Submission No 279

INQUIRY INTO NSW WORKERS COMPENSATION SCHEME

Name: Name suppressed

Date received: 25/05/2012

To: workerscompinquiry@parliament.nsw.gov.au;
Subject: AMA guide - ".....AMA IV, the current guidelines used for the assessment of permanent impairment, do not recognise chronic pain as an impairment....." WorkCover NSW advice!
To the WorkCover Reform Committee 2012,

I have received concerning advice from the authorising body being WorkCover NSW in charge of implementation and use of the AMA guide on email Tue, 7 Sep 2010 15:06:39 +1000. This involved the General Manger of Workers Compensation NSW,
The issues I wish to address to the WorkCover Reform Committee are the following:
1.The current impact WorkCover legislation (AMA Guide) has on Complex Regional Pain Syndrome (CRPS) a chronic pain related injury.
2. Use of the AMA guide for diagnostic criteria regarding recognition (A Medical Label) that often delays treatment, reduces assistance and often stops rehabilitation.
3. The compounding factors regarding suggested legislative changes to allow only, one Whole Person Impairment (WPI) assessment under the WorkCover reform and how it will impact CRPS related injuries long term.
I have attached research in regards to the spreading nature of CRPS, a progressive disease that causes long-term permanent disability. Attached: kenny doctor pt relationships.pdf (170482) Remove Spreading of complex regional pain syndrome not a random process.pdf (122571) Remove Increased systemic catecholamines in CRPS and relationship to psychological factors.pdf (171536) Remove
The current AMA guide as I understand looks for 8 out of 11 objective diagnostic criteria for Complex Regional Pain Syndrome such as changes in skin temperature, color, sweating, swelling, etc
".....On May 14, 2003, a member of the AMA and Chairman of the Scientific Advisory Committee of the International Research Foundation for RSD/CRPS, filed a complaint with the AMA putting the AMA on notice that it was causing ongoing injury to patients by disseminating false and misleading information about the diagnosis of reflex sympathetic dystrophy (RSD) also referred to as complex regional pain syndrome (CRPS Type I). also stated ".....nowhere in the scientific literature will you find such stringent criteria for the diagnosis of RSD/CRPS....." (http://www.rsdfoundation.org/test/AMA.html).
On email Date: Tue, 7 Sep 2010 15:06:39 +1000,
"From: "
Date: Tue, 7 Sep 2010 15:06:39 +1000

????.AMA IV, the current guidelines used for the assessment of permanent impairment, do not

recognise chronic pain as an impairment....."
advice referrers to the AMA guide no 5, WorkCover clearly identifies on email Tue, 7 Sep 2010 15:06:39 +1000 that the AMA IV, the current guidelines used for the assessment of permanent impairment, do not recognise chronic pain as an impairment? How does the AMA guide no 6 identify ways to assist people with CRPS?
If the AMA IV, guide does not recognise chronic pain how can WorkCover allow such legislation to be used for assessment? If Minister Pearce is looking at changing legislation for a Whole Person Impairments (WPI) to one assessment under the ?WorkCover NSW Reform 2012? how will legislative changes impact injured workers of NSW who end up with Complex Regional Pain Syndrome (Chronic Pain) as a result of a work injury if CRPS is a progressive disease?
From my own perspective after an injury at age 27 and diagnosed with CRPS, apart from desperately trying to understand what was happening to my body, becoming very ill from prescribed medications and spending 5 years defending my integrity and being bullied by medically uneducated claims managers and labelled by the very own system that is supposed to help someone with a permanent injury. I have watched in horror as barristers, lawyers, AMA doctor?s, even claims managers and the Workers Compensation Commission staff are all paid in an attempt to dispute/ resolve medical evidence over legislation, legislation that WorkCover acknowledge in writing " AMA IV the current guidelines used for the assessment of permanent impairment, do not recognise chronic pain as an impairment.
The NSW Government, WorkCover should be made accountable for the legislation they have implemented. In my view they need to become accountable for the costs spent fighting to refuse acknowledgement for such a life debilitating disease. In my view the system needs to focus on formal education strategies for treatment and management for people diagnosed with CRPS. An education packaged should be implemented by WorkCover before any treatment is put in place for the patient and the Nominated Treating Doctor.
The matters I raised with Minister Pearce and Matthew Mason-Cox 7 February 2012 have not been met with a written response to date. (SEE EMAIL BELOW)
I would appreciate that the issues above and my email ignored by Minister Pearce 7 Feb 2012 are taken into consideration for injured workers diagnosed with Complex Regional Pain Syndrome in NSW.
Sincerely,

Subject: FW: AMA Guide - ".....AMA IV, the current guidelines used for the assessment of permanent impairment, do not recognise chronic pain as an impairment....." Update current info
Date: 7 February 2012 5:33:49 PM AEDT
To:

Dear Minister Pearce
This advice came from WorkCover NSW- and the Director of the Provider and Injury Management Services Group of WorkCover NSW -General Manager at the time). I understand she is responsible for designing the frameworks that enables service providers to effectively participate in the workers compensation system in NSW and to improve the services available to injured workers and their employers.

Date: Tue, 7 Sep 2010 15:06:39 +1000

" .....AMA IV, the current guidelines used for the assessment of permanent impairment, do not recognise chronic pain as an impairment..... "
If WorkCover state that this guide does not recognise chronic pain why is the AMA guide used to asses people injured at work and diagnosed with a chronic pain condition such as CRPS (Complex Regional Pain Syndrome)?
What is the amount of money spent on "Approved Medical Assessments for the Workers Compensation Commission" or "Legal Fees" for both parties when "the current guidelines used for the assessment of permanent impairment, do not recognise chronic pain as an impairment"? What

happens to the injured workers seeking appropriate medical help while the above mentioned parties fight for recognition of an injury which most often is dragged out for months sometimes years? Current Claim example QBE vs Injured Worker , injured in 2007, as i understand she is still in her 20's ? A young woman who's health is clearly very severe.

".....On May 14, 2008, , a member of the AMA and Chairman of the Scientific Advisory Committee of the International Research Foundation for RSD/CRPS, filed a complaint with the AMA putting the AMA on notice that it was causing ongoing injury to patients by disseminating false and misleading information about the diagnosis of reflex sympathetic dystrophy (RSD) also referred to as complex regional pain syndrome (CRPS Type I).

