The Natural History of Complex Regional Pain Syndrome

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Objective: Complex regional pain syndrome (CRPS) is a severe chronic pain condition characterized by sensory, autonomic, motor, and dystrophic signs and symptoms. This study was undertaken to expand our current knowledge of the evolution of CRPS signs and symptoms with duration of disease.

Method: This was a retrospective, cross-sectional analysis using data extracted from a patient questionnaire to evaluate the clinical characteristics of CRPS at different time points of disease progression. Data from the questionnaire included pain characteristics and associated symptoms. It also included autonomic, motor, and dystrophic symptoms and also initiating events, ameliorating and aggravating factors, quality of life, work status, comorbid conditions, pattern of pain spread, family history, and demographics. Comparisons were made of different parameters as they varied with disease duration.

Results: A total of 656 patients with CRPS of at least 1-year duration were evaluated. The average age of all participants was 37.5 years, with disease duration varying from 1 to 46 years. The majority of participants were white (96%). A total of 80.3% were females. None of the patients in this study demonstrated spontaneous remission of their symptoms. The pain in these patients was refractory showing only modest improvement with most current therapies.

Discussion: This study shows that although CRPS is a progressive disease, after 1 year, the majority of the signs and symptoms were well developed and although many variables worsen over the course of the illness, the majority demonstrated only moderate increases with disease duration.

Key Words: complex regional pain syndrome (CRPS), natural history, questionnaire, disease progression

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Complex regional pain syndrome (CRPS) is a condition that usually results from an injury or a surgical procedure. However, in some cases, no precipitating event can be identified. CRPS is now generally regarded as a systemic condition that involves both central and peripheral components of the neuraxis[1,2] and interactions between the immune and nervous systems.[3,4] Factor analysis reveals that the signs and symptoms in CRPS patients cluster into 4 distinct subgroups: (1) abnormalities in pain processing; (2) skin color and temperature changes; (3) edema, vasomotor, and sudomotor abnormalities; and (4) motor dysfunction and trophic changes.[5,6] The recent Budapest consensus panel proposed diagnostic criteria for CRPS requires at least 1 symptom in each of the 4 factors and 1 sign in at least 2 of the 4 factors. It also requires that there be no other diagnosis that better explain these signs and symptoms.[7]

The reported incidence of CRPS after injuries is highly variable.[8–14] Some of the variability is due to the fact that in some studies, patients were evaluated early in the disease process (weeks to months) whereas in others they were seen after prolonged illness. Bickerstaff and Kanis[15] report an incidence of CRPS of 28% after Colles fracture. However, the percent of patients with CRPS symptoms decreased to 1% to 2% after 1 year, which may account for the much lower incidence of CRPS after Colles fracture in their series than that quoted in the literature. Similarly Zyluk[16] reported that 87% of his patients resolved at 1 year after radial fracture.

There is also variability in the few population-based studies on the incidence of CRPS. However, there is agreement that the incidence of CRPS in females is greater than in males. A resent population-based study from the Netherlands reports an incidence of 40.4 for females and 11.9 for males per 100,000 person years at risk.[17] An earlier population-based study from Olmsted County, Minnesota report a much lower incidence of 8.57 for females and 2.16 for males per 100,000 person years at risk.[18] The earlier study also reported that the majority of CRPS patients underwent resolution of their symptoms, often spontaneously, and in only a minority of patients the disease became chronic.[18] This study was undertaken to expand our current knowledge of the natural history of refractory CRPS. Comparisons were made of the factors validated for CRPS.[7]

METHODS

A questionnaire was developed in 1995 and given to all of the patients referred to the pain clinic of Drexel University College of Medicine. The data presented in this study was derived from patients seen between July 1995 and January 2006. All of the patients who completed the questionnaire were examined by the same neurologist (R.J.S.). In some cases, the patients had been seen regularly by Robert J. Schwartzman for over 20 years (33 patients). All of the data for this study were derived from the patient responses to the questionnaire. Data from the questionnaire were entered in a relational database (Microsoft Access). Data analysis was performed by means of Structured Query Language queries from the database tables. Comparisons were made of different parameters as they varied with disease duration. The natural history was determined not by following any 1 patient over time, but by evaluating the response of many patients with varying durations of disease. This retrospective study was approved by the

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Drexel University College of Medicine Institutional Review Board.

