Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): Prospective study on 596 patients with a fracture

Annemerle Beertuizen a,⇑, Dirk L. Stronks b, Adriaan van’t Spijker a, Ameeta Yaksh b, Barbara M. Hanraets b, Jan Klein c, Frank J.P.M. Huygen b

⇑ Corresponding author. Address: Department of Medical Psychology and Psychotherapy, P.O. Box 2040, Erasmus MC, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 7044234; fax: +31 10 7044695. E-mail address: a.beertuizen@erasmusmc.nl (A. Beertuizen).

Abstract

Limited data are available on the incidence of complex regional pain syndrome type 1 (CRPS1) and on demographic and medical risk factors for the development of CRPS1. The objective of this study was to investigate the incidence of CRPS1 in patients with a fracture using 3 sets of diagnostic criteria and to evaluate the association between demographic/medical factors and the development of CRPS1 diagnosed with the Harden and Bruehl criteria. A prospective multicenter cohort study of 596 patients (ages 18 years and older) with a single fracture of the wrist, scaphoid, ankle, or metatarsal V, recruited patients from the emergency rooms of 3 Dutch hospitals. Of the 596 participants, 42 (7.0%) were diagnosed with CRPS1 according to the Harden and Bruehl criteria, 289 (48.5%) according to the International Association for the Study of Pain criteria, and 127 (21.3%) according to the criteria of Veldman. An analysis of the medical and demographic differences revealed that patients in whom CRPS1 later developed more often had intra-articular fractures, fracture dislocations, rheumatoid arthritis, or musculoskeletal comorbidities. An ankle fracture, dislocation, and an intra-articular fracture contributed significantly to the prediction of the development of CRPS1. No CRPS1 patients were symptom free at 12 months (T3). At baseline, patients with CRPS1 had significantly more pain than patients without CRPS1 (P < .001). The incidence of the diagnosis of CRPS1 after a single fracture depends to a large extent on the diagnostic criteria used. After a fracture, 7% of the patients developed CRPS1 and none of the patients were free of symptoms at 1-year follow-up.

© 2012 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.
the incidence of CRPS1 in patients after a fracture, using 3 different criteria sets, and the prevalence of CRPS1 in patients at 3 and 12 months after fracture.

For patients fulfilling the Harden and Bruehl criteria, the following items are addressed:

demographic differences between patients with a fracture who do and do not develop CRPS1; differences in the following medical variables between patients who do and do not develop CRPS1: occurrence of CRPS1 in the past, number of comorbidities, type/location of fracture, intra-articular fracture, dominant hand, fracture reduction, type of treatment, and duration in plaster; and the extent to which CRPS1 can be predicted by demographic and medical variables.

2. Patients and methods

2.1. Participants

Patients were recruited from the emergency rooms of 3 hospitals in Rotterdam: 1 university hospital (Erasmus MC) and 2 general hospitals (St. Clara Hospital and Zuider Hospital). Patients who were 18 years or older with a single fracture of the wrist, scaphoid, ankle, or metatarsal V were eligible for the study. Patients were treated conservatively with plaster cast (88.1%), with tape (0.7%), or with both plaster and surgery (10.9%); of 0.3% of the participants the type of treatment is unknown. Exclusion criteria were being unable to complete a questionnaire, living more than 50 km away from the hospital, having nerve damage that could result in a CRPS type 2, or having fractures in more than 1 extremity.

2.2. Design

This was a prospective, multicenter cohort study.

2.3. Procedure

This study was approved by the local medical ethics committee of the Erasmus MC (MEC 223.922/2003/18). After providing written informed consent, participants completed a questionnaire by telephone within 2 weeks after trauma (T0; Fig. 1) covering demographic variables and medical functioning. Immediately after removal of the plaster (T1), patients were interviewed using a form describing 23 symptoms related to CRPS1. When a patient fulfilled 4 of the 4 IASP criteria [37], the patient was referred to a pain specialist (F.H.) at the Pain Treatment Center of the Erasmus MC to assess the symptoms and signs of CRPS by using the criteria of Harden and Bruehl. Patients fulfilling the Harden and Bruhl criteria received the standard medical treatment according to the guidelines used in the Netherlands, namely dimethyl sulfoxide cream [42] and physical therapy (to improve functionality). Three months after trauma (T2), all patients completed a second questionnaire.