The original complaint was sent to , AMA's Senior Acquisitions Editor and then to the highest levels within the AMA, including the President. 1 "The false assertions by the AMA are particularly egregious because RSD/CRPS is a syndrome that must be treated in a timely manner in order to avert exacerbation of symptoms leading to irreversible impairment and suffering. I have personally witnessed patients with RSD/CRPS lose hope and commit suicide following denial of authorization for care by insurance carriers."

There are an estimated 1.5 million Americans who have been affected by this chronic, neurological syndrome. The syndrome can start after minor trauma, such as one caused by a sprained finger, or by a gunshot wound. But it can also be triggered by a heart attack, a stroke, surgery or repetitive vibration motion ? such as the kind that comes from a jackhammer or weed-cutting tool. While the cause of the disorder remains unknown, experts believe it is the result of a malfunction or misfiring in the body's sympathetic nervous system, the part of the nervous system that regulates involuntary reactions to stress. The injury heals but the pain continues.

As RSD progresses over time, especially without treatment, the syndrome tends to become more unresponsive to treatment. Hence, early diagnosis and treatment are imperative. RSD can remain localized to one region of the body indefinitely. In other cases, it spreads to large segments of the body spontaneously or by trauma leading to permanent deformities and widespread immobility of limbs. At an advanced stage of the illness, all patients develop significant psychiatric problems and narcotic dependency, and are left completely incapacitated. Some commit suicide.

The critical issue raised by , contained in the AMA GUIDES TO THE EVALUATION OF PERMANENT IMPAIRMENT, 5th Edition. On page 496, the clinical guidelines state that there "must" be at least eight (8) concurrent, objective signs for RSD in order to make the diagnosis.2 The AMA clinical guidelines refer to objective diagnostic criteria such as changes in skin temperature, color, sweating, swelling, etc. informed the AMA, "...nowhere in the scientific literature will you find such stringent criteria for the diagnosis of RSD/CRPS." ...."
(http://www.rsdfoundation.org/fast/AMA.html)

did not sustain CRPS from a Work related injury however her story highlights how devastating CRPS can be when treatment is delayed. ABC catalyst — http://www.abc.net.au/catalyst/stories/2621516.htm , you can review her log http://laurascrpajourney.weebly.com/my-story.html and hopefully grasp the severity of this disease. 's story : http://www.yumasun.com/articles/worley-70114-pain-day.html another victom of this monster disease CRPS.

As ' s advised and I am sure many other specialists can confirm, including RNSH Pain Clinic sponsored by WorkCover " As RSD progresses over time, especially without treatment, the syndrome tends to become more unresponsive to treatment. Hence, early diagnosis and treatment is imperative,"

I am well aware that the current guide clearly delays treatment and would increase costs to the workers compensation scheme in the process of fighting recognition of the diagnosed condition.

I would ask that you review the AMA guidelines used to asses CRPS (Complex Regional Pain Syndrome) and explain why the current guidelines do not recognise chronic pain as an impairment ? Why does the AMA place such strict criteria for CRPS in insurance when "nowhere in scientific literature will you find such stringent criteria for the diagnosis of RSD/CRPS"

If the WorkCover scheme is suffering financial loss , why not focus on rehabilitation through educating CRPS patients by providing information on treatment options through publications online at the WorkCover site to allow patients a comprehensive perspective about managing the condition along with treatment options, rather than only focusing on fighting a label (diagnosis) when CRPS is real and has life long devesting effects. Workcover could make a positive difference, rather than what appears to be a negative approach with its contracted scheme agents.

Your's Sincerely,

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Spreading of complex regional pain syndrome: not a random process

Monique A. van Rijn · Johan Marinus · Hein Putter · Sarah R. J. Bosselaar · G. Lorimer Moseley · Jacobus J. van Hilten

Received: 22 December 2010 / Accepted: 6 February 2011

Abstract 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. The objective is to study patterns of spread of CRPS from a first to a second limb and the factors associated with this process. One hundred and eighty-five CRPS patients were retrospectively evaluated. Cox's proportional hazards model was used to evaluate factors that influenced spread of CRPS symptoms. 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. 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 processes in the spinal cord as well as supraspinal changes are responsible for spontaneous spread in CRPS.

Keywords CRPS • Spread • Multiple • Peripheral trauma • TREND Study

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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 (Allen et al. 1999; Merskey and Bogduk 1994; Veldman et al. 1993). CRPS usually remains restricted to one limb, but it can spread to other body parts (Maleki et al. 2000; Veldman and Goris 1996). Although several small studies have reported spread of specific sensory, autonomic or motor features of the syndrome, the overall picture remains unclear (Bhatia et al. 1993; Maleki et al. 2000; van Hilten et al. 2001; Veldman and Goris 1996). CRPS in one limb may extend to another limb either as a 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 (Maleki et al. 2000; van Rijn et al. 2007; Veldman and Goris 1996).

As a tertiary care center for CRPS we were able to characterize a large sample of patients in whom CRPS in one limb spread into involve another limb. We were

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particularly interested in patients in whom spreading occurred spontaneously (i.e., without a new trauma), 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 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 (Merskey and Bogduk 1994), we only included patients who identified an initiating noxious event in the first affected limb.

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. Sensory features that were recorded included pain, hypoalgesia, hyperalgesia and allodynia. Hypoalgesia, hyperalgesia and allodynia were assessed by testing sensitivity to light touch and pinprick. 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. We did not consider muscle weakness a movement disorder as this could result from pain or oedema. 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 were 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 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. This analysis involves a regression model to quantify the relationships between one or more factors of interest and 'survival' (time to the occurrence of spread). At any point in time, an individual has an instantaneous risk ("hazard") to reach the endpoint (in our study defined as "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 a 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) (Putter et al. 2007). 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 using a sandwich estimator, accounting for possible correlations of event times within patients (Lin and Wei 2009). P values B 0.05 were considered significant. All statistical analyses were performed with SPSS (version 14.0), except for the survival analyses, which were performed with the statistical program R (version 2.0.1).

