A Web-Based Cross-Sectional Epidemiological Survey of Complex Regional Pain Syndrome

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Background and Objectives: Complex regional pain syndrome (CRPS) is a poorly understood pain disorder with little information on the natural course of the disease. Changes in its diagnostic criteria have simplified the identification of this syndrome, but convincing epidemiological data regarding this disorder are still lacking. Here, we collected epidemiological and other relevant information regarding CRPS via a Web-based survey to develop a better understanding of the epidemiology, symptoms, progression, therapy, and associated psychosocial factors related to CRPS.

Methods: A survey of 75 questions was hosted on the Web site of the Reflex Sympathetic Dystrophy Syndrome Association of America for 5 months. One thousand three hundred fifty-nine subjects responded, and 888 of these satisfied the inclusion criteria for CRPS and were accepted for data analysis.

Results: Complex regional pain syndrome affected mostly white women in the 25- to 55-year-old age group. It was often precipitated by trauma (surgical or nonsurgical) and commonly involved the lower (~56%) and upper (~38%) extremities. Pain was usually accompanied by edema, vasomotor, sudomotor, motor, and trophic changes. The syndrome commonly progressed and spread to involve other body areas. Affected patients failed multiple pharmacological and nonpharmacological interventions. The syndrome frequently interfered with job (~62% disability rate), sleep (~96%), mobility (~86%), and self-care (~57%). Remissions and relapses were both common.

Conclusions: Complex regional pain syndrome is a severe disabling pain disorder that results in physical as well as emotional and financial consequences to patients. The disease complexity requires coordination of multidisciplinary care that can be achieved by educational efforts directed to general practitioners.

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In recent years, considerable advancement has been made in the understanding of chronic pain, and many new therapies have been recognized for its treatment. However, certain chronic pain states continue to be poorly understood and hence inadequately treated. Complex regional pain syndrome (CRPS) is high on the list of these challenging disorders. Complex regional pain syndrome is the new term for the chronic pain syndrome that often results from trauma to an extremity and has been referred to in the past as reflex sympathetic dystrophy (RSD) or causalgia.[1] The process of developing preventive measures or defining the optimal treatment of a disease is usually based on an understanding of the disease's epidemiology, identifying the pathophysiology, and targeting the etiological factors and symptoms individually. Unfortunately, in the case of CRPS, information is inadequate at many of these levels.[1,2] The purpose of this study was to gather data via a Web-based survey to develop a better understanding of the epidemiology, symptoms, progression, therapy, and associated psychosocial factors related to CRPS.

METHODS

A Web-based cross-sectional survey consisting of 75 multiple-choice and open-ended questions related to CRPS was designed. Appropriate approval was obtained from the Johns Hopkins University institutional review board before the final survey was hosted on the RSDSA (Reflex Sympathetic Dystrophy Syndrome Association of America) Web site, http://www.rsdsa.org, by BusNet, Inc. The RSDSA is a nonprofit organization aspiring to promote public and professional awareness about CRPS. Its members include CRPS patients, patrons, physicians, and researchers. Its Web site is accessed by more than 6000 active members and receives more than 32,000 hits per month. It is frequently among the top 5 results on most search engines using the key word "RSD." The survey was maintained on the Web site from October 2004 to February 2005 (see supplemental information in electronic form of survey questionnaire, **Appendix, Supplemental Digital Content 1**, http://links.lww.com/A796).

The target population for the survey was CRPS patients who would visit the RSDSA Web site. The association sent periodic e-mails to its members, urging them to encourage all known CRPS patients to participate in the survey. Patients could enroll in the study by logging on to the survey Web site. The data from the respondents were stored in a secure database connected to the survey. Incomplete or partial responses were not included in the data analysis. Respondents were screened based on our inclusion criteria, as follows:

1. Continuing pain
2. At least 1 symptom in each of the following 4 categories[3,4] at the time of disease onset:
   a. Sensory: subjects reporting ongoing pain and/or hypersensitivity
   b. Vasomotor: subjects reporting temperature asymmetry, skin color changes, and/or skin color asymmetry in the affected region
   c. Sudomotor/edema: subjects reporting edema, sweating changes, and/or sweating asymmetry in the affected region

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d. Motor/trophic: subjects reporting decreased range of motion, motor dysfunction (weakness, tremor, dystonia), and/or trophic changes (hair, nail, skin) in the affected region

