; 10 months	+[1]	+[2]		1. L carpal tunnel surgery 2. Crush injury to R leg
17	R shoulder; 25 days	+[1]	+[2] +[3]		1. None 2. L arm after L brachial plexus injury 3. R leg: ongoing L/S radicular pain
18	R hand; 1.3 months	+[1]		+[2]	1. Casting 2. Compensatory overuse of L hand
19	R hand; 7 days	+			Casting
20	R hand; 2 months	+[1]	+[2]		1. Ongoing cervical radicular pain 2. R foot: none
21	R foot; 7 days	+[1]	+[2]		1. Ongoing L/S radicular pain 2. L leg: altered gait and compensatory overuse
22	R knee; 1.5 months	+[1]	+[2]		1. Initially none, later worsening after neuroma resection 2. L hip: compensatory overuse
23	L foot; 2 days	+[1]	+[2]		1. Ongoing L/S radicular pain 2. Mid-back and R buttock: after epidural block
24	Low back; 2 months	+[1]	+[2] +[3]		1. None 2. L leg: crush injury to lumbar spine 3. L arm: plexus injury after fall
25	L shoulder; 3 months	+			None
26	R hand; 7 days	+[1]	+[2]		1. None 2. R leg: none
27	L foot; 6 months	+[1]	+[2]		1. None 2. R foot: crush injury

[a] L, left; R, right; L/S, lumbosacral.

present, the patient has a generalized susceptibility for the condition. At first thought, it seems difficult to reconcile such a generalized susceptibility with the hypothesis of an abnormal inflammatory response that was discussed in the case of CS. However, the inflammatory response is known to contain a significant neurogenic component that is at least partly under CNS control. The neurogenic component's primary contribution is to the inflammatory response at the site of tissue injury, but it is well established that it can produce effects contralaterally or at spatially remote locations (e.g. Levine et al., 1985; van der Laan and Goris, 1997; Green et al., 1998).

Aberrant CNS regulation of neurogenic inflammation might play a role in both the initial presentation and the spread of CRPS-I/RSD. The existence of such a generalized CNS abnormality is supported mostly by studies showing the contralateral effects of unilateral nerve injury (see below). But in CRPS-I/RSD (where nerve injury is absent by definition), abnormal CNS regulation of neurogenic inflammatory phenomena might also constitute a generalized susceptibility to develop an abnormal inflammatory response. But in the case of IS, as in the case of CS, the possibility of an abnormal inflammatory process is difficult to reconcile with the frequent long intervals between the initial CRPS-I/RSD presentation and the onset of IS. In our series the onset intervals ranged from 1 month to 12 years, with an interval of 3 months or more in about 80% of the subjects. In the Veldman and Goris (1996) series the interval ranged from 2 weeks to 15 years.

Our data and reports in the literature suggest that MS is relatively uncommon; it was not encountered in the 1183-patient series of Veldman and Goris (1996). It is logically correct to use the term "mirror-image", as they do, when referring to a symmetrical bilateral initial presentation (e.g. when it appears simultaneously in both feet after unilateral trauma). However, this condition may be distinct from what we have called mirror-image spread, where there is a distinct interval between the initial and second presentations. A simultaneous appearance of bilateral pain hypersensitivity following unilateral nerve injury has been noted in animal models of post-traumatic painful neuropathy (Seltzer et al., 1990; Kim and Chung, 1992), but MS, as defined here, has not (the animal models have also not shown any instances of IS).

It is tempting to speculate that MS is due to the spread of aberrant neural processing via commissural pathways (especially the dorsal spinal commissure). In experimental animals, over a dozen different phenomena have been described in dorsal root ganglia cells of the same segment following nerve injury to the opposite side, and at least four different phenomena have been noted in the contralateral autonomic ganglia (Koltzenburg et al., 1999). For example, contralateral sprouting of sympathetic postganglionic efferent axons onto dorsal root ganglion cells and the upregulation of bradykinin receptors in contralateral sensory afferent neurons has been detected following unilateral nerve injury (McLachlan et al., 1993; Petersen et al., 1998). There is also evidence that unilateral nerve injury produces transsynaptic changes in the contralateral spinal cord dorsal horn (Sugimoto et al., 1990; Stevens et al., 1991; Mao et al., 1992).