Results

One-hundred and eighty-five patients were included in the study (Table 1, Fig. 1). During assessment, 96 patients (52%) had a single affected limb, whereas 89 (48%) had multiple affected limbs. The signs and symptoms are presented in Table 2. In the Multiple-CRPS group, the syndrome started in 1 limb in 78 patients (i.e. 88%), a simultaneous start in 2 limbs in 10 patients (11%) and a simultaneous start in 4 limbs in 1 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 five patients and from one to four limbs in one patient (Fig. 1, section A). The severity of CRPS symptoms in the second limb did not differ significantly from that in the first limb (Table 2). CRPS spread from 1 to 2 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 (14.8)
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)

Spontaneous spread versus spread after separate trauma

In 38 patients who showed spontaneous spread of CRPS from a first to a second limb, contralateral spread occurred in 24 patients (63%, 11 arm to arm and 13 leg to leg) (Table 3). Ipsilateral spread occurred in 13 (34%, 8 arm to leg and 5 leg to arm) and diagonal spread occurred in 1 patient (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) patients. Ipsilateral spread occurred in 10 (29%, 4 arm to leg and 6 leg to arm) and diagonal spread occurred in 10 (29%, 4 arm to leg and 6 leg to arm). Patterns of spread were significantly different between patients with spontaneous spread and spread after a separate trauma ($v^2(2) = 10.2$; $P = 0.006$). Patient characteristics (including symptom severity) 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 analyses were performed on data from this subgroup.

Characteristics of spontaneous spread

The median interval between the 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) (Fig. 2). Age at onset, sex, or onset of symptoms in arm or

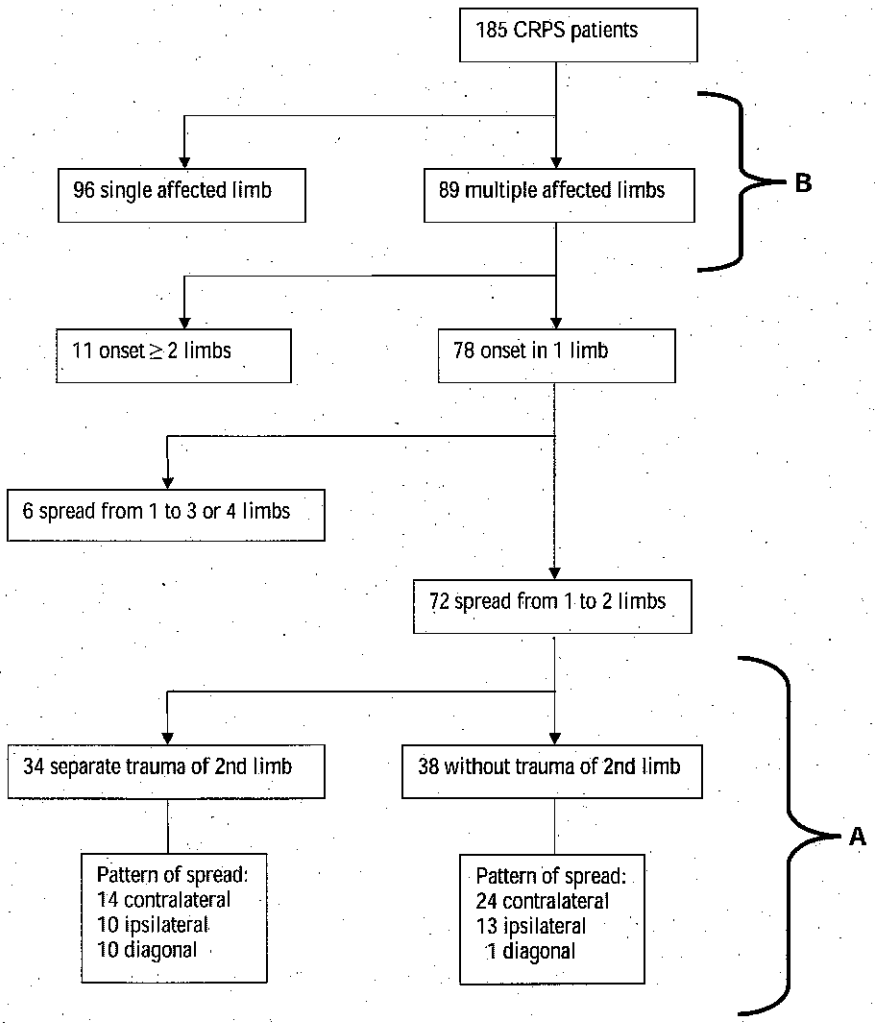

Fig. 1 Flow diagram of patients included in the study. Section A shows the included patients in which CRPS symptoms spread from one to two limbs and who were evaluated for different patterns of spread. Section B shows the included patients with multiple and single affected limbs that were compared for differences in clinical characteristics

leg, or in left or right sided limbs, did not affect the hazard. Compared to the 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 of CRPS symptoms in patients with left sided onset.

Comparison of Single- and Multiple-CRPS patients

Ninety-six patients with Single-CRPS were compared with 89 patients with Multiple-CRPS (Fig. 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 the type of trauma ($v^2(2) = 5.67$; P = 0.06) between groups. Movement disorder was more common in those with Multiple-CRPS than it was in those with Single-CRPS [78% vs. 54%, mean (95% CI) difference = 23% (10–37%)]. No difference between the groups was found in the type of sensory symptoms ($v^2(2) = 0.73$; P = 0.69). Patients with spontaneous spread had a shorter disease duration than those with secondary trauma-related spread (6.4 vs. 9.6 years, mean difference 3.2 years, 95% CI: 0.4–5.8) but there were no other differences between these two groups.