Inclusion Criteria

Patients who met the diagnostic criterion for CRPS[7] with disease duration greater than 1 year were included in this study. This entry point was chosen to allow for spontaneous resolution of any inciting event such as fracture, nerve injury, or surgical procedure. No distinction was made between CRPS I and II.

Sample Size and Duration of the Study

There were 844 patients seen at the pain clinic of Drexel University College of Medicine between July 1995 and December of 2006 who met the diagnostic criteria for CRPS. Six hundred fifty-six patients had CRPS duration of greater than 1 year and completed the questionnaire to a sufficient degree to be included in this study. The 656 patients included in this study were afflicted with CRPS for periods between 1 and 46 years. The number of CRPS patients included in this study at different years of disease duration is shown in Table 1.

Statistical Analysis

Relations between any of the response variables and duration of disease were examined by regression analysis with the statistical data analysis software, SYSTAT version 11 (SYSTAT Software Inc, Richmond, CA).

RESULTS

Demographics

There were 656 patients with CRPS of at least 1-year duration, 129 males and 527 females. Males made up 19.7% of the patients, their age at onset varied from 10 to 69 years with an average (± standard deviation) of 37.8 ± 12.3 years. Females made up 80.3% of the patients, their age at onset varied from 7 to 74 years with an average age of 36.7 ± 12.1 years (Fig. 1). Most of the patients were white (96%), there were 2.5% African Americans, 1% Hispanics, and 0.5% Asians.

TABLE 1. Number of Questionnaires Completed for Each Year of Disease Duration

Duration of CRPS (y)	No. Completed Questionnaires
1	81
2	78
3	79
4	70
5	44
6	44
7	39
8	36
9	14
10	21
11	18
12	12
13	10
14	14
15	14
16	14
17	8
18	15
19	12
>20	33

CRPS indicates complex regional pain syndrome.

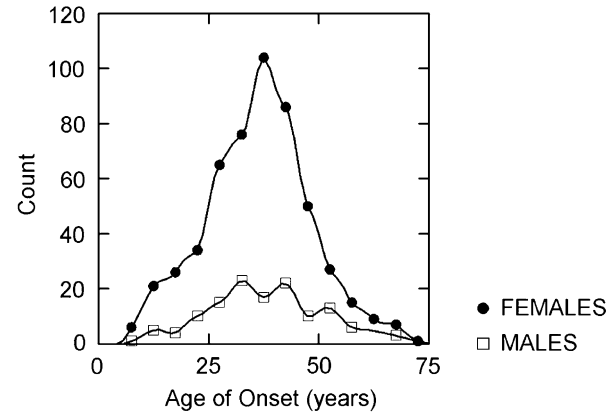

FIGURE 1. Complex regional pain syndrome patient distribution by age and sex.

Initiating Event

Injuries were listed as the initiating event of their pain problem by 77.6% of the respondents. In 11.5% of the patients, surgery was listed as the initiating event, 1.0% listed stroke, 7.8% could not identify the initiating event, and 1% of the patients did not answer the question. The most common causes of the injuries were motor vehicle accidents 23.6%, falls 14.6%, struck by object 3.4%, lifting heavy objects 3.2%, assault 2.2%, and medical procedures 1.6%. In 10% of the patients, a surgical procedure was performed after their injury. These patients could not discriminate whether the injury or the surgery initiated their pain problem. The most common injuries were bone fractures, sprains, blunt trauma (struck by objects), or lacerating trauma (knife stabbing, gunshot wounds, animal bites). Fifty percent of the patients who listed an injury as the initiating event had their extremity immobilized after the injury. In general, the patient's initial pain problems were slightly more prevalent in the upper part of the body (53%) (arms, neck, and shoulders) than the lower parts (47%) (legs, hips, and lower back). There was also a small preponderance for the right side of the body (54%) versus the left (46%).