These inclusion criteria were formulated from the recently proposed revisions by Harden and Bruehl[4,5] to the criteria originally recommended by the International Association for the Study of Pain. Briefly, the criteria are a set of symptoms and signs grouped in 4 categories each (see **Appendix, Supplemental Digital Content 2**, http://links.lww.com/A797, for additional details). The specificity of the diagnosis for research purposes is enhanced by using the criteria of no fewer than 1 symptom in all 4 categories and at least 1 sign in 2 of the 4 categories.[4,5]

Because examination is not possible during an online survey, the inclusion criteria were modified as 1 or more symptom in each category. Data from participants who fulfilled these criteria were analyzed qualitatively and quantitatively and summarized by averaging across all responses or by categorizing and creating frequency tables of open-ended questions. The frequencies of the categorical data were analyzed by χ^2 analysis, where appropriate.

During the study interval, 1359 respondents completed the survey. Of those, 888 met the inclusion criteria for CRPS and were incorporated for data analysis. Among the 888 subjects, 83.7% were women, and 16.3% were men, giving a female-to-male ratio of approximately 5:1. The survey respondents were predominantly white (93.2%). Others included African Americans (2%) and Hispanics (2.4%). The distribution of the survey population by age and sex is shown in Figure 1. The majority (70%) of patients were in the age group of 25 to 55 years at the time of survey. Most of the patients were from the United States (94%), with minor contributions from Europe (2.6%), Australia–New Zealand (1.5%), and Canada (1.4%). We received input from all 50 states in the United States.

RESULTS

Onset and Presentation

All 888 subjects reported that their disease was triggered by either an injury or a trauma. A small proportion (5.2%) of the participants identified a positive family history, and 29.2% believed that they were under considerable stress at the time of the initial injury that led to the onset of CRPS. Common injuries included surgery (30.9%), fractures (17%), sprains (11.8%), crush injuries (11.4%), contusions (3.2%), and dislocations (1.2%). Miscellaneous injuries were listed by 24.4% of patients as a leading precipitating factor to their disease, most often from motor vehicle accidents.

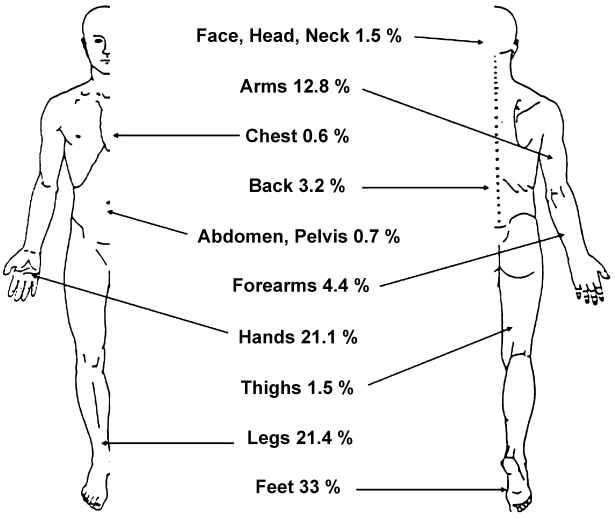

FIGURE 2. Initial site of onset.

Among the study population, 26% of patients reported the onset of disease during spring, 24% during summer, 27.3% during fall, and 22.7% during winter. Associated symptoms at the time of disease onset included temperature differences (94.1%); edema (93.4%); color variations (86.1%); sweat alterations (57.2%); hair, nail, or skin changes (37.4%, 50.9%, and 74.9%, respectively); and motor weakness (66.7%). The pain was frequently described as burning (87.8%), sharp (72.1%), shooting (62%), aching (59.8%), throbbing (60.4%), and stabbing (58.8%) in quality. It frequently involved lower (55.9%) and upper (38.3%) extremities and less frequently other sites such as the face, head, chest, abdomen, pelvic region, and back (Fig. 2). The average maximal baseline intensity of this pain during the early phase of CRPS was 8.2 on a numeric pain rating scale of 0 to 10. Many patients (76%) conveyed a history of pain problems before developing

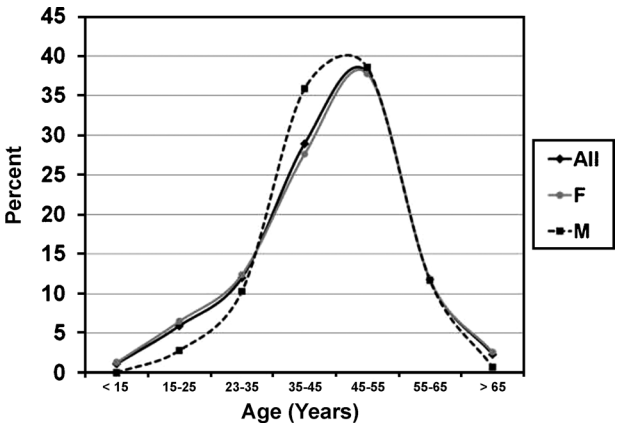

FIGURE 1. Distribution of cases by age and sex.