Discussion

We set out to determine patterns of spread of CRPS and the factors that are associated with spread. Our results show

Table 2 Signs and symptoms of CRPS in affected limbs

Variable	Affected limb			
	First (n = 185)	Second (n = 89)	Third (n = 44)	Fourth (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[a]				
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

[a] 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[a]	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)

[a] Patterns of spread were significantly different between patients with spontaneous spread and spread after a separate trauma; $v^2(2) = 10.2$; $P = 0.006$

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 that 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 (Veldman and Goris 1996) 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 (de Rooij et al. 2009a). Additionally, CRPS patients younger than 50 have an increased risk of having siblings with CRPS (de Rooij et al. 2009b). 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

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

[a] Regression coefficient with 95% CI

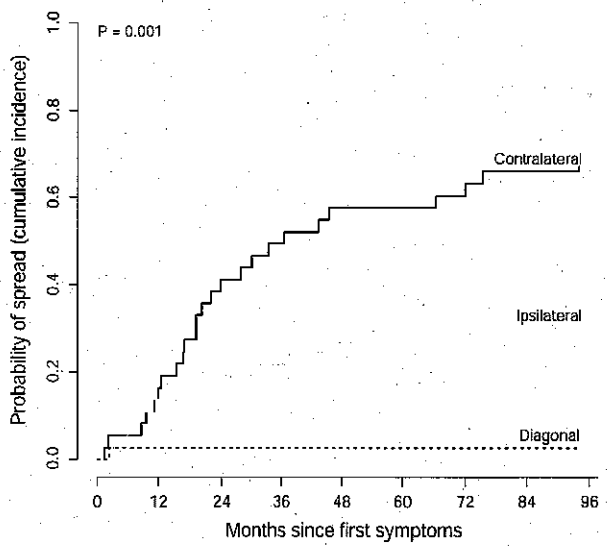

Fig. 2 The probability of spread of CRPS. The probability on the occurrence of different types of spread in CRPS patients since the onset of symptoms in the first limb. In this multivariate model differences in patient characteristics were accounted for

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 (de Rooij et al. 2009c; Kemler et al. 1999; van Hilten et al. 2000; Vaneker et al. 2002). Interestingly, HLA class I molecules have been implicated in non-immune roles including neuroplasticity (Corriveau et al. 1998; Goddard et al. 2007).

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 (Woda and Pionchon 2000), phantom limb pain (Pohjolainen 1991) and repetitive strain injury (Miller and Topliss 1988). Several animal models of neuropathic pain and CRPS have reported contralateral spread of symptoms after nerve lesions or inflammation (Coderre et al. 2004; Coderre and Melzack 1992; Koltzenburg et al. 1999). In a recent rat model of CRPS, 57% of the animals exhibited contralateral hindpaw mechanical hypersensitivity after unilateral needle stick distal nerve injury (Siegel et al. 2007). Following an intradermal injection of capsaicin, human subjects developed contralateral hyperalgesia and allodynia (Shenker et al. 2008). 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 (Koltzenburg et al. 1999; Watkins and Maier 2002). 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 (Hatashita et al. 2008; Milligan et al. 2003).

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 (Brooks 1991). 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 (Del Valle et al. 2009). 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 also 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 also extend more rostrally and caudally from the initially affected segment. Interestingly, this latter study (Del Valle et al. 2009) 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 the spread of symptoms may be found at the supraspinal level. Rommel et al. (1999)

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 (4.7t)	8.1 (6.6)	4.0 (2.3-.7)
Age at onset CRPS—mean (SD) year	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)	v^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)	v^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

showed hemisensory impairment in CRPS patients with only one affected limb, and that this was more common in those with left-sided CRPS. They proposed that the result 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 (Moseley et al. 2009). 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 (Bisiach et al. 1979).

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 (Bantick et al. 2002; Urban and Gebhart 1999). Additionally, the growing body of data implicating cortical changes in CRPS (see Swart et al. 2009 for review), offer potential mechanisms. For example, watching the mirror-image of the unaffected limb being touched elicits pain on the affected side (Acerra and Moseley 2005) and referred sensations of a tactile or painful stimulus were also experienced outside its expected somatic territory (McCabe et al. 2003). Forrs et al. (2005) describe a patient with chronic CRPS type-1 in whom pain and motor symptoms spread to the contralateral arm, and whole-head-magnetoencephaloghy 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 (Watkins and Maier 2002). 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 reflects 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 (Harrison 1999; Linazasoro 2005; Sutula 2004; Woolf and Salter 2000).

Interpretation of our results should consider some methodological issues and limitations. 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. As it is likely that major traumas are better recalled than minor ones, the frequency of minor trauma may be underestimated. One can argue that these patients may be incorrectly labeled as "spontaneous spread". However, to address the objective of this study we felt it was best to use a clear definition of trauma (soft tissue

injury, fracture, surgery) that does not include "microtraumata". Notably, this study was performed in a tertiary center for movement disorders which may lead to overrepresentation of patients with severe or multiple CRPS. However, the objective of this study was to evaluate the spread of symptoms and not the prevalence of multifocal CRPS. Finally, we are aware that this is a descriptive study, and that the pathophysiological aspects we discussed have not been tested.

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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Increased Systemic Catecholamines in Complex Regional Pain Syndrome and Relationship to Psychological Factors: A Pilot Study

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We have demonstrated that subjects with complex regional pain syndrome (CRPS) have asymmetric venous pool plasma concentrations of norepinephrine (NE) when affected and unaffected limbs are compared, with most demonstrating decreased NE levels in the affected limb. This pilot study explored whether systemic venous plasma catecholamine levels in CRPS subjects with sympathetically maintained pain (SMP) differ from those found in healthy volunteers. We also explored whether catecholamine levels were correlated with scores on psychometric measures of depression, anxiety, and personality. Venous blood samples from 33 CRPS/SMP patients (from unaffected limbs) and 30 healthy control subjects were assayed for plasma NE and epinephrine (E) concentrations. Plasma NE levels were significantly higher in the CRPS group ($P < 0.001$). Statistical comparisons of E levels across groups did not achieve significance ($P < 0.06$), although 52% of CRPS/SMP patients had E levels exceeding the 95% confidence interval based on control data. Significant positive correlations were found between E levels and scores on the Beck Depression Inventory and Scales 1, 3, and 6 on the Minnesota Multiphasic Personality Inventory-2 (all $P < 0.05$). This preliminary work suggests that increased NE and E levels in CRPS/SMP patients may result from the pain of CRPS, consequent affective distress, or both. Alternatively, our findings could reflect premorbid adrenergic hyperactivity caused by affective, endocrine, or other pathology, which might predispose these individuals to develop the syndrome. Definitive studies are needed to examine these hypotheses in detail.