Pain Intensity

Patients were asked to enter the overall intensity of their pain based on a 0 to 10 numerical rating scale (NRS) where 0 was no pain and 10 was unbearable pain. The average pain intensity for each year after the initiating event varied between 6.53 and 8.75 with a mean ± standard deviation of 7.33 ± 0.6. During the first 5 years, the average pain was 6.91 ± 0.5 and it increased to 7.92 ± 0.6 after 15 years (Fig. 2). The overall pain intensity demonstrated a statistical significant increase with disease duration ($r = 0.60$, $P = 0.005$). Early in the disease a smaller percent of patients (87%) reported continuous pain, which increased to 98% after 15 years. In contrast to average pain intensity, the increase in percent of patients reporting continuous pain did not show a statistically significant correlation with progression of disease ($r = 0.258$, $P = 0.273$). When asked to select the time of

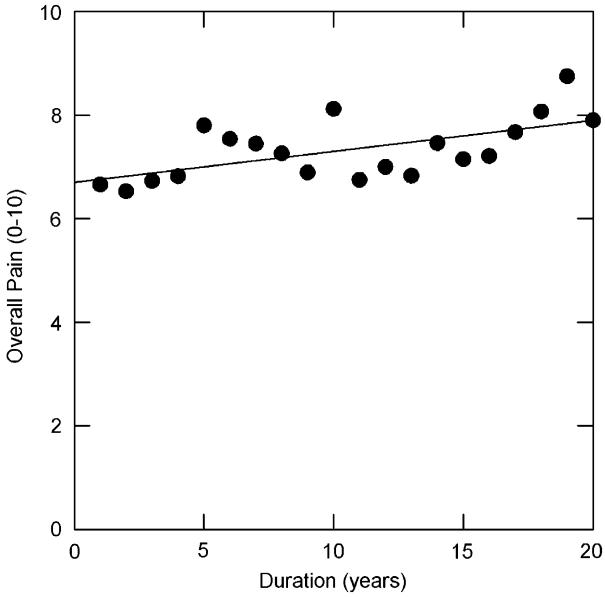

FIGURE 2. Variations in the intensity of overall pain on a 0 to 10 numerical rating scale versus duration of disease. The intensity of overall pain demonstrated a statistically significant positive correlation with progression of disease ($r = 0.60$, $P = 0.005$).

the day that their pain was worse (morning, afternoon, evening, or night), approximately one-third of the patients selected all 4 periods. The majority of the remaining patients selected night and evening as the most painful part of the day.

The Short Form McGill Pain Questionnaire in CRPS

The responses to the short form of the McGill pain questionnaire[19] were tabulated by year from the onset of CRPS. The average total pain score was 23.47 for the sensory component, 7.41 for the affective component with an average total score of 30.88. Neither the sensory component nor the affective component demonstrated a statistically significant positive correlation with progression of disease. The sensory descriptors with the greatest values were hot burning and aching. Those with the lowest values were splitting, gnawing, and cramping. Most of the sensory descriptors demonstrated a trend toward higher scores as the disease progressed, however in only gnawing ($r = 0.57$, $P < 0.01$) and splitting descriptors ($r = 0.45$, $P < 0.05$) were the positive correlation statistically significant. None of the affective components of the McGill questionnaire showed a statistically significant correlation with progression of disease. The affective descriptor with the highest score was tiring and exhausting and the one with the lowest score was fearful.