Patients not fulfilling the criteria at T0, but reporting symptoms suspected for CRPS1 at T1, were at that time referred to the Pain Treatment Center. When the patients fulfilled the criteria of Harden and Bruehl, the earlier-mentioned standard therapy was also started in these patients. All patients diagnosed at T2 with CRPS1 according to the IASP criteria and/or the criteria of Harden and Bruehl were asked to fill in a short questionnaire 1 year after trauma (T3) to evaluate symptoms related to CRPS1. Patients not fulfilling the criteria at plaster removal or at T2, but reporting symptoms suspected for CRPS1 at T3, were at that time referred to the Pain Treatment Center (and treated if necessary).

2.4. Measurements

2.4.1. Demographic and medical

Age, gender, and education level were established. Medical variables concerned the type and location of fracture, intra-articular fracture, fracture reduction, and type of treatment. Medical questions covered occurrence of CRPS1 in the past, dominant hand, type of treatment, pain severity (Numeric Rating Scale), and comorbidities. At T1, the number of weeks in the plaster cast was determined.

2.4.2. Diagnosis of CRPS1

Three sets of criteria for diagnosing CRPS1 were used: the criteria of Veldman [39], the IASP criteria [37], and the criteria of Harden and Bruehl [21] (Appendix 1). In addition, a pain specialist (F.H.) performed a physical examination to establish signs of CRPS. A diagnosis of CRPS1 was made when a patient fulfilled the symptoms and at least 2 signs of the criteria of Harden and Bruehl.

2.4.3. Health-related quality of life

Health-related quality of life was measured at T0 and T2 using the SF-36 scale, which includes 8 subscales (physical functioning, role limitations because of physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations because of emotional problems, and general mental health). The SF-36 has good validity and reliability [1]. A physical and a mental composite score can be computed.

2.4.4. Statistical analysis

Descriptive statistics were used to determine (multiple response) frequencies. Differences in continuous variables between CRPS1 patients and non-CRPS1 were analyzed with the Mann-Whitney U test because of the skewed distribution of these variables. Differences in nominal variables between CRPS1 patients and non-CRPS1 patients were analyzed using the Pearson χ² test. In case of a 2 × 2 table, the Fisher exact test (2-sided) was used.

Binary logistic regression analysis (the backward Wald method) was used to evaluate the value of medical variables to predict the development of CRPS1. The hand as fracture location was not entered into the model because none of the patients who developed

---

Fig. 1. Time points of measurements in the present study. T0 = baseline, T1 = plaster removal, T2 = 3 months after trauma, T3 = 1 year after trauma. IASP = criteria of the International Association for the study of Pain.
CRPS had a fracture of the hand. A significance level of \( P \)-out \( \leq 0.10 \) was used for the final step of the logistic regression analysis.

To prevent overfitting of the model, before performing this multivariate logistic regression analysis, univariate binary logistic analyses performed using 1 demographic or medical variable were entered into the analyses. Only those of these variables with a regression weight with a significance level of \( P < 0.20 \) were entered into the final multivariate logistic regression.

The following variables appeared to fulfill this criterion and were therefore entered into the model: age, sex, education, location of the fracture (wrist, ankle, and foot), fracture reduction, intra-articular fracture [yes/no], dislocation [yes/no]. To prevent multicollinearity, the correlations between the variables that were selected based on the univariate analyses were calculated. As an outcome variable, the diagnosis of CRPS1 according to the Harden and Bruehl criteria was used. Levels of sensitivity and specificity were considered to be of equal value.

To evaluate the power of the logistic regression model’s predicted values to discriminate between positive and negative cases, a receiver-operator characteristic curve analysis was performed using the predicted probabilities. To analyze differences between the scores of patients with CRPS1 for both composite scores of the SF-36 (i.e., physical and mental), a Student \( t \)-test was performed for independent samples in cases of normal distribution. When the distribution was not normal, a Mann-Whitney \( U \)-test was applied. Analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 14.0.