(Anesth Analg 2004;99:1478–85)

Despite considerable advances in our understanding of pain pathophysiology, complex regional pain syndrome (CRPS) (1) remains a challenging and enigmatic disorder. The processes underlying CRPS remain incompletely understood and are the focus of intense research. Numerous precipitating events, most involving physical trauma or prolonged immobilization, have been identified (2), but why only a small subset of individuals develop CRPS after common traumas remains a mystery.

CRPS is often associated with apparent dysfunction in the sympathetic nervous system; it clinically presents as dysautonomic changes (e.g., edema, increased sweating, and decreased temperature) in the affected limbs, which superficially appear to reflect a state of chronic sympathetic hyperactivity. However, sympatholytic treatments such as nerve blocks (3) and surgical sympathectomies often have incomplete or temporary effects, and a significant portion of CRPS patients do not respond to them at all. Raja et al. (4) classify these nonresponders as having sympathetically independent pain (SIP), whereas those whose symptoms improve after chemical or surgical sympatholysis have sympathetically maintained pain (SMP) (5).

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If the sympathetic nervous system is not "overdriven," then the dysautonomia so prominent in chronic CRPS may suggest some form of adrenergic supersensitivity (6,7). Studies using models of peripheral nerve injury (8,9) support this concept, suggesting that tissue injury can trigger adrenosensitivity in injured afferent axons and surrounding vessels independently of sympathetic activity. Therefore, after nerve injury, circulating catecholamines may directly trigger nociceptive firing (10) and the vasomotor changes characteristic of the syndrome (6,7). Drummond et al. (11) found that CRPS patients experience more pain during states of sympathetic arousal, lending further support to this hypothesis.

We previously compared venous pool plasma catecholamine levels between affected and unaffected limbs of CRPS patients with SMP, all of whom manifested the dysautonomic changes classic in this syndrome, and we observed a small but significant decrease in venous plasma norepinephrine (NE) on the affected side (7). Drummond et al. (6) reported similar findings. Although the reasons for the decrease require further exploration, these results further contradict the hypothesis that the dysautonomia of CRPS is mediated by sympathetic hyperactivity in the affected limb. Instead, the more likely mechanism is peripheral adrenosensitivity, with circulating catecholamines causing an exaggerated peripheral autonomic response (6,7).

In this previous work, we noted that many CRPS patients had systemic plasma NE and epinephrine (E) levels in excess of prototypical normal ranges (derived from only five control subjects in that study) (7). In individuals without chronic pain, plasma NE and E levels increase during dysphoric emotional states such as anxiety, hostility, and depression (12,13) and may be reduced by relaxation techniques (14). Depression and anxiety are reported to be increased in CRPS patients (15), and these individuals' increased systemic NE and E may be a consequence of the pain or the affective distress accompanying the syndrome. In a patient with peripheral adrenosensitivity in the affected limb, increased plasma NE and E would be expected to result in dysautonomia and, hypothetically, pain.

No study has formally compared systemic plasma catecholamine levels in CRPS patients with those in healthy controls, which is the purpose of this pilot work. CRPS patients with SMP were specifically chosen because their responsiveness to sympathetic blockade suggested direct or indirect involvement of sympathetic nervous system function in the production or maintenance of symptoms. This study also reports our preliminary investigation of interactions between psychological variables and plasma catecholamine levels with a series of standardized psychometric tests. If affective distress is positively correlated with catecholamine levels in CRPS patients and if our hypothesis that chronic CRPS subjects have peripheral adrenosensitivity is correct, then this relationship would suggest one mechanism by which psychological factors might influence the development, maintenance, and exacerbation of the syndrome.

Methods

The study protocol was reviewed and approved by the Northwestern University and Medical University of South Carolina (MUSC) IRBs. All subjects provided informed consent after thorough explanation of the protocol, potential risks, and potential benefits.

Thirty-three individuals with upper limb CRPS were recruited from among the patients enrolled in the MUSC chronic pain treatment program. Each met published International Association for the Study of Pain (IASP) criteria for CRPS (1). All patients were also classified as having SMP, as indicated by at least a 50% decrease in visual analog pain ratings in response to paravertebral sympathetic ganglion blockade. All subjects were at least 1 wk out from their last block. This response to block was required for inclusion in the data set, with the assumption that this defined a more homogeneous group than the IASP diagnostic criteria alone—a group that was responsive to gross sympathetic manipulation and therefore exemplary of the hypothesis. The study was not designed to assess the effect of sympathetic blockade on pain, affect, or catecholamine levels. Twenty-three patients were subjects in our previous catecholamine investigation (7). In this pilot study, no attempt was made to control for medications.

Control subjects were 30 healthy volunteers who were recruited from the faculty and support staff of MUSC and the Rehabilitation Institute of Chicago. Criteria for inclusion as a control were 1) absence of any major physical or psychiatric disorder (by bedside history/assessment); 2) no regular psychoactive, endocrine, or antihypertensive medication (diuretics were permissible); 3) no known allergy or sensitivity to heparin; 4) age between 18 and 70 yr; 5) no history of exaggerated bleeding tendency or thrombocytopenia; and 6) ability to provide informed consent. Efforts were made to match ages of patients and control subjects, but these attempts were limited by control subject availability.

Subjects were asked to refrain from using any medication or caffeine on the day of blood collection and to refrain from smoking for 4 h before collection time. For patients, the limb affected by CRPS was identified, and blood was drawn from the contralateral limb. Twenty-three of the patients were preparing to undergo therapeutic IV regional (Bier) block of the affected limb, as previously described (7). For control

subjects, limb laterality for blood collection was determined by subject preference.

An IV catheter was started by using sterile technique in a distal vein of the chosen limb, usually in the dorsal venous arch of the hand or wrist. After confirmation of catheter placement by observation of blood return, an intermittent infusion cap was attached, and the catheter was flushed once with heparin sodium (100 U in 1 mL of solution) to maintain catheter patency.

Efforts were made to minimize the noxious or visual effects of stimuli related to blood collection that might artificially increase plasma catecholamine levels. To reduce the immediate effects of pain and anxiety surrounding the needlestick, each subject rested alone in the supine position in a quiet, dimly lit room for 30 min after IV insertion. The investigator then reentered the room and asked each subject to remain supine, facing away from the IV site. The infusion lock was removed, and 3 mL of blood was withdrawn through the IV and discarded to minimize the risk of heparin contamination. A second syringe was used to draw an additional 10 mL of blood for analysis. Either the IV catheter was then maintained for access during the Bier block, or it was removed and a sterile dressing was applied.