Pain Processing

There were several questions that evaluated whether nonpainful mechanical stimuli were perceived as pain (allodynia): (1) Do you feel pain now or within the last month when touched or lightly brushed (touch allodynia)? (2) Do you feel pain now or within the last month when light pressure is applied to a limb or a joint (static mechanoallodynia)? In addition, the patients were asked to rate the severity or intensity of the pain on a 0 to 10 NRS scale with zero being no pain and a 10 representing unbearable pain. The percent of patients that reported touch allodynia did not demonstrate a statistically significant positive correlation with progression of disease. During the first 5 years, 84% of all patients reported touch allodynia and after 15 years, the percent was greater than 90%. The severity of touch allodynia increased from 6.1 ± 0.4 during the first 5 years to 7.1 ± 0.5 after 15 years. The severity of touch allodynia demonstrated a statistically significant positive correlation with progression of disease ($r = 0.46$, $P = 0.04$).

As with touch allodynia, the percent of patients that reported static mechanoallodynia did not demonstrate a statistically significant positive correlation with progression of disease. During the first 5 years, 91% of all patients reported dynamic mechanoallodynia and after year 15, the percent was greater than 96%. An increase in the severity of the static mechanoallodynia was statistically significant during progression of disease ($r = 0.495$, $P = 0.026$) increasing from 6.8 ± 0.3 during the first 5 years to 8.1 ± 1.1 after 15 years.

The patients were also asked if they felt internal organ (visceral) pain. Early in the disease, during the first 5 years, 47% of the patients reported visceral pain and after year 15, the percent increased to 62%. The severity of the visceral pain increased from 3.0 ± 0.6 during the first 5 years to 4.2 ± 0.8 after 15 years. Both the percent of patients reporting visceral pain ($r = 0.57$, $P < 0.01$) and its severity ($r = 0.54$, $P < 0.05$) demonstrated a statistically significant positive correlation with disease duration.

Patterns of Pain Spread

When asked if their pain spread over time, 31.1% of the patients reported spread to areas contiguous to the initial injury, 11.5% to the same extremity on the contralateral side of the body in a mirror pattern (ie, right arm to left arm), 10.8% to the other extremity on the ipsilateral side (ie, right arm to right leg), and 11.3% to the other extremity on the opposite side (ie, right arm to left leg). Thirty-five percent of the patients reported that their pain had spread to their whole body and 8% did not answer the question. At least 92% of the respondents had spread of their pain in some pattern (it cannot be assumed that the 8% who did not respond demonstrated no spread). Although all of the different types of spread occurred throughout the disease process, the following patterns emerged. Contiguous spread occurred in most patients early (1 to 2 y) and remained the most common type of spread during the first 10 years. Spread to other extremities occurred throughout the disease process with no specific pattern whereas generalized (all extremities) spread was most prominent late in the disease process (after 15 y).

Ameliorating Factors

Patients were asked to list all things that made their pain better. The major relieving factors for CRPS pain were: medication (50%), rest (42%), hot weather (12%), and hot or warm water (11%). Elevation of the affected extremity was helpful to 7.6% of patients. Massage and physical therapy were equally effective aiding 5.8% of patients. Biofeedback, dorsal column stimulators, meditation, and acupuncture were considered effective by less than 5% of patients. Fifteen percent of the patients reported that "nothing made their pain better."

Medications

The patients were asked to list all of the medications, therapies, or devices that they had used for the treatment of their CRPS. All of the patients were taking (or had taken) multiple medications during treatment of their CRPS. The percent of patients taking the following class of medications were: narcotics (74.7%), anticonvulsants (68.8%), nonsteroidal anti-inflammatory drugs (60.0%), antidepressants (52.8%), antianxiety agents (15.3%), sleeping pills (11.5%), and steroids (11.3%). A large percent of patients (66.4%) underwent blocks (sympathetic, somatic, or trigger point), 18.6% had spinal cord stimulators implanted, and approximately 7% of the patients were implanted with intrathecal pumps for the delivery of baclophen or morphine. When asked, on a scale of 0% to 100%, how much relief these medications provided, the average response was 33.2% with little variation with duration of disease.

Aggravating Factors

When asked to list all things that made their pain worse, cold weather (48.2%) and physical activity (37.0%) were the most common items listed. Within the physical activity category, 17.3% of the patients noted that walking increased their pain. Specific categories of movement such as standing for too long (15.4%), holding the arms above the shoulders (12.9%), hand activity (8.7%), driving or riding in a car (5.4%), and repetitive movements (4.0%) were listed as aggravating factors. Stress was a significant aggravating factor in 12.3% of the respondents.

