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Phenotypic Variation in Complex Regional Pain Syndrome: Comparison Between Presentation in Knee Alone or in Ankle/Foot

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ABSTRACT

Objective: To compare the phenotypes of patients with complex regional pain syndrome (CRPS) of the knee to those with CRPS of the ankle/foot.

Setting: A retrospective study.

Subjects: Patients with CRPS of the knee and patients with CRPS of the ankle/foot.

Methods: We used electronic patient databases to identify patients with CRPS of the knee and patients with CRPS of the ankle/foot. The following variables were recorded: age, gender, duration of complaints, initial injury, and symptoms and signs. Frequency distributions and statistical significant differences between the groups were determined.

Results: Included were 50 patients with CRPS of the knee and 64 patients with CRPS of the ankle/foot. These patients were all diagnosed with CRPS according to the criteria used at the time of diagnosis. No significant differences were found in demographic characteristics. A few symptoms and signs appeared to be proportionally more prevalent in patients with CRPS of the ankle/foot. However, patients with CRPS of the knee suffered significantly longer from the disease than patients with CRPS of the ankle/foot.

Conclusions: Some signs and symptoms appeared to be statistically significant more prevalent in CRPS of the ankle/foot than in CRPS confined to the knee. We conclude that the phenotypes of CRPS confined to the knee and CRPS of the ankle/foot are comparable, but not identical. This can be a reason why CRPS in patients with pain of the knee, that is disproportionate to the initial trauma, is sometimes not recognized.

KEYWORDS

Signs, symptoms, phenotype, complex regional pain syndrome, knee, ankle/foot

INTRODUCTION

Complex regional pain syndrome (CRPS) is a painful, potentially disabling disease. The clinical features include pain, sensory, sudomotor/vasomotor disturbances, impaired motor function and trophic changes (1). Diagnosing CRPS is based on the patient history (symptoms) and the physical examination (signs). Symptoms are defined as subjective; that is, what the patient tells the physician during the visit to the outpatient clinic. Signs are defined as objective; that is, what the physician finds during the physical examination. CRPS can appear after a fracture, after surgery, and even spontaneous origination has been described (2, 3). Several diagnostic criteria sets have been used to diagnose CRPS (4-8). In 2012, the Taxonomy Committee of the International Association for the Study of Pain (IASP) validated the clinical Budapest or “new IASP” criteria for diagnosing CRPS (9).

CRPS is seldom considered as a reason of disproportionate pain of the knee. Only sporadic reports involving patients diagnosed with CRPS confined to the knee have been published (10). Nevertheless, our interest focused on a group of patients whose continuing pain of the knee was disproportionate to the initial trauma. Our recent systematic review on CRPS concluded that CRPS confined to the knee is an acknowledged entity and that some of these patients meet the IASP clinical Budapest diagnostic criteria for diagnosing CRPS (11).

Cooper *et al.* have described in their report that patients diagnosed with CRPS of the knee had continuing pain, stiffness and atrophy. In contrast, changes in skin, burning sensations and/or decrease range of motion were variably present (12). Our group of patients had, next to the continuing pain, symptoms and signs (for example changes in skin, decreased range of motion or asymmetry in temperature) which could be part of CRPS. The aim of this study was to compare the phenotype of CRPS of the ankle/foot with that of CRPS confined to the knee. In addition, we want to improve the knowledge of CRPS confined to the knee and to aid in the recognition of this diagnosis, so patients will be recognized as early as possible.

METHODS

Design

A retrospective study to compare the phenotype (in terms of symptoms and signs) of patients diagnosed with CRPS of the knee with that of patients with CRPS of the ankle/foot.

Patient selection

Every patient who was included in this study was referred to the outpatient clinic of our hospital during the period 2000-2013 with symptoms and signs possibly due to CRPS.

Every patient was seen by the same pain specialist (FH) or under direct supervision of this specialist. The diagnosis CRPS was set according to the Bruehl and Harden criteria and the IASP clinical Budapest criteria. For the purpose of future research, the data of the patients diagnosed with CRPS were entered into the database from the Trauma Related Neuronal Dysfunction (TREND) consortium. TREND is a Dutch knowledge consortium that integrates research on epidemiology, assessment technology, pharmacotherapy, biomarkers and genetics on CRPS and serves as a research platform in which the various research lines of CRPS are integrated (www.trendconsortium.nl). The data of the included patients were retrieved from this database. However, because the diagnosis CRPS confined to the knee was not (yet) well recognized, we also made a manual check of all hospital records of patients with the diagnostic code for CRPS, visiting the outpatient clinic of our hospital during the above mentioned period. Most of the patients with CRPS confined to the knee were identified by this procedure.