The 10 mL of blood was immediately transferred into 2 sterile 5-mL vacuum collection tubes containing EDTA. The tubes were labeled with patient initials and the date of collection and were immediately transported on ice to a centrifuge, where plasma was separated, extracted, and stored at • 70°C.

A subset of 18 CRPS patients completed standardized psychometric questionnaires before blood collection. Instruments included the Beck Depression Inventory (BDI) (16) and Beck Anxiety Inventory (BAI) (17), which are well validated measures of depression and anxiety states, respectively, and the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (18), an extensively validated measure of personality functioning.

Frozen plasma samples were transported on dry ice to the MUSC chemistry laboratory for analysis. NE and E were extracted from plasma onto activated alumina and assayed with high-pressure liquid chromatography with electrochemical detection, with dihydroxybenzylamine as the internal standard. The sensitivity of the assay was 15 pg/mL for both compounds. NE levels were determined on all samples submitted for analysis. E levels were determined for 25 (83%) of 30 controls and for 30 (91%) of 33 patients.

All analyses were conducted with SPSS statistical software (SPSS Inc., Chicago, IL). Age matching between groups was tested with an independent-samples Student's t-test. Sex matching was tested with nonparametric 2 • 2 •^{2} analysis. Control ranges for plasma NE and E were calculated on the basis of the upper and lower limits of the 95% confidence interval for the control sample. Because NE values were normally distributed, control and patient plasma NE distributions were compared by using simple factorial analysis of variance. E values did not approach a normal distribution in either patients or controls; groups were therefore compared by using the nonparametric Mann-Whitney U-test.

Although the available sample size was small, we were able to conduct a preliminary test of the relationships between catecholamine levels and scores on the BDI, BAI, and MMPI-2. NE distribution was normal within the subset of CRPS patients who completed psychometric instruments, although the distribution of E was nonnormal. Therefore, correlations between the psychometric measures and NE levels were examined by using parametric correlations (Pearson's r), whereas correlations with E levels were analyzed with nonparametric correlations (Spearman's •).

Fourteen (47%) of 30 CRPS patients and 14 (56%) of 25 controls had E concentrations less than the lower limit of detection of the assay, and these were coded as 0 for statistical analyses. Sample sizes for analyses of psychometric measures in this pilot study varied because of missing data (ranging from 12 for the BDI and BAI to 16 for the MMPI-2). The maximum number of subjects available for each variable was used in all analyses.

A priori directional hypotheses regarding relationships between depression/anxiety and catecholamines were tested by using one-tailed probability values to increase statistical power, given the limited sample size for these variables. Probability values for all other analyses were two tailed.

Results

Group demographics are summarized in Table 1. Seventy-three percent of the CRPS patients and 50% of control subjects were female. The sex ratio across groups approached, but did not reach, statistical significance (Pearson •^{2} • 3.442; P • 0.08). Age distributions across the two groups were not significantly different (P • 0.10). Within-group analyses indicated that mean age was not significantly different across sexes in either the CRPS or control groups (P • 0.10).

The 95% confidence intervals for the control group were used to define "normal" catecholamine ranges. Results for NE are summarized in Table 2. Seventy-eight percent of CRPS patients had NE levels more than the upper limit (210 pg/mL) of the control range. The largest NE concentration seen in the CRPS group (932 pg/mL) was more than fourfold larger than this upper limit. Not surprisingly, analysis of variance demonstrated significantly larger NE concentrations for the patient group compared with controls ($F_{1,57}$ •

Table 1. Demographics for Complex Regional Pain Syndrome (CRPS) Patients and Control Subjects

Sex	n	Mean age (yr)	sd
CRPS patients			
Male	9	41.4	11.9
Female	24	42.6	14.1
Total	33	42.3	13.4
Controls			
Male	15	31.4	7.3
Female	15	40.5	11.2
Total	30	35.9	10.4

14.82; P • 0.001), and this difference was not explained by between-group differences in age or sex distribution (analysis of covariance: $F_{1,57}$ • 11.43; P • 0.001).

Results for E are summarized in Table 3. Fifty-two percent of CRPS patients had levels more than the upper limit (26 pg/mL) of the control range, and the highest patient E value (2370 pg/mL) was approximately 90 times the upper normal limit. Nonparametric analysis of E data indicated a trend for larger plasma E concentrations in the CRPS group than in controls; the difference approached, but did not reach, statistical significance (Mann-Whitney U-test, 259.0; P • 0.06). There was no significant correlation between plasma NE and E levels among CRPS patients (Spearman's • • 0.05; P • 0.10) or controls (Spearman's • • • 0.04; P • 0.10).

Among CRPS patients, plasma NE was unrelated to sex, but men displayed significantly higher levels of E ($•_{27}$ • • 0.41; P • 0.05). In contrast, there was a significant relationship between NE and sex among controls, with higher plasma NE levels in female patients ($•_{28}$ • 0.64; P • 0.001). Male controls displayed a trend toward higher E levels, but this did not reach statistical significance ($•_{23}$ • • 0.38; P • 0.1). Grossly, no significant differences were found between men and women on any of the psychometric tests (P • 0.1); however, this sample was too small to make any definitive statements as to sex/psychometric effects.

Age and E were significantly related in the control group, with higher E levels in younger individuals (Spearman $•_{23}$ • • 0.46; P • 0.05). In contrast, neither NE nor E was significantly correlated with age in the CRPS group (all correlations: P • 0.10).

Table 4 presents exploratory correlations between psychometric measures (BDI, BAI, and MMPI-2) and plasma E and NE levels for a subset of CRPS patients. Because correlations were not based on a specific directional hypothesis, P values are given strictly for descriptive reasons. Plasma NE was not significantly correlated with any of the psychometric scores. However, several significant relationships were observed between psychometric results and plasma E levels.