3. Results

3.1. Patients

A total of 748 consecutive patients fulfilling the inclusion criteria were asked to participate, and 596 (79.7%) agreed: 217 (36.4%) male and 379 (63.6%) female patients (Fig. 2). The median age was 52.8 (interquartile range [IQR] 33.4 to 63.9) years. The most common education levels were junior (23.8%) or senior vocational education (19.3%). Patients who declined participation did not differ significantly from the participants in gender or preceding trauma, but were older (median age 61.8, range 18 to 89, IQR 37.9 to 74.1 years, \( P < .001 \)).

In 311 patients (52.2%) the upper extremity was affected, and in 285 patients (47.8%) the lower extremity was affected. Median time in plaster was 42 (SD 14.5) days. At T2, 550 patients participated and 46 (7.7%) were lost to follow-up. Patients lost to follow-up at T2 did not differ significantly from those completing follow-up at T2 with regard to age, gender, or pain at T0. At T3, the 246 patients (44.7%) who met the IASP criteria at T2 were asked to fill in a third questionnaire on symptoms of CRPS1; of these, 205 (83.3%) responded. Patients who participated at T3 were significantly older (\( P < .01 \), median age 55.1, IQR 37.8 to 66.3 years) than patients who did not participate at T3 (median age 52.1, IQR 31.3 to 60.7 years). Patients who participated at T3 were more often female (72.7%) than patients who did not participate at T3 (58.6%) (\( P < .001 \)).

3.2. Symptoms of the criteria sets at the measurement time points

Fig. 3 shows the number of patients at the measurement time points per criteria set. In this figure, only the symptoms of the Harden and Bruehl criteria are shown. The peak of CRPS1 symptoms is seen at 3 months after trauma. In addition, we analyzed the number of patients diagnosed with CRPS1 at any of the time points of measurement. When the IASP criteria are used, 289 (48.5%) patients are diagnosed with CRPS1, compared with 127 (21.3%) using the criteria of Veldman and 76 (12.8%) using the symptom score of the Harden and Bruehl criteria. In total, 42 (14.3%) participants met both the symptoms and signs of the Harden and Bruehl criteria for CRPS1, which is 7.0% of all participants at baseline. Of the 293 patients who fulfilled the criteria of IASP, 53 (18.1%) refused or were unable to attend their referral to the Pain Treatment Center.

3.3. Demographic and medical variables

Table 1 presents the differences in demographic and medical variables between the patients with and without diagnosed CRPS1. An analysis of the medical and demographic differences revealed that patients who developed CRPS1 at a later time more often had intra-articular fractures (50.0% CRPS1 vs 29.4% non-CRPS1), fracture dislocations (64.3% vs 39.4% non-CRPS1), rheumatoid arthritis (14.3% vs 5.3% non-CRPS1), or musculoskeletal comorbidities (54.8% vs 27.6% non-CRPS1).

3.4. Binary logistic regression analysis

Table 2 presents the results of the binary logistic regression analysis. Dislocation, an intra-articular fracture, and the location of fracture (ankle) contributed significantly to the prediction of CRPS1. Using a cutoff value of 0.10, sensitivity was 61.9%, specificity was 70.4, and the overall percentage was 69.6. In this analysis, 319 patients without and 42 patients with CRPS1 were included. The model discriminates quite well between positive and negative cases (receiver-operator characteristic-area under the curve: 0.75).

The median number of comorbidities in patients with CRPS1 was 2 (IQR 1 to 3.25) compared with 1 (IQR 0 to 2) in those without CRPS1; this difference is significant (\( P < 0.027 \)). Patients with CRPS1 suffered significantly more often from rheumatoid arthritis compared with those without CRPS1 (\( P < 0.020 \)). Also, there were significantly more musculoskeletal comorbidities (back pain and arthrosis) in patients with CRPS1 compared with those without CRPS1 (\( P < 0.001 \)). When the binary logistic regression analysis was performed using 1 demographic or medical variable were entered in the analysis, 319 patients without and 42 patients with CRPS1 were included. The model discriminates quite well between positive and negative cases (receiver-operator characteristic-area under the curve: 0.75).