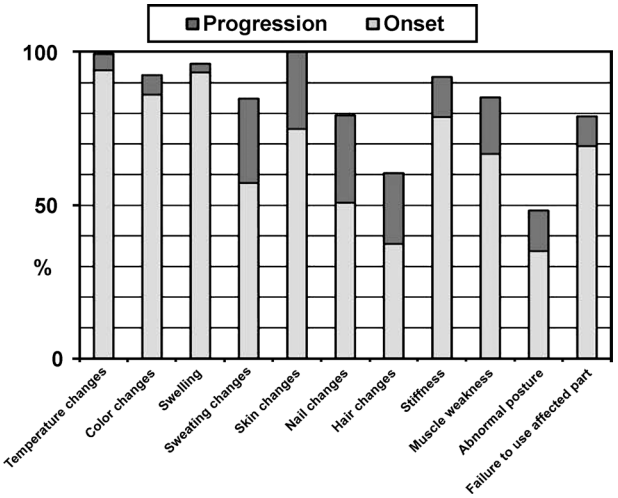

FIGURE 3. Progression of symptoms in CRPS patients.

CRPS, with back pain (25.5%), headache (23.1%), and arthritis (14.3%) being the predominant associated conditions.

A patient was seen by an average of 4.9 physicians before and 4.4 physicians after the diagnosis of CRPS was made. As many as 45.5% of patients reported that their physicians used no specific tests or modality to formulate the diagnosis of CRPS. Many of the remaining patients underwent sympathetic nerve blocks (48.9%), bone scanning (34.9%), magnetic resonance imaging (34%), computed tomography (18.6%), and thermography (15.9%) before their diagnosis. The average duration of disease was 5.5 years at the time of our study.

Course and Progression

After the disease onset, most patients reported the appearance of additional symptoms at the site of initial involvement. Typically, hypoesthesia (17.9%) and sudomotor (27.6%), motor (18.5%), and trophic (25.1%) changes were noted (Fig. 3). Furthermore, many patients (78.8%) described a spread of symptoms to a new location. The symptoms at the secondary site were often similar to those of the initial disease presentation (Fig. 4). Some subjects (21.3%) reported remission of their symptoms at some point during their disease course, and 15.9% were pain-free at the time of the survey.

The average daily pain score reported at the time of the survey was 6.9, in contrast to 8.2 at the time of disease onset. More than 90% of the subjects described constant or nearly constant pain with a burning (75%), aching (71%), throbbing (53%), or stabbing (47%) quality. Common factors that exacerbated pain included physical and emotional stress (94% and 83%, respectively), cold weather (90%), movement involving the affected part (86%), and work (86%). Associated symptoms at the time of the survey were hypersensitivity (81.6%), temperature differences (84.8%), and swelling (73.4%). Between the onset of the syndrome and the time of the survey, hypersensitivity, temperature differences, color variations, and swelling decreased by 18.4%, 9.3%, 18.2%, and 20%, respectively. A corresponding increase in muscle weakness (11.8%) and disability (18.2%) occurred during this period.

Nearly half (44%) of the subjects had visited an emergency department at least 3 times during the past 5 years for issues related to CRPS. A large majority of patients reported that pain affected sleep (95.7%), mobility (85.5%), self-care

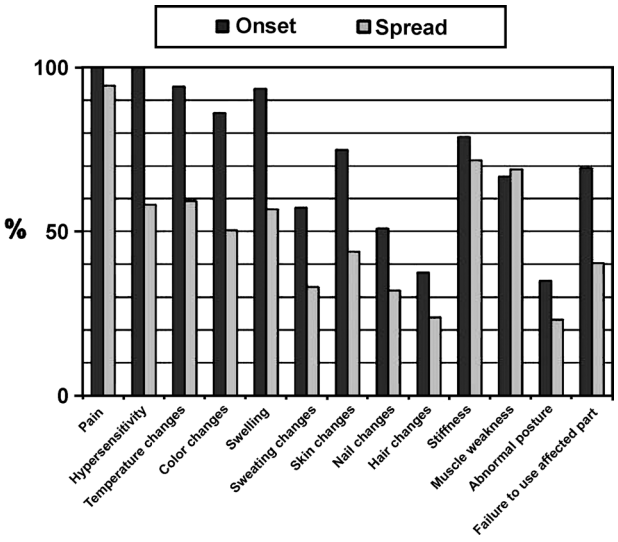

FIGURE 4. Spread of CRPS symptoms.