Despite the small sample size, a significant positive relationship was observed between plasma E and depression scores on the BDI. Similar significant positive relationships were noted between E levels and Scales 1, 3, and 6 on the MMPI-2. Scale 1 measures an individual's tendency toward denial of good health and admission of a variety of somatic symptoms (somatic focus). Scale 3 reflects denial of psychological and emotional problems, discomfort in social situations, and a general denial of physical health (avoidance or denial/suppression as a coping style). Scale 6 reflects social sensitivity, suspiciousness, rigid opinions and attitudes, and ideas of reference. (This scale is sometimes called the paranoia subscale, but in the context of these findings, it may best be understood as reflecting a sensitive, suspicious, or hostile attitude toward the world.)

Given the small sample size available for this analysis, we considered the possibility that extreme cases could bias the results. However, exclusion of statistical outliers for both E and NE did not appreciably alter the pattern of significant relationships observed.

Discussion

Research has increased our understanding of the pathogenesis of neuropathic pain states, including CRPS. Histochemical studies in animal models suggest that catecholamines are involved in the pathophysiology of some types of neuropathic pain (10,19,20). Acute tissue injury is accompanied by the local release of multiple compounds, including neuropeptides (21), which ultimately sensitize peripheral afferent nerve endings (both nociceptors and nonnociceptive terminals) to usually innocuous stimuli. One mechanism for this sensitization is the upregulation of excitatory receptors, including NE receptors, at the terminals of injured nociceptive and nonnociceptive afferents (9,22). New axonal sprouts from injured afferents develop abnormal, painful sensitivity to both NE (23) and E (24,25). This hypersensitivity to catecholamines can develop in the absence of postganglionic sympathetic input (8) and may be the result of catecholaminergic receptor upregulation (26). Sensitized nerve terminals may produce spontaneous discharges even in the absence of external stimulation (27). Taken together, these findings suggest that exposure of injured tissue to circulating NE and E may contribute to the spontaneous pain and allodynia of CRPS.

The original theoretical concept of reflex sympathetic dystrophy (also known as CRPS) implicated sympathetic nervous hyperactivity in the affected limb as the mechanism driving the syndrome. However, current research indicates that regional venous plasma NE (and, indirectly, sympathetic function) may be decreased in the affected limb relative to the contralateral unaffected limb (6,7). If tissue injury sensitizes peripheral nociceptors to catecholamines, then

Table 2. Plasma Norepinephrine (NE) Levels in Complex Regional Pain Syndrome Patients and Controls

Variable	n	NE (pg/mL) (mean)	sd	SEM	Range	Mean-centered CV (interassay)
Controls						
All	30	189.6	55.1	10.1	104–326	0.29
Women	15	224.5	52.1	13.4	141–326	0.23
Men	15	154.7	31.3	8.1	104–210	0.20
Patients (unaffected side)						
All	33	326.8	187.4	32.6	76–932	0.57
Women	24	324.6	162.2	33.1	98–836	0.500
Men	9	332.8	254.5	84.8	76–932	0.76

CV • coefficient of variability.
Control group 95% confidence interval for plasma NE: 169–210 pg/mL.

Table 3. Plasma Epinephrine (E) Levels in Complex Regional Pain Syndrome Patients and Controls

Variable	n	Median score	E (pg/mL) (mean)	sd	sem	Range	Mean-centered CV (interassay)
Controls							
All	25	0	15.8	24.5	4.9	0–93	1.55
Women	14	0	7.6	16.0	4.3	0–52	2.10
Men	11	23	26.1	30.0	9.0	0–93	1.15
Patients							
All	30	23	207.7	500.1	91.3	0–2370	2.41
Women	21	0	71.3	171.6	37.4	0–626	2.41
Men	9	77	526.1	818.6	272.9	0–2370	1.56

CV • coefficient of variability.
Control group 95% confidence interval for plasma E: 5–26 pg/mL.

Table 4. Correlations Between Psychometric Measures and Plasma Catecholamine Levels

Variable	E[a]	NE[b]
BDI	0.52*	0.13
BAI	0.34	0.12
MMPI L scale	0.24	• 0.10
MMPI F scale	0.11	• 0.04
MMPI K scale	• 0.01	0.15
MMPI Scale 1	0.54*	• 0.06
MMPI Scale 2	0.31	• 0.04
MMPI Scale 3	0.55*	• 0.25
MMPI Scale 4	0.10	0.22
MMPI Scale 5	0.09	0.29
MMPI Scale 6	0.54*	0.00
MMPI Scale 7	0.35	0.14
MMPI Scale 8	0.39	0.15
MMPI Scale 9	• 0.07	0.22
MMPI Scale 0	0.11	0.01

BDI • Beck Depression Inventory (16); BAI • Beck Anxiety Inventory (17); MMPI • Minnesota Multiphasic Personality Inventory (18); E • epinephrine; NE • norepinephrine.
[a] Spearman's •
[b] Pearson's r.
* P • 0.05.

the pain and dysautonomic phenomena seen in CRPS could be caused by normal (or high) systemic levels of catecholamines affecting supersensitive tissue, rather than by high regional levels of catecholamines produced by an overactive sympathetic system (6,7). Indeed, the decrease in NE seen in CRPS patients may actually reflect local sympathetic hypofunction that is perhaps related to damage to sympathetic efferents (7), and this is consistent with the clinical observation that many patients go through a period of apparent sympathetic hypofunction acutely (hot, red, and dry) before developing the characteristic chronic presentation (cold, blue, and sweaty) (7).

Although the sympathetic nervous system efferents may not be overdriven in CRPS, experimental evidence does suggest functional sympathetic/sensory coupling at the dorsal root ganglion (DRG) in animal models of neuropathic pain. The nociceptive barrage of pain signals from sensitized afferent terminals induces windup of wide dynamic range neurons in the DRG, manifested by increased firing frequency and decreased discrimination between noxious and normally innocuous stimuli (28). Postganglionic sympathetic activation has been shown to potentiate ectopic discharges from primary DRG neurons during windup (29). This relationship may have a structural basis; sympathetic postganglionic axons form basket-like skeins around the somata of DRG sensory neurons in animal and human neuropathic pain states (30). There are thus sound arguments for both peripheral noradrenergic sensitization (8,9) and for direct sympathetic nervous involvement (31) in the maintenance of neuropathic pain states. Both mechanisms may be involved in CRPS to varying degrees.