Skin Color and Temperature Changes

In response to the following questions: (1) Have you experienced skin color changes within the last month; and (2) Have you experienced temperature changes within the last month? Early in the disease, the first 5 years, 71% of the patients reported skin color changes and 83% reported temperature changes. After year 15, the percent of patients reporting skin color changes increased to 81% and to 95% for those reporting temperature changes. The percent of patients reporting skin color changes ($r = 0.46$, $P = 0.041$) and temperature changes ($r = 0.44$, $P = 0.050$) demonstrated a statistically significant positive correlation with duration of disease.

Swelling and Sweating

In response to the question: Have you experienced swelling within the last month? Swelling was noted by 75% of respondents at 1 year. It worsened over time and was reported by 90% of patients after 15 years. The percent of patients reporting swelling demonstrated a statistically significant ($r = 0.50$, $P = 0.024$) positive correlation with duration of disease. When asked to list other symptoms, 40% of the patients listed increased sweating. Increased sweating was reported by 33% of patients during the first 5 years and by 4 4% of patients after 15 years. The percent of patients reporting increased sweating was not statistically significant ($r = 0.174$, $P = 0.463$) with duration of disease.

Motor Dysfunction

The questions posed to patients were: (1) Are you experiencing loss of strength now or within the last month?; (2) Are you experiencing difficulty initiating movement now or within the last month?; (3) Are you experiencing abnormal hand or foot posture now or within the last month?; (4) Are you experiencing muscle spasms now or within the last month?; and (5) Are you experiencing spontaneous falls now or within the last month?

Loss of strength was reported by the majority of the patients and varied little throughout the course of the illness. It was reported by 93% of patients during the first 5 years and by 94% of the patients after 10 years of illness. Loss of strength did not demonstrate a statistically significant correlation with duration of disease ($r = 0.22$, $P = 0.340$). The percent of patients reporting difficulty in initiating movement increased slightly throughout the course of the illness. It was reported by 88% of the patients during the first 5 years and by 94% of the patients after 10 years, which was not statically significant with disease duration ($r = 0.22$, $P = 0.353$).

Abnormal limb posture was noted in 57% of patients at year 1 and increased to 80% of the patients after 10 years. Abnormal limb posture demonstrated a statistically significant increase with disease duration ($r = 0.52$, $P = 0.018$). The percent of patients reporting muscle spasms varied little throughout the course of the illness. It was reported by 84% of patients during the first 5 years of illness and increased to 93% of patients by year 10, it did not demonstrate a statistically significant correlation with disease duration ($r = 0.342$, $P = 0.14$).

The percent of patients reporting spontaneous falls increased slightly throughout the course of the illness. It was reported by 27% of patients during the first 5 years of illness and increased to 35% of patients by year 10. This increase was not statistically significant with duration of disease ($r = 0.154$, $P = 0.519$).

Medical History

The CRPS patients were asked to list, besides their pain, other symptoms or medical conditions. The following medical conditions (including the percent afflicted if $> 1\%$) were reported by the respondents: cardiovascular disease (25%), anxiety (13.3%), depression (10.8%), arthritis (8.5%), high cholesterol (5.8%), thyroid problems (5.4%), esophageal reflux disease (5.1%), Raynaud syndrome (4.9%), asthma (4.3%), diabetes (2.8%), seizures (2.8%), and cancer (1.3%).