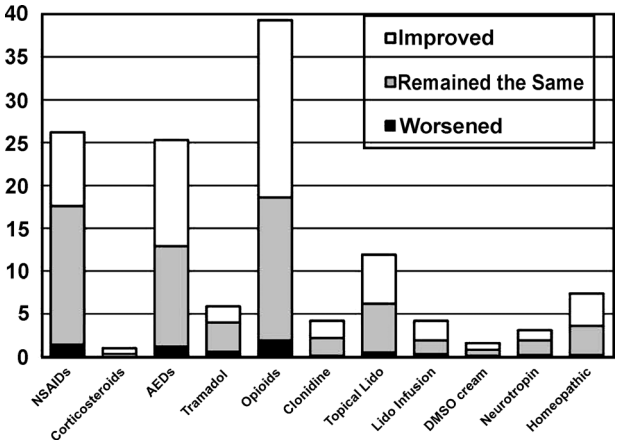

FIGURE 5. Current status of pharmacological therapies in CRPS patients. AED indicates antiepileptic drugs; Lido, lidocaine.

(57.3%), and activities of daily living (96%). Complex regional pain syndrome was commonly associated with feelings of anxiety (78.2%) and depression (77.2%). Suicidal ideations were reported by 49.3% (438/888) of subjects at some point during the course of their illness, and 15.1% (66/438) of those acted on those impulses. The average number of suicide attempts in this subgroup was 2.1.

Treatments

Most subjects had tried multiple pharmacological and nonpharmacological treatment modalities. Pertinent pharmacological trials included steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs; used in 27% and 100% of patients, respectively); antiepileptic drugs (80.5%); tramadol and opioids (45.9% and 91%, respectively); topical and intravenous lidocaine (42.4% and 21.9%, respectively); clonidine (25.6%); homeopathic medications (20.4%); neurotropin (18.9%); and dimethyl sulfoxide (DMSO) cream (9.7%). At the time of the survey, 39.3% of patients were taking opioids; 26.2%, NSAIDs; 25.3%, antiepileptic drugs; 11.9%, topical lidocaine; and a small number were using other medications (Fig. 5). Improvement was reported with topical lidocaine (47.9% of recipients), DMSO cream (50% of recipients), NSAIDs (33% of recipients), antiepileptic drugs (49% of recipients), opioids (52.7% of recipients),

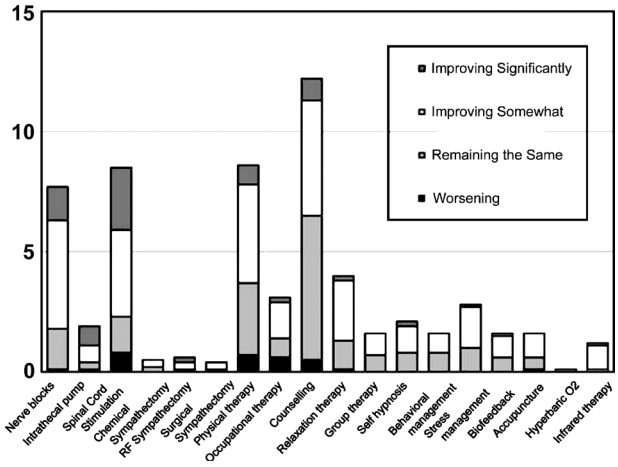

FIGURE 6. Current status of nonpharmacological therapies in CRPS patients.

intravenous lidocaine (55% of recipients), and homeopathic medications (51% of recipients) (Fig. 5).

Many patients had tried nonpharmacological options, including physical therapy (88.3%), nerve blocks (77.8%), counseling (51.1%), occupational therapy (36.9%), spinal cord stimulation (22.6%), and intrathecal drug delivery systems (7.6%). At the time of the survey, 12.2% of subjects were receiving counseling, 8.6% were receiving physical therapy, 8.5% were using a spinal cord stimulator, 7.7% were undergoing nerve blocks, 3.1% were receiving occupational therapy, and 1.9% were receiving intrathecal drugs (Fig. 6). Benefits from these treatment modalities were reported to be moderate for physical and occupational therapies, counseling, and stress management, and good for nerve blocks, intrathecal drug delivery, and spinal cord stimulation (Fig. 6).