In this pilot study we found that levels of circulating NE were higher than normal control levels in 78% of our CRPS sample, a statistically significant difference. If CRPS patients are regionally sensitized to NE at the tissue level and if upregulation of peripheral NE receptors is tied to abnormal nociception and vasomotor function, then increased circulating NE levels would have marked clinical significance. Patients with high plasma NE would be expected to experience greater regional pain and manifest increased edema, vasoconstriction, and other hyperadrenergic manifestations of CRPS. Subsequent investigations should assess these variables and correlate them with NE levels.

This finding raises questions about the clinical distinction between SMP and SIP (4,32). Patients with SMP respond to sympatholytic therapies, whereas SIP patients do not. This difference in response could reflect differing regional or circulating NE levels, differing tissue sensitivities to NE, or both. All CRPS patients involved in this study had documented SMP. Further research comparing SMP and SIP patients and the relationship of these subsets of CRPS to catecholamine levels, clinical presentation, and psychometric testing is indicated.

We found levels of circulating E to be higher than normal control values in 52% of CRPS patients, with concentrations up to 90 times larger than normal in one patient. (None of the individuals with increased E levels had known pheochromocytomas or other endocrine, gastrointestinal (GI), or kidney pathology, nor were any found on subsequent workup.) However, the difference in plasma E levels between groups was not statistically significant. Whether the marked E increases in certain individuals reflect preexisting emotional distress, anxiety over the sampling technique, some other premorbid or comorbid hyperadrenergic state, or another process entirely (such as an artifact) is unexplained. One source of variance not controlled for in this pilot study was the fact that some of the subjects were taking antidepressant drugs for pain or depression, and these drugs theoretically may influence blood catecholamine levels. This factor should be considered in a definitive trial.

One might hypothesize that increased E and NE levels in CRPS are a consequence of the pain and distress that accompany the syndrome, rather than a manifestation of endocrine pathology or an autonomic or psychological state peculiar to CRPS. For this hypothesis to be correct, chronic pain patients as a group would be expected to have increased catecholamine levels. A review of the literature fails to support this hypothesis. NE and E levels are similar to control values in patients with fibromyalgia (32,33), painful diabetic neuropathy (34), and cluster headaches (35). Plasma NE was less than control levels in patients with migraine (36), and concentrations of NE, E, and dopamine were decreased in patients with tension-type headaches (37). The only studied pain states besides CRPS that were accompanied by increases of plasma NE and E were acute pain conditions, i.e., venipuncture (34) and early myocardial infarction (38,39). Please note our efforts to minimize the acute effect of venipuncture, in the Methods section.

As noted, one possible reason for plasma NE and E increases is affective distress. The mechanisms underlying this relationship include both central activation of the sympathetic nervous system (primarily accounting for systemic NE) and pituitary/adrenal activation (primarily accounting for E). Several studies suggest that CRPS patients may have more emotional distress than patients with other types of chronic pain conditions (15,40-45), but they also may experience "more" pain. Of course, there is no way to compare absolute pain levels across diagnoses.

Anxiety, stress, and pain all increase circulating catecholamine levels (34,46–48). In our small sample, we found that plasma E was positively correlated with scores on psychometric measures that reflected depression, high somatic focus, avoidant coping style, and emotional sensitivity/suspiciousness ("paranoia/hostility"). Our findings support the hypothesis that psychological distress and increased plasma catecholamines are related in CRPS patients (41,49–51), although no causal connection with CRPS development can be assumed, given the correlational nature of these data and the small sample size. We did not correlate pain severity with depression, anxiety, or E levels, and these relationships should be explored carefully in future investigations.

The kidneys and GI tract are also significant sources of peripheral circulating NE and E. The differential contribution of various organs to circulating NE and E was not addressed in this pilot investigation.

By contrast, no significant correlations were demonstrated between NE levels and psychometric scores, and the concentration of one measured catecholamine did not predict that of the other. These were unexpected findings; one possible explanation is separate roles for E and NE in the development or maintenance of CRPS. Whereas NE has been experimentally linked to peripheral sensitization, allodynia, and hyperalgesia, E may be more involved in the realm of emotional distress and the stress response to pain. Further investigation is necessary to clarify these relationships.

Do increased E and NE levels predispose individuals to develop CRPS (52)? Our data provide no ready answers. Whether increased NE and E predate the development of CRPS is unknown. No published studies have documented psychological status and catecholamine levels before the onset of the syndrome. Whatever the ultimate cause of CRPS, our findings are consistent with the theoretical effects of many of the treatments recommended for the syndrome (53). Early

and aggressive treatment of stress, anxiety, and depression by methods such as relaxation training (14) may reduce plasma NE and E levels, theoretically decreasing peripheral sensitization and pain and thereby alleviating emotional distress. Pharmacologic management of pain, depression, and anxiety may also help to reduce affective distress, the adrenergic stress response, and circulating catecholamine levels, leading to further beneficial effects.

The connection between plasma catecholamines, psychological state, and CRPS certainly deserves exploration beyond this pilot study. A group of patients with SIP should be studied and compared with SMP patients to examine any differences in plasma catecholamine levels or psychometric scores. Enlargement of sample size, expansion of the psychometric battery, and use of a control group (perhaps one with a different chronic pain condition) will increase the statistical power and robustness of the study. We did not control for the duration of CRPS symptoms, time since the last sympathetic block (except that there was at least one week since the last block), type of block, comorbid medical conditions, or the roles of any long-acting medications taken by the patients on the days before sampling. These variables must be considered in further investigations.

Even as we understand more about the complex pathophysiology of neuropathic pain, many aspects of CRPS remain a mystery, and each new piece of knowledge tends to raise more questions. The exact role of catecholamines in the genesis and maintenance of CRPS is still incompletely understood. In this study, CRPS patients with SMP demonstrated increases in plasma NE and (to a lesser extent) E compared with normal control subjects, and increased E was correlated with psychometric scores that indicated affective distress and certain personality characteristics. Whether these psychological characteristics originated before or after the onset of CRPS remains unclear. Further investigation may lead us toward techniques for the identification of individuals at high risk for CRPS and may eventually lead to effective preventive measures and more effective treatments.

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