Other Symptoms

In addition to the medical conditions listed above, patients reported a number of other symptoms. The symptoms reported by more than 10% of the respondents are tabulated in Table 2. The table includes: (1) the reported symptoms in descending order (most frequently reported to least frequently reported); (2) the percent of patients that reported the symptom; and (3) the correlation coefficient (r), the probability (P), and the slope (the average percent change per year) were listed if the symptom demonstrated a correlation with duration of disease with a P value less than or equal to 0.05. Figure 3 illustrates the changes with disease duration in 2 categories. The first variable, tiredness, was reported by 68.5% of the patients and demonstrated a statistically significant positive correlation with duration of disease ($r = 0.47$, $P = 0.036$) with an average increase of 1.0% per year. The second variable, weakness, was reported by 64.7% of the patients and did not show a statistical change with duration of disease ($r = 0.015$, $P = 0.951$).

TABLE 2. List of Other Symptoms and Percent Affected in Descending Order Reported by More Than 10% of Respondents. The Correlation Coefficient (*r*), Probability (*P*), and Slope are Listed for Symptoms That Demonstrated Significant ($P<0.05$) Changes With Disease Duration

	Other Symptoms			
Symptom	Affected %	Correlation (*r*)	Probability (*P*)	Slope %
Difficulty sleeping	71.9			
Tiredness	68.5	0.475	0.036	1.0
Weakness	64.7			
Headaches	61.5			
Memory problems	54.5			
Difficulty thinking	52.6			
Sweating	48.5			
Feeling drowsy	38.9			
Constipation	38.9	0.576	0.008	1.4
Dizziness	35.1			
Nausea	33.4			
Indigestion	26.6			
Lack of appetite	26.6			
Urinary problems	24.9	0.572	0.008	1.1
Blurred vision	24.5			
Itching	24.5	0.516	0.024	1.0
Weight changes	23.0			
Rash	19.5			
Diarrhea	17.8	0.552	0.014	0.6
Swallowing difficulties	16.9			
Nightmares	16.3			
Difficulty breathing	15.7	0.638	0.006	1.0
Vomiting	12.0			
Depression	10.8			

Family History

The following medical conditions (including the percent afflicted if >2%) were present in the immediate family of the respondents: cardiovascular disease (70.1%), arthritis (42.9%), pulmonary disease (26.7%), cancer (26.7%), diabetes (18.5%), kidney or urinary problems (10.1%), autoimmune disorders (7.7%), musculoskeletal disorders (5.3%), gastrointestinal problems (2.6%), mental illness (2.6%), and thyroid diseases (2.1%).

Social History

Approximately 50% of the patients provided their cigarette smoking and alcoholic beverage consumption history. The smoking history of patients revealed that 44% of the patients never smoked and 2.8% do not smoke but did not specify if they ever did. The percent of patients that stopped smoking was 21.9%, some stopped before (15.7%) and others after (6.2%) being diagnosed with CRPS. Fourteen percent of the patients reported that they smoked more, 9.9% the same, and 6.8% less than they did before being diagnosed with CRPS. The alcoholic beverage consumption history revealed that 22% of the patients never drank, 4% do not drink but did not specify if they ever did, 30% stopped drinking, some before (15.2%) and others after (14.8%) being diagnosed with CRPS. Four percent of the patients reported that they drink more, 20% the same amount, and 21% less than they did before being diagnosed with CRPS.

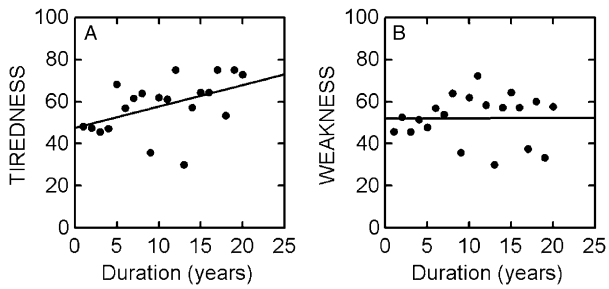

FIGURE 3. Illustration of 2 entries (A) Tiredness and (B) Weakness from the ''Other Symptoms or Medical Problems'' question. The percent of patients reporting ''Tiredness'' demonstrated a statistically significant positive correlation with progression of disease ($r=0.47$, $P=0.036$), whereas the percent reporting ''Weakness'' did not ($r=0.015$, $P=0.951$).