Financial Aspects

The study population included members of many different professions. Although health care and social work (11.1%) and homemaking (8.6%) were the most commonly reported occupations, 31.5% of subjects were unemployed before the onset of disease. At the time of the survey, most patients (61.8%) stated disability as their current employment status, but 15% were fully and 5.9% were partly employed. In 43.4% (385/888) of cases, the initial injury was related to their work, and 76.1% (293/385) of those were receiving benefits from the workers' compensation (WC) program. Of those receiving WC benefits, 45% were unsatisfied with their coverage. Approximately two thirds (590/888) of patients had applied for social security benefits; 24% of these applications were under process at the time of our survey, and 48.13% had been rejected. Of those who made second claims, only 32.7% (93/284) were successful at receiving approval for their applications.

DISCUSSION

A lack of uniform nomenclature and an absence of clear diagnostic criteria has hindered CRPS-related research. The previous set of diagnostic criteria (1994 IASP Task Force Criteria, **Appendix, Supplemental Digital Content 1**, http://links.lww.com/A796) was ambiguous and led to an overdiagnosis of CRPS.[3,6] The proposed new terminology and diagnostic criteria[7] for CRPS are likely to benefit clinicians and researchers.[5,6,8]

Epidemiological data on CRPS are still scant, in part because of its relatively low prevalence.[9–11] Given the low estimated incidence of CRPS (5.46–26.2 per 100,000 person-years),[9,12] a study conducted at a single center is unlikely to be able to recruit an adequate number of subjects in a reasonable period. The previous largest epidemiological study[10] required nearly 9 years to recruit 829 patients. We opted for an online patient survey method as Internet-based surveys offer numerous advantages, including ease of design and execution. This technique has been tested in other epidemiological studies[13–15] and has proven to be as effective as paper-based surveys.[16–20]

Demographic measures acquired in our study are consistent with results from other similar studies. Our data showed that females are affected far more commonly by CRPS than their male counterparts (female-male ratio, ~5:1). Previously published ratios range from 2.3:1 to 4:1.[9–12] In general, white women between the ages of 35 and 55 years outnumbered any other subgroup. Whites were also the predominantly affected subgroup (79%–99%) in earlier studies.[9–11] The age group is consistent with that of other studies that reported median ages of onset of 46 and 42 years.[10] The survey observations are, however, discrepant with a recent population-based survey from the Netherlands where the highest incidence was in women 61 to 70 years of age.[12]

A possible genetic predisposition is suggested by the observation that 5.2% of subjects in the current study claimed a family history of CRPS. Associations between distinct CRPS phenotypes and major histocompatibility complex alleles, including centromeric locus in HLA class I, HLA-DR13, HLA-DR2, and HLA-DQ1 have been reported.[21–24] Nearly 94% of participating subjects were from the United States with high participation in California, Florida, and Pennsylvania (nearly 8% each). Our data, however, suggest that the onset of CRPS is not correlated with any specific weather or geographic location.

Although Veldman et al[10] reported that nearly 10% of patients had no precipitating event, all 888 patients included in our survey claimed that their disease was associated with a traumatic event. The most common event associated with disease was surgery (30.9%), followed by fracture (17%), contusion (11.8%), and crush injuries (11.4%). These findings are consistent with earlier reports indicating that nonsurgical trauma (fractures, contusions, crush injuries, dislocations, and electric injuries) collectively was a common inciting factor in about 50% of patients.[9,10] An interesting observation in this study is that nearly a third of patients described stressful events in their lives at the time of initial injury. Major psychologic trauma has been shown to precipitate autonomic hyperarousal and conversion symptoms.[25] Whether this autonomic hyperactivity during these stressful periods can contribute to the onset of CRPS is worthy of future studies.

In the present study, progression was defined as appearance of additional symptoms at the site of initial involvement. Classically, CRPS was described as a disease with 3 distinct sequential stages: initial "warm" stage with vasomotor symptoms, intermediate stage with sudomotor symptoms, and late "cold" stage with dystrophic and motor changes. Many patients described motor and sudomotor symptoms at the time of disease onset and vice versa. These observations confirm earlier reports on the lack of such sequential stages in CRPS.[26] A noteworthy finding was the presence of hypoesthesia or sensory deficits in more than 20% of patients at the time of disease onset, with an additional 18% reporting these symptoms later. Similar findings have been reported in other studies,[27,28] but hyposensitivity per se is not yet included in any diagnostic categories.