Concerning quality of life, at both T0 and T2 the patients with CRPS1 had a similar score to patients without CRPS1 on the mental composite score of the SF-36. For the physical component score at T0, patients with CRPS1 reported a significantly lower quality of life than patients without CRPS1 (CRPS1 mean 27.3, SD 7.42; without CRPS1 mean 34.6, SD 8.56; \( t(246) = 5.29; P < 0.001 \)). At T2, patients with CRPS1 also had a significantly lower physical composite score than patients without CRPS1 (CRPS1 mean 30.8, SD 8.34; without CRPS1 mean 44.9, SD 10.0; \( P < 0.001 \)).

4. Discussion

This is one of the first prospective studies to describe the incidence of CRPS1 in a large number of patients (\( n = 596 \)) after a fracture. In this study, the incidence rate of the diagnosis CRPS1 based on the Harden and Bruehl criteria was 7.0%. In the literature, incidence rates of CRPS1 after a fracture vary between 0.9% and 51% [3,4,6,11–16,23,30,32,34–36,41]. The lower incidence in the present study might be explained by the use of diagnostic criteria with a higher specificity [3,4] [8]. The lack of a gold standard for diagnosing CRPS1 leads to varying results across studies; our results indicate that the method used to diagnose CRPS1 to a large extent determines the incidence of CRPS1. After the onset of our study, the
Fig. 2. Flowchart for patient inclusion in the present study. IASP = International Association for the Study of Pain.

Fig. 3. Percentage of patients fulfilling the different sets of criteria by time points of measurement.
Budapest criteria [22] were first published. These criteria are those of Harden and Bruehl extended with allodynia to deep somatic pressure and to joint movement. We recommend the use of the Budapest criteria [22] in future studies on CRPS1.

Another explanation for the lower incidence is the exclusion of comminuted fractures in the present study; others have shown that patients with a comminuted fracture have a higher chance of developing CRPS1 [9,41,43]. Also, the different relative frequencies in the distribution of the various types of fractures in our participants might explain the difference in CRPS1 rates compared with the literature.

In the present study, the majority of patients with CRPS1 were female (73.8%), which is similar to other reports [28,29]. However, no significant difference was found in the proportion of women who developed CRPS1 compared with the proportion of men who developed CRPS1. This finding is in accordance with the proposed explanation that the prevalence of wrist fractures in women is the main cause of their relatively higher representation among CRPS1 patients; however, this remains a matter of dispute [26,41].

A relationship between specific fractures and the occurrence of CRPS1 has also been proposed. Sarangi et al. reported that 30% of patients with a rib fracture develop CRPS1; in our study a similar number was identified (27.3%). The occurrence of CRPS1 after a (displaced) distal radius fracture ranges from 0.9% to 18% [12,13,19,23,30,35,36]. A problem with comparing hazard ratios in future studies on CRPS1.

Concerning quality of life, CRPS1 patients did not score differently on mental health, but their physical functioning was lower than that of patients without CRPS1 at both T0 and T2. This difference might be explained by the fact that these patients suffer from more symptoms than patients without CRPS1.

The number of patients fulfilling the CRPS1 criteria 1 year post-trauma is relatively low. One explanation is the fact that several symptoms of these criteria (e.g., swelling and temperature asym-
metry) are related to inflammation, which is less pronounced in chronic CRPS.

Of the patients who were referred to the Pain Treatment Center for diagnosis, 18.1% refused or were unable to attend. Nevertheless, we assume that few CRPS cases were missed, because patients with only a few symptoms apparently felt no need to visit a physician and the chance of these patients developing CRPS is low.

Conflict of interest statement

All authors declare that they have no conflicts of interest.

Acknowledgments

The authors thank Professor R. de Wit for her significant contribution to developing the methodological design and to the data acquisition. This study was supported by a grant from the Erasmus Foundation for Pain Management (Stichting Erasmus Fonds Pijnbestrijding) and the Department of Anesthesiology (Pain Knowledge Center) of the Erasmus MC, Rotterdam. Both funders had no role in the design or conduct of the study or in the preparation, review, or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2012.01.026.

References