Measures

Clinical measures included demographic information (age and gender), duration of complaints, precipitating injury, symptoms as reported by the patient and signs as objectified by the physician. Also, we recorded whether or not the patient met the currently recommended IASP clinical Budapest diagnostic criteria set for diagnosing CRPS (see figure 1).

| <i>IASP Clinical Budapest Criteria in diagnosing CRPS</i> | |
|--|--|
| 1. Continuing pain that is disproportionate to any inciting event | |
| 2. At least one symptom reported in at least three of the following categories: | |
| Sensory | Hyperesthesia or allodynia |
| Vasomotor | Temperature asymmetry, skin color changes, skin color asymmetry |
| Sudomotor | Edema, sweating changes, sweating asymmetry |
| Motor/trophic | Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin) |
| 3. At least one sign at time of evaluation in at least two of the following categories: | |
| Sensory | Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure or joint movement) |
| Vasomotor | Evidence of temperature asymmetry (>1 C°), skin color changes or asymmetry |
| Sudomotor | Evidence of edema, sweating changes or sweating asymmetry |
| Motor/trophic | Evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin) |
| 4. No other diagnosis can better explain the symptoms and signs | |

Figure 1. IASP clinical Budapest criteria in diagnosing CRPS.

Statistical analysis

Descriptive statistics were used to determine the frequencies of the demographic and outcome parameters. The Kolmogorov-Smirnov test was used to analyse whether or not parameters were normally distributed. For parameters with a normal distribution, central tendency and dispersion are described in terms of the mean and the standard deviation (SD); parameters with a non-normal distribution are described in terms of the median and the interquartile range (IQR). Differences between the cohorts in the proportions of patients exhibiting a particular sign or symptom were tested using the Fisher's exact test. Differences in continuous variables were evaluated using the independent samples Mann-Whitney U-test or the independent samples T-test dependent on the shape of their distribution. For all statistics, P was set at the 0.05 level. The data were analysed using IBM SPSS Statistics version 21.0 (Armonk, NY: IBM Corp).

RESULTS

Patients with CRPS of the ankle/foot

The data of 161 patients diagnosed at our outpatient clinic with CRPS were found in the TREND database. From these, 94 patients were diagnosed with CRPS of the wrist/hand and were therefore excluded. Of the remaining 67 patients, three patients were diagnosed with CRPS confined to the knee and included in the relevant group. All remaining 64 patients were diagnosed with CRPS of the ankle / foot.

Patients with CRPS confined to the knee

The subsequent manual search of all the hospital records resulted in the identification of a total of 1193 patients coded with CRPS. The patients' charts were manually checked and screened on problems with one or both knees. Sixty-eight (5.7%) of them had complaints of the knee(s). After reading the complete charts of these 68 patients, 18 patients were excluded because they were not diagnosed by the specialist with CRPS confined to the knee. This resulted in a cohort of 50 patients with CRPS of the knee based on the diagnostic criteria set used at the time of referral to our hospital (see figure 2).

Analyses of the included patients revealed no significant difference between both cohorts in gender ($P=0.44$) or age ($P=0.13$), whereas there was a significant difference in the duration of symptoms and signs before diagnosing CRPS ($P=0.02$). Patients with CRPS of the knee suffered longer from their complaints than those with CRPS of the ankle/foot before diagnosis (Table 1). The duration of complaints in the knee cohort had a median of 21.50 months (IQR 10.50-48.00) and the duration of complaints in the ankle/foot cohort had a median of 9.50 months (IQR 3.25-40.50). In addition, both cohorts were checked to see whether patients fulfilled the currently recommended IASP clinical Budapest criteria

