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Critical Review

The Outcome of Complex Regional Pain Syndrome Type 1: A Systematic Review

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Abstract: **The purpose of this systematic review was to examine the outcome of complex regional pain syndrome (CRPS) type 1. We searched MEDLINE, Embase, and PsycINFO for relevant studies and included 18 studies, with 3,991 participants, in this review. The following data were extracted: study details, measurement tools used, and rates or severity scores for the symptoms/signs of CRPS at baseline and follow-up, or in groups of patients with different disease durations. A quality assessment revealed significant limitations in the literature, with many studies using different diagnostic criteria. The 3 prospective studies demonstrated that for many patients, symptoms improve markedly within 6 to 13 months of onset. The 12 retrospective studies had highly heterogeneous findings, documenting lasting impairments in many patients. The 3 cross-sectional studies showed that rates of pain and sensory symptoms were highest among those with the longest duration of CRPS. Additionally, most studies showed that motor symptoms (stiffness and weakness) were the most likely to persist whereas sudomotor and vasomotor symptoms were the most likely to improve. Overall, this suggests that some CRPS patients make a good early recovery whereas others develop lasting pain and disability. As yet little is known about the prognostic factors that might differentiate between these groups.**

Perspective: ***We found evidence that many CRPS patients recover within 6 to 13 months, but a significant number experience some lasting symptoms, and some experience chronic pain and disability. The quality of the evidence was poor. Future research should examine the factors associated with recovery and identify those at risk of poor outcomes.***

Key words: *Complex regional pain syndrome, outcome, prognosis, recovery, systematic review.*

Complex regional pain syndrome (CRPS) is a painful condition that can occur after fracture, stroke, surgery or trauma, and most commonly affects a hand, wrist, foot, or ankle. In CRPS, pain is accompanied by a range of symptoms, including allodynia, hyperalgesia, swelling, and abnormalities in color, temperature, sweating, nail and hair growth, and movement.

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Traditionally, CRPS was considered a progressive condition with distinct "stages." For example, Bonica[10] described 3 stages. Stage 1, the "acute stage," was characterized by a painful, swollen, warm, red limb. In stage 2, the "dystrophic stage," the limb was said to cool and appear cyanotic, with changes to hair and nail growth, osteoporosis, stiffness, and muscle wasting. In stage 3, the "atrophic stage," irreversible atrophy of bones, muscles, and nails was described. However, relatively little research data have been offered to support the 3 specific stages, and at least 1 study has refuted the idea that 3 stages exist.[11] Long-term follow-ups of CRPS patients report contradictory findings regarding the outcome of the condition. A number of studies have found that although the nature of symptoms might fluctuate over time, CRPS tends to persist, and only a minority of patients recover from the condition.[14,15,21,41,44,47] For example, a prospective study of 42 patients with CRPS

after fracture found that no patient was symptom-free 12 months later.[6] A follow-up of 134 CRPS patients at a mean of 5.8 years after diagnosis found that 64% still met the International Association for the Study of Pain (IASP) diagnostic criteria for CRPS,[15] and 1 study of more than 600 CRPS patients showed that symptoms tended to be worse in those with a longer duration of CRPS compared to those with a shorter duration.[41] In addition, research has suggested that over time, CRPS patients can develop more widespread pain, and some researchers have described symptoms of CRPS "spreading" to affect multiple limbs.[41,46]

In contrast, there are also studies that present more optimistic data and suggest that the majority of patients will recover from the condition within 12 months.[8,17,24,38,49] A population-based study of medical records found that 74% of CRPS cases resolved, usually spontaneously, at a mean of 11.6 months post onset.[38] A prospective study requiring patients to have no treatment found that of the 30 participants, only 3 had severe symptoms and had to withdraw from the study for treatment, and of the 27 remaining participants, only 1 continued to have CRPS at the 1-year follow-up.[49] Several studies have also shown that the majority of CRPS patients will return to employment following the condition.[17,18]

This review aims to examine these discrepancies in the literature, to synthesize the published data concerning the course of CRPS symptoms over time, and to answer the following questions: In what proportion of CRPS patients do symptoms persist? To what extent do CRPS symptoms persist? We chose to limit the review to CRPS type 1 (CRPS-1, without a major nerve injury) because CRPS type 2 (CRPS-2) is associated with a specific nerve injury that likely affects outcome. We hypothesized that the majority of patients would show improvements in CRPS symptoms with time, but some would display chronic severe symptoms.

Methods

Selection of Studies

We systematically reviewed prospective, retrospective, and cross-sectional studies that provided data on the outcome of CRPS type 1. A literature search was conducted using the databases MEDLINE, Embase, and PsycINFO, from inception until April 4, 2012 (search date). We used the search terms recommended for systematic reviews on prognosis[2]: "exp epidemiologic studies," "incidence.sh," "follow-up studies.sh," "prognos:.sh," "predict:.tw," OR "course:.tw" AND "complex regional pain syndrome.mp," "Reflex sympathetic dystrophy.mp," OR "algodystrophy.mp." The search was limited to peer-reviewed journals and to studies including human subjects. The personal electronic libraries of the researchers were also searched for possible references. The reference lists of all relevant papers were searched by hand and an electronic search for citing articles of each paper was also conducted to ensure that all possible references were obtained.

Studies were considered for inclusion in the systematic review if they

1. Reported on "complex regional pain syndrome type 1," "reflex sympathetic dystrophy" (RSD), "algodystrophy," or "sudeck's dystrophy." Studies with patients combined from several diagnostic groups (eg, CRPS-1 and CRPS-2) were included if >80% of the sample had CRPS-1;
2. Had the stated aim of investigating the course, natural history, or outcomes of CRPS; or
3. Had one of the following characteristics:
   a. Reported on rates or severity of CRPS symptoms/signs or presence of CRPS diagnosis at more than 1 time point, where the time points are at least 6 months apart, or
   b. Provided cross-sectional or correlational data comparing the symptoms/signs of CRPS between patients with differing CRPS duration or correlating symptom severity with duration, or
   c. Were retrospective studies documenting self-report of how symptoms changed over time, or
   d. Were retrospective studies or audits documenting residual symptoms/signs in a follow-up of a cohort more than 6 months after the CRPS patients were identified. Cohorts had to have been previously assembled or patients previously identified, so that the review only included retrospective studies that had a chance of capturing CRPS cases that had resolved.

Studies were excluded if they 1) had a sample size of less than 10; 2) were not published in full article format or data could not be extracted from the article; 3) conducted in pediatric samples or in adult samples where the CRPS onset was during childhood (as there is suggestion that CRPS can manifest differently in children and adolescents); 4) published in languages other than English, French, or German; or 5) had follow-up or response rates <50%.

Quality and Relevance Assessment and Data Extraction

To assess study quality and relevance of studies for this review, we used a modified version of the quality evaluation method recommended for systematic reviews of prognostic variables.[12,28] Few studies assessed prognostic variables. Therefore, our review focused on clarifying the course of CRPS, so we excluded quality items on prognostic factor measurement and confounder measurement.

We assessed quality and relevance on the following 4 sources of bias: study participation (sampling method described, sample described, inclusion/exclusion criteria described, diagnostic criteria described, response rate, representative sample, assembled at common time point >3 months, follow-up >6 months), study attrition (attrition described, attrition adequate, information on drop-outs), outcome measurement (outcomes defined, objective, measured appropriately), and analysis (relevant statistical analysis conducted, and statistical analysis appropriate). For each question, each study was scored