It is unclear whether the contralateral effects of unilateral nerve injury are germane to the case of CRPS-I/RSD, where evidence of nerve injury is absent. However, there are also reports of contralateral effects following unilateral injury to non-neural tissue. For example, Nachemson and Bennett (1993) found an increased incidence of pyknotic spinal neurons in contralateral laminae I–III (presumed to be inhibitory interneurons) following a unilateral surgical incision in the rat. Abnormalities of joint pressure-pain thresholds, an increased scintigraphic signal, decreased bone density, and abnormal cutaneous vasomotor sympathetic reflexes, have been noted in the pain-free contralateral extremity of CRPS-I/RSD patients (Kozin et al., 1976a,b; Bej and Schwartzman, 1991; Kurvers et al., 1996). There is no explanation for any of the contralateral changes that follow experimental unilateral injury to nerve or other tissue. In particular, there is no evidence concerning the role of commissural spinal pathways. The possibility exists that they are somehow related to the aberrant CNS regulation of neurogenic inflammation that we have hypothesized.

CS, IS and MS may be distinct phenomena and it is possible to hypothesize different underlying causes for each. However, it is also possible that all three kinds of spread may be expressions of a generalized disorder of CNS regulation of neurogenic inflammation. Neurogenic inflammation is almost certainly a multi-dimensional phenomenon involving, for example, the generation of antidromic impulses in primary afferent sensory neurons (resulting in the peripheral release of neuropeptides like substance P and calcitonin gene-related peptide), an interaction between primary afferent terminals and the terminals of postganglionic sympathetic efferents, and CNS regulation of the immune system's contribution to inflammation (Eliav et al., 1999). Aberrant CNS regulation of neurogenic inflammation may account for the initial appearance of CRPS-I/RSD, for all three kinds of spread, for the movement disorder (Schwartzman and Kerrigan, 1990; Bhatia et al., 1993; Veldman et al., 1993; Baron et al., 1996), and for the dysregulation of vasomotor and sudomotor function (Kozin et al., 1976a,b; Jänig, 1985; Schwartzman and Kerrigan, 1990; Bej and Schwartzman, 1991; Herrick et al., 1994; Baron and Maier, 1996; Kurvers et al., 1996; Birklein et al., 1998; Wasner et al., 1999).

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where parts of the CRPS-I/RSD symptom complex other than pain (abnormal vasomotor or sudomotor function, and/or difficulty with movement) were the first to be noted in the new area. This phenomenon has been described previously (Schwartzman, 1995). The variable presentation of CRPS-I symptoms is well known (Stanton-Hicks et al., 1995; Baron et al., 1996; Schwartzman, 1996), and it has been suggested that some patients may present with all of the symptoms except pain (Blumberg, 1988; Baron et al., 1996). The significance of DS is unclear. In particular, it is difficult to say whether or not the appearance of the other symptoms first implies that they cause the pain. It does, of course, suggest the opposite – that pain need not be the only cause of the associated symptoms.

4. Discussion

Although the patients reported here all met the IASP criteria for CRPS-I/RSD (Merskey and Bogduk, 1994), we cannot exclude the possibility that clinically unverifiable nerve damage was sometimes associated with the initial presentation and/or with spread. This is particularly likely in the cases with arthroscopic knee surgery, where damage to small articular nerve twigs would be nearly impossible to identify with certainty. It may also be possible for the cases with radicular and brachial plexus pain. Although none of these had radiological or electrodiagnostic evidence of nerve injury, we suspected that partial nerve injury was present in some.