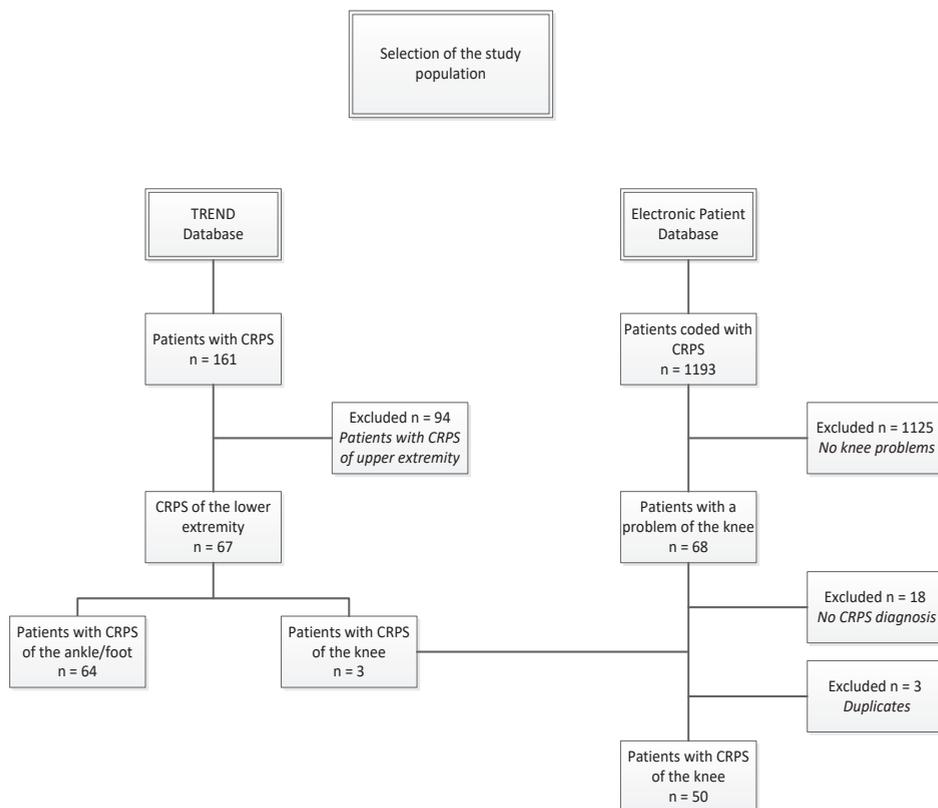


Figure 2. Flow chart of selection of the study population

for diagnosing CRPS. There was no significant difference in the proportion of patients in both groups who met the IASP clinical Budapest criteria ($p=0.52$): in the knee cohort, 36/50 patients (72%) met these diagnostic criteria and in the ankle/foot cohort 47/64 patients (73%) fulfilled these criteria.

At presentation, all participants mentioned severe, continuing pain, with a pain score of at least 5 on the numeric rating scale (NRS), where 0 = no pain and 10 = worst imaginable pain. Table 2 summarizes the patients' symptoms and signs. In both patient groups allodynia, color asymmetry, temperature asymmetry, edema and decreased range of motion were the most frequently reported symptoms as well as seen signs. Concerning the reported symptoms, a statistically significant difference between the groups in the prevalence of hyperesthesia, hyperalgesia, decreased range of motion and dystonia was found. With regard to the signs, a significant difference was found between the groups in hypoesthesia, hyperalgesia, color asymmetry, and sweating asymmetry. These specific symptoms and signs were more often mentioned and seen in the CRPS of the ankle/foot cohort.

Table 1. Characteristics of the patients by location of CRPS

| | Knee cohort n = 50 | Ankle/Foot cohort n = 64 | P |
|--|---------------------|--------------------------|-------|
| Female gender n (%) | 44 (88%) | 52 (81.3%) | 0.44 |
| Age/years mean (SD) | 41.44 (14.37) | 41.05 (16.56) | 0.13 |
| Duration/months median (IQR) | 21.50 (10.50-48.00) | 9.50 (3.25-40.50) | 0.02* |
| Met the Budapest diagnostic criteria set n (%) | 36 (72%) | 47 (73%) | 0.52 |

CRPS, complex regional pain syndrome; SD, standard deviation; IQR, interquartile range,
* significant difference

Table 2. Symptoms (subjective) and signs (objective) by location of CRPS in 114 patients