Quality of Life

The patients were asked if their pain interfered with the following categories: their general activity, enjoyment of life, mood, work (both outside and inside their home), relationships with others, ability to concentrate, and ability to sleep. If their pain interfered with a specific category, they were asked to rate the level of interference on an NRS scale of 0 to 10. A score of 0 reflected no interference whereas a score of 10 complete interference. Most of the respondents (>97%) replied that their pain interfered with their general activity, enjoyment of life, mood, work, ability to concentrate, and ability to sleep. The percent of patients reporting that pain interfered with their relationships with others was 93%. In all categories, the percent that reported interference varied little throughout the course of the illness. The degree of interference on a 0 to 10 NRS scale followed a similar pattern, with patients reporting average values between 7.5 and 8.5 for general activity, enjoyment of life, mood, work, ability to concentrate, and ability to sleep and 6.5 for interference with their relationships with others.

Work Status

In response to the queries: (1) Did your pain problem cause you to stop working?; and (2) If you stopped working have you been able to return? In 81% of the patients, their pain problem caused them to stop working whereas the remaining 19% continued to work. Of the 81% who stopped working, 27% were able to return to work.

DISCUSSION

The demographic patterns in this natural history study of refractory CRPS patients are in agreement with the previous publications in regard to sex. The reported female to male ratio in CRPS varies from 2:1 to 4:1.[13,17,18] The patient population in this study demonstrated a 4:1 female to male preponderance. The reported average age of onset is also variable, ranging from 37 to 60 years old.[16,20] Our cohort of patients was at the younger end of this range with onset at 37 years old. As in previous studies, bone fracture, sprains, and trauma were the most common initiating events and the upper body was slightly more involved than the lower. As previously noted,[21] greater than half of the patients in this study had the affected extremity immobilized after the injury. This study shows that although CRPS is a progressive disease, after 1 year, most of the signs and symptoms were well developed and demonstrate only moderate increases with disease duration.

The pain intensity reported by the patients in this study increased with disease duration. However, the percent of patients reporting continuous pain remained relatively constant. The data from the McGill questionnaire showed that many of the sensory components of the score increased with disease duration whereas the affective components did not. The majority of the patients reported abnormalities in pain processing. Dynamic or static mechanoallodynia were present in more than 90% of patients by 5 years and in 96% of patients at 15 years. The severity of the pain and its maintenance in this group of patients may result from multiple mechanisms that include changes in the peripheral nervous system,[22] active processes involving both the peripheral nervous system and the central nervous system[2,23]; or from a sickness like response involving interactions between the immune and nervous systems.[3,4] These mechanisms are not mutually exclusive and may act individually or in concert.[24]

Spread of initial pain occurred in 92% of patients during the course of the illness. Contiguous spread was most common early (1 to 2 y) whereas spread to all extremities was most often seen after 15 years of illness. Functional imaging suggests that the spread of symptoms may be due to the plasticity of the pain system and its ability to reorganize after injury.[2,25] Skin color and temperature changes were prevalent within the first 5 years and significantly ($P < 0.05$) increased with disease duration. Early studies of CRPS patients demonstrated a loss of the normal vasoconstriction response after a Valsalva maneuver or cold pressor stimulus, and loss of normal sympathetically mediated spontaneous wave-like fluctuations (vasomotion).[26] Recent studies confirm this observation and also have shown that the reduced vasoconstriction noted in early CRPS may return to normal with recovery from acute CRPS.[27,28] With disease progression, autonomic dysregulation seems to become centralized and the affected body parts become colder.[2,29] This is possibly related to sensitization or up-regulation of adrenergic receptors in injured tissue, which would then become responsive to low levels of circulating humoral catecholamines.[30]

Swelling was noted by 75% of patients by year 1 and was reported by 90% of patients after 15 years. Several mechanisms have been proposed including increased capillary filtration capacity, sympathetic stimulation of the lymphatics, and neurogenic inflammation.[31,32] The vasoactive neuropeptide substance P when perfused subcutaneously or released by transcutaneous antidromic stimulation evokes protein extravasation. This effect has been reported in the extremities of CRPS patients[33,34] and may be partially responsible for the increased swelling seen with disease duration.