Our data do not permit an estimation of the frequency of any of the three types of CRPS-I/RSD spread, but the ease with which patients were identified suggests that spread is not uncommon. CS, in particular, is likely to be very common. Veldman and Goris (1996) have reported on multi-site CRPS-I/RSD in a series of 1183 consecutive patients. They do not include what we identify as CS, and they did not observe MS; thus all of their 76 cases of spread (we omit their patients with bilateral initial presentation) would be termed IS in our classification. This gives an estimate of IS in 6.4% of CRPS-I/RSD patients.

In the majority of the cases described here, spread (of all three types) was associated in time with an event (another trauma, a therapeutic intervention, or an ongoing pain problem like radiculopathy) that might reasonably be thought to have been causative. But there were no cases where a causative relationship could be established with confidence (mere temporal association is, of course, logically inadequate). Particularly striking were the numerous cases where no possible causative event for spread could be found. Although the initial presentation in all of our cases was clearly associated with a trauma, many cases of onset without apparent antecedent are reported in the literature. In the series reported by Veldman and Goris (1996) the initial presentation was without antecedent in 10.5% of cases. It is difficult to accept the idea that a condition as severe as CRPS-I/RSD could literally appear spontaneously, and one is tempted to posit some minor and unnoticed trauma as being causative for enigmatic initial presentations. There is less temptation for such a presumption in cases of CS onset without antecedent because a plausible explanation is at hand (see below). But it is as difficult to accept the idea of spontaneous IS and MS as it is to accept the idea of a spontaneous initial presentation. We can offer no solution to this problem, except to note those minor everyday traumas are often not remembered (witness, for example, the common experience of discovering that one has a bruise, but cannot recall its cause).

CS appears to be common, although few prior studies describe it clearly. Its existence is consistent with the hypothesis of a localized pathology that spreads contiguously from the site of initial tissue injury. For example, it has been hypothesized that CRPS-I/RSD is an abnormal inflammatory response; abnormal in the sense that the response is exaggerated in magnitude and does not resolve when the tissue injury heals (Sudeck, 1942; Goris et al., 1987; Veldman et al., 1993; van der Laan and Goris, 1997). One can easily imagine how such an abnormality might spread to contiguous tissue, and how a second trauma might facilitate such a spread. However, it is not easy to imagine why such spread would take a long time to appear. In our series, 67% of the CS cases were not noted until 1 month or more after the initial trauma and in eight cases (30%) the interval was 3 months or more. Of course, it is conceivable that the tendency for local pathology to spread contiguously is weak, and that the probability of its appearance is increased by a second trauma even long after the initial presentation.

A large percentage of patients experienced IS (70%). This phenomenon has been described clearly in a relatively small number of cases (Kozin et al., 1976a,b; Bentley and Hameroff, 1980; Barrera et al., 1992; Bhatia et al., 1993; Schiffenbauer and Fagien, 1993; Teasell et al., 1994; Veldman and Goris, 1996). Veldman and Goris (1996) describe 76 cases that we would classify as IS. However, they refer to their cases as 'recurrent' CRPS-I/RSD and it is not clear to us whether the initial site of presentation was still symptomatic at the time of IS onset in their patients. In our series, the initial site was symptomatic at the onset of IS in all but one case.

In the majority of cases, IS was associated in time with a possible causative event. But here also it was impossible to be certain of causation, and there was a large minority of cases (26%) without apparent antecedent. We suspect that brachial plexus injury due to improper use of crutches in cases of lower extremity CRPS-I/RSD, and compensatory overuse of the other arm in cases of upper extremity CRPS-I/RSD, may be real precipitating factors. Insistence on the proper use of crutches, or the prescription of arm-supported crutches or a walker, may be a prudent prophylactic measure for patients with lower extremity CRPS-I/RSD.

The IS phenomenon suggests that once CRPS-I/RSD is

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