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Original Reports

Intense Pain Soon After Wrist Fracture Strongly Predicts Who Will Develop Complex Regional Pain Syndrome: Prospective Cohort Study

G. Lorimer Moseley,[*,†,‡] Robert D. Herbert,[†,§] Timothy Parsons,[‡] Samantha Lucas,[‡] Jacobus J. Van Hilten,[||,¶] and Johan Marinus[¶]

[*]Sansom Institute for Health Research, The University of South Australia, Adelaide, Australia.
[†]Neuroscience Research Australia, Randwick, New South Wales, Australia.
[‡]Department of Physiology, Anatomy & Genetics, University of Oxford, Oxford, United Kingdom.
[§]The University of Sydney, Darlington, New South Wales, Australia.
[||]Leiden University Medical Center, Albinusdreef, Leiden, The Netherlands.
[¶]Trauma RElated Neuronal Dysfunction Consortium (TREND), The Netherlands.

Abstract: Complex regional pain syndrome (CRPS) is a distressing and difficult-to-treat complication of wrist fracture. Estimates of the incidence of CRPS after wrist fracture vary greatly. It is not currently possible to identify who will go on to develop CRPS after wrist fracture. In this prospective cohort study, a nearly consecutive sample of 1,549 patients presenting with wrist fracture to 1 of 3 hospital-based fracture clinics and managed nonsurgically was assessed within 1 week of fracture and followed up 4 months later. Established criteria were used to diagnose CRPS. The incidence of CRPS in the 4 months after wrist fracture was 3.8% (95% confidence interval = 2.9–4.8%). A prediction model based on 4 clinical assessments (pain, reaction time, dysynchiria, and swelling) discriminated well between patients who would and would not subsequently develop CRPS (*c* index .99). A simple assessment of pain intensity (0–10 numerical rating scale) provided nearly the same level of discrimination (*c* index .98). One in 26 patients develops CRPS within 4 months of nonsurgically managed wrist fracture. A pain score of ≥5 in the first week after fracture should be considered a "red flag" for CRPS.

***Perspective:** This study shows that excessive baseline pain in the week after wrist fracture greatly elevates the risk of developing CRPS. Clinicians can consider a rating of greater than 5/10 to the question "What is your average pain over the last 2 days?" to be a "red flag" for CRPS.*

***Key words:** Complex regional pain syndrome, reflex sympathetic dystrophy, chronic pain, dysynchiria.*

Complex regional pain syndrome (CRPS) is a distressing complication of some minor injuries. It is characterized by disproportionate pain and disability, with disturbed autonomic and motor function, usually confined to 1 arm or leg (see[20] for review of clinical features and pathophysiology of CRPS). The incidence of CRPS in Western countries is about 26 per 100,000 person-years (95% confidence interval [CI] = 23–30). That is, about 80,000 Americans are diagnosed with CRPS every year.[8] Total annual lost income due to CRPS exceeds US$1 billion.[18] Despite many treatments for CRPS, including physical and occupational therapy, sympathetic nerve block, spinal cord stimulation, systemic analgesics, and cognitive-behavioral pain management, more than half of all CRPS patients report continuing or worsening symptoms 5 years after diagnosis.[10]

The most common trigger in prevalent cases of CRPS is wrist fracture.[8] The incidence of CRPS after wrist fracture is uncertain because available estimates vary widely (eg,

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Address reprint requests to G. Lorimer Moseley, PhD, FACP, The University of South Australia, Sansom Institute for Health Research, Adelaide, SA 5000, Australia. E-mail: Lorimer.Moseley@unisa.edu.au
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estimated incidence proportions in the first 3–4 months include <1%,[17] 37%,[2] and 58%[11]). The mechanisms by which wrist fractures trigger CRPS are not known. The best available data, from a large cross-sectional study,[8] exclude cast tightness, preinjury psychological profile or mood, stressful life events, injury severity, location of fracture, mode and biomechanical characteristics of injury, time to surgery and surgical approaches, compensation, and previous illness history.[8] The same study concluded that the presence of several previous or current morbidities, including osteoporosis, migraine, and asthma, and the current use of angiotensin-converting enzyme inhibitors are risk factors for CRPS.