Sweating increased from 33% of patients during the first 5 years to 44% of patients after 15 years. This could result from an adrenergic sweat response seen in CRPS-affected limbs rather than the expected response to cholinergic stimulation, suggesting adrenoreceptor activation of systems not normally under adrenergic control.[35] Loss of strength and difficulty initiating movement were reported by approximately 90% of the patients during the first 5 years and varied little during the duration of the illness. Ninety-four percent of the patients reported difficulty in initiating movements at 10 years. Sustained abnormal limb posture (dystonia) increased from 57% of patients at 1 year to 80% at 10 years. Muscle spasms were frequent in 84% of patients during the first 5 years and increased to 93% by year 10. Spontaneous falls increased throughout the course of the illness.

Motor abnormalities have been shown to occur at all levels of the neuraxis in CRPS. At the spinal level, substance P and calcitonin gene-related peptide have been shown to induce prolonged depolarization (in vitro) of anterior horn cells.[36] Nociceptive afferents release these neuropeptides, which may modulate the gain of nociceptive flexor withdrawal reflexes.[37] Autonomic dysregulation seems to progress and centralize during the course of CRPS[2] and sympathetic effects on motor function may be substantial as demonstrated by improvement of movement in some patients after sympathetic blockade.[38]

The increase in dystonia seen with disease progression may result from impaired reciprocal inhibition, a decreased threshold of tonic and phasic components of the stretch reflex and failure of dorsal horn interneuronal circuits that mediate presynaptic inhibition reported in CRPS patients.[39,40] It has been postulated that GABAergic interneurons, which mediate primary afferent depolarization are impaired in CRPS-induced dystonia.[40]

Impairment of sensorimotor integration is pivotal in the movement disorder of CRPS as demonstrated by motor cortical disinhibition,[41] a neglect-like syndrome,[42] abnormalities of target reaching and grip analysis,[43] and a mismatch between sensory input and motor output.[44] It is clear that motor dysfunction progresses over time with dystonia increasing to a greater degree than other components. The mechanism of increasing falls is probably multifactorial. Sleeping difficulties were reported by more than half of the patients early in the disease and increased to more than 70% with disease duration. Sleeping difficulties have been previously reported in CRPS[45] and other chronic pain conditions.[46,47]

More than half of the patients in this study reported cognitive and memory difficulties. Deficits in information processing[48] and short-term memory[49] have been reported in patients afflicted with chronic pain. Chronic pain has also been shown to impair working memory[50] and decision-making.[51] The disruption of cognitive performance in chronic pain patients could result from a number of factors such as pain medications,[50] stress,[52] the engagement of the prefrontal cortex by chronic pain,[51] and the fact that pain may act as a distractor resulting in impaired working memory.[50] Pain alleviation in CRPS treated by ketamine coma has been shown to result in a significant improvement in attention and information processing.[53] The quality of life and work history component of the questionnaire demonstrate the great social and employment disruption caused by refractory CRPS.

Weaknesses of the study are that it is retrospective with inherent amnestic errors, some ambiguities of the queries, and that not all responses were evaluated with patients at each return visit. Its strength is its relatively large size, the very strict inclusion criteria, and that the same neurologist followed all patients over the course of the study.

None of the patients in this study demonstrated spontaneous remission of their symptoms. The pain in these patients was refractory showing only modest improvement with most current therapies. However, there are new treatments that show promise in the management of CRPS. The use of the *N*-methyl D-aspartate receptor antagonist ketamine in both subanesthetic[54,55] and anesthetic[56,57] doses and also immune modulation with

thalidomide[58,59] or lenalidomide[60] have been demonstrated to be effective in patients with short duration disease and also those who have had it for over 5 years. Our hope is that the refinements of these novel agents and the development of more selective drugs will lead to better therapies for this very severe life-altering illness.

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