Spread was defined as involvement of additional area(s), excluding the site of initial involvement. Three patterns of CRPS spread have been described in case reports or small case series.[10,29–32] Most patients (~79%) attributed similar symptoms in other parts of their body to their CRPS. This spread of disease was more frequently associated with pain (~94%), stiffness (~72%), and motor weakness (~69%). The clinical signs and symptoms of CRPS may be waxing and waning in nature in some patients. In contrast to the 74% resolution rate reported by Sandroni et al,[9] only 21% of our study population stated resolution of their symptoms at some point, and most reported relapse of the disease later. Whether this difference is reflective of a selection bias of the study methodology needs to be determined by future studies. The persistence of CRPS may explain the high predilection toward anxiety, depression, and suicidal tendencies in these patients.

Similar to our findings, NSAIDs, intravenous lidocaine,[33] DMSO cream,[34] physical therapy,[35] and spinal cord stimulation[36] have been shown to have efficacy for CRPS in recent years. However, patients are often disinclined to continue their pharmacological therapies. Potential reasons for

discontinuation of therapy might include poor analgesia, intolerable side effects, or physicians' concerns with continuation of long-term therapy, especially with NSAIDs and opioids.

Many subjects in our survey were left disabled by CRPS. Although initial injury was related to work in many patients, their compensatory benefits were often inadequate. Insufficient medical insurance coupled with poor financial benefits could potentially prevent many of these patients from accessing optimal therapeutic choices. Many of the overwhelming problems with sleep, mobility, and self-care together with unrelenting chronic pain cumulatively lead to anxiety and depression. These associated comorbidities should be identified and treated in the primary care setting early in the disease process.[37–39]

Our study methodology had certain unique limitations. The survey shares the shortcomings of cross-sectional study designs. Answers were based on subjects' memories over the span of a few years, perhaps reducing the specificity of responses. Selection of the sample population from a survey hosted at a single Web site of RSDSA's homepage was another weakness of our survey. It is possible that many of these patients become members of the RSDSA support group only after the disease becomes unremitting. The mean duration of disease at the time of survey was 5.5 years, suggesting that most patients included in the survey were chronic sufferers of CRPS.

Another shortcoming of this survey is related to our inclusion criteria. The initial design and implementation were carried out using the 1994 IASP criteria (**Appendix, Supplemental Digital Content 1**, http://links.lww.com/A796), which were the standard until 2005. Using these standards, a diagnosis of CRPS could be made more reliably with history alone and would not have posed any problems in study execution. Because of the introduction of a revised criteria[4,5] (**Appendix, Supplemental Digital Content 1**, http://links.lww.com/A796), we opined that incorporating these recommendations before data analysis would improve the specificity of our inclusion criteria. Because the study design precluded the possibility of any clinical examination of the subjects, fulfillment of at least 1 symptom in each of the 4 diagnostic categories was accepted as the inclusion criteria. This paradigm might have reduced the specificity of differentiating true CRPS patients from other neuropathic pain problems.

Finally, the study used a Web-based experimental method that has not been extensively used in studying epidemiological aspects of chronic pain disorders. The shortcomings of this methodology include possible multiple submissions by individuals, self-selection bias, potential for higher dropout due to lack of motivation, and absent interaction with participants that may affect the quality of the data obtained.[40] However, the potential advantages include access to a large number of demographically and culturally diverse population, ease of access to relatively uncommon participant populations, avoidance of time constraints for the participants, completely voluntary participation, cost savings, and reduction of experimenter bias. Our finding that many of the epidemiological aspects of CRPS observed in this study are consistent with those reported from retrospective case-cohort studies helps validate that the Web survey method may be a useful tool in the study of the epidemiology of chronic pain states.[41–43]

SUMMARY

Complex regional pain syndrome is a well-recognized clinical pain syndrome that frequently affects the extremities of young white women after some inciting surgical or nonsurgical trauma and involves a complex group of symptoms and signs along with pain. It is often associated with significant disability, anxiety, and depression. Patients frequently fail trial of multiple medications and nonpharmacological therapeutic options. Finally, Web-based survey methodology may be a useful additional tool to study chronic pain disorders.

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