We conducted a multicenter prospective cohort study of patients with wrist fracture. The study was designed to quantify the incidence of CRPS, diagnosed using established criteria, in the 4 months after wrist fracture. A second aim was to develop a prediction rule that uses data from clinical assessments conducted in the first week after wrist fracture to identify people who develop CRPS within 4 months of wrist fracture. We sought to predict who would develop CRPS, not to identify causes of CRPS.[14]

Methods

Study Design and Participants

The cohort was recruited between January 2006 and December 2008. It consisted of a near-consecutive sample of patients who presented with acute wrist fracture to 1 of 3 hospital fracture clinics. Participants were assessed within 1 week of fracture (baseline) and were followed up 4 months later.

Patients were eligible to participate if they had radiologic evidence of fracture to the carpal bones, the distal radius or ulna, or both; were aged between 18 and 75 years; and did not require external fixation other than a cast. Those who presented with additional orthopedic or neurologic injuries or who had an established diagnosis of CRPS were excluded. Written informed consent was obtained from all participants, procedures conformed to the Declaration of Helsinki, and the protocol was approved by the NHS Research Ethics Committee.

Detailed clinical assessment procedures, undertaken in the first week after fracture, are presented in the Appendix and included assessment of the signs and symptoms of CRPS. The following variables were assessed: pain (average pain over the last 2 days and pain on touching together the thumb and index finger, both assessed using a 0–10 numerical rating scale, anchored at left with "no pain at all" and at right with "worst possible pain"); swelling (the circumference of the thumb and the first 3 fingers on the fractured side, expressed as a proportion of that measured on the opposite side); performance on a left/right hand judgment task (response time for correct judgments of images of the affected hand expressed as a proportion of that for correct judgments of images of the unaffected hand[22]); the presence or absence of dysynchiria, a sensory response on the fractured side to stimulation of the opposite side while watching in the mirror the reflected image of the opposite limb being touched[1]; and catastrophizing (using the Pain Catastrophizing Scale[24]).

Outcome Measures

Four months after fracture, participants were telephoned and asked whether they had symptoms of CRPS, as stipulated in the International Association for the Study of Pain (IASP) diagnostic criteria for research that were widely accepted at the time of study design and data collection.[6] Those participants who reported pain, and any other symptoms consistent with CRPS, also underwent a physical examination by a pain specialist to confirm the diagnosis of CRPS using the same criteria. That is, we used the diagnostic criteria for research. The specialist was unaware of the results of the baseline assessments.

Statistical Analysis

The incidence proportion of CRPS 4 months after wrist fracture was estimated in 2 ways. A naïve estimate was obtained by expressing the number of observed cases as a proportion of the number followed up. As it was expected that there would be some loss to follow-up, the primary estimate was obtained by imputing missing CRPS data using a multiple imputation procedure (20 imputations, using the "ice" routine in Stata v10.1 [StataCorp, College Station, TX]) based on age, gender, reaction time, dysynchiria, swelling, pain, and catastrophizing measured at baseline. Where data are missing at random (ie, missing randomly, conditional on covariates), estimates based on multiple imputation are unbiased.[19] The missing-at-random assumption was considered to be plausible.

A predictive model was developed using the following procedures. Before conducting the analysis, we nominated 7 potential predictors based on evidence from cross-sectional studies of an association with CRPS or chronic pain.[1,9,22,25] They were age, gender, response time, dysynchiria, swelling, pain, and catastrophizing. All of the predictors except gender and dysynchiria were treated as continuous variables. Only those variables with significant univariate associations with CRPS (logistic regression, likelihood ratio test, $P < .05$) were considered further. We used the criterion of $P < .05$ (not a higher value, as used by some researchers) because our aim was to develop a clinically useful and therefore parsimonious prediction model. The remaining candidate variables were subject to a bootstrap variable selection procedure.[4] The purpose of this procedure is to generate prediction models that are likely to be applicable to other samples drawn from the same population, rather than just to the sample used in the study. This involved drawing 10,000 bootstrap samples from the original sample and subjecting each bootstrap sample to backwards stepwise regression (P value to remove = .2) in a logistic model. Those variables selected in at least 80% of bootstrap samples were retained in the final model. Regression coefficients were zero-corrected to reduce the bias associated with variable selection procedures.[3] Goodness of fit was evaluated by inspecting calibration