| | Symptoms | | | Signs | | |
|---------------------------|-------------|-------------------|---------|-------------|-------------------|---------|
| | Knee cohort | Ankle/Foot cohort | P | Knee cohort | Ankle/Foot cohort | P |
| | n (%) | n (%) | | n (%) | n (%) | |
| Sensory | | | | | | |
| Allodynia | 32 (64) | 45 (70) | 0.55 | 30 (60) | 45 (70) | 0.32 |
| Hyperalgesia | 17 (34) | 36 (56) | 0.02* | 6 (12) | 32 (50) | <0.001* |
| Hyperesthesia | 7 (14) | 44 (69) | <0.001* | 11 (22) | 24 (38) | 0.10 |
| Hypoesthesia | 1 (2) | 6 (9) | 0.13 | 3 (6) | 16 (25) | 0.01* |
| Vasomotor | | | | | | |
| Asymmetry in temperature | 40 (80) | 54 (84) | 0.62 | 34 (68) | 41 (64) | 0.70 |
| Asymmetry in color | 36 (72) | 53 (83) | 0.18 | 23 (46) | 44 (69) | 0.02* |
| Sudomotor | | | | | | |
| Edema | 43 (86) | 48 (75) | 0.16 | 30 (60) | 42 (66) | 0.56 |
| Asymmetry in sweating | 14 (28) | 24 (38) | 0.32 | 0 (0) | 12 (19) | 0.001* |
| Motortrophic | | | | | | |
| Decreased range of motion | 25 (50) | 48 (75) | 0.01* | 29 (58) | 46 (72) | 0.16 |
| Weakness | 21 (42) | 36 (56) | 0.19 | 14 (28) | 28 (44) | 0.12 |
| Trophic disturbances | 20 (40) | 36 (56) | 0.09 | 19 (38) | 29 (45) | 0.45 |
| Dystonia | 2 (4) | 20 (31) | <0.001* | 1 (2) | 2 (3) | 1.00 |
| Tremor | 5 (10) | 5 (8) | 0.75 | 2 (4) | 2 (3) | 1.00 |

CRPS, complex regional pain syndrome, * significant difference

The precipitating events for development of CRPS are presented in table 3. In the knee cohort, surgery and arthroscopy were the most frequently occurring precipitating events: 15 patients (30%) had (arthroscopic) surgery and 14 (28%) had an arthroscopy before the onset of CRPS. In the ankle/foot cohort, a fracture of the lower leg (20 patients, 31.3%) and a trauma, for example, distortion and/or inversion, (16 patients, 25%), were the most frequently reported precipitating events.

Table 3. Precipitating events for development of CRPS in both cohorts

| Event | Knee cohort | Ankle/Foot cohort |
|--------------------------------|-------------|-------------------|
| | n (%) | n (%) |
| (Arthroscopic) surgery | 15 (30) | 14 (21.8) |
| Arthroscopy | 14 (28) | 0 (0) |
| Anterior knee trauma | 10 (20) | - |
| Luxation | 4 (8) | 1 (1.6) |
| Burns | 1 (2) | 0 (0) |
| Fracture | 1 (2) | 20 (31.3) |
| Twisting injury | 1 (2) | 0 (0) |
| Trauma (inversion, distortion) | 0 (0) | 16 (25) |
| Spontaneous | 0 (0) | 7 (10.9) |
| Other | 4 (8) | 6 (9.4) |
| Total | 50 (100) | 64 (100) |

CRPS, complex regional pain syndrome

DISCUSSION

The aim of this retrospective study was to compare the phenotype (in terms of symptoms and signs) of CRPS confined to the knee to that of CRPS of the ankle/foot. The results indicate that a limited phenotypical variation exists, but the phenotypes are not identical.

This study included 50 patients with CRPS of the knee and 64 with CRPS of the ankle/foot. For reasons of comparability, we excluded patients diagnosed with CRPS of an upper extremity (i.e. the hand or wrist). All patients were diagnosed with CRPS based on the criteria applied at the time they visited our outpatient department. When applying the IASP clinical Budapest criteria to the included patients, a minority in both cohorts (28% and 27%) did not completely meet these criteria currently recommended. However, as the complaints could not be explained by any other diagnosis, these patients would nowadays probably be diagnosed with CRPS-NOS (not otherwise specified). CRPS-NOS was added as a subtype, next to CRPS type 1 (without nerve damage) and type 2 (with nerve damage), to capture patients who were diagnosed with CRPS previously and who did not fulfill the criteria anymore (8).

Although both cohorts were similar with regard to gender and age, patients with CRPS of the knee had suffered from this condition for a significantly longer time than those with CRPS of the ankle/foot. This fact can probably be attributed to physicians' unfamiliarity with diagnosing CRPS of the knee (13). A delay in diagnosing CRPS confined to the knee is not uncommon. Katz *et al.* described an average delay of 29 months (range: 3 weeks to 11 years) and Cameron *et al.* described a delay of 26 months before receiving the diagnosis CRPS of the knee (10, 14). An average of 11.2 months (range: 3 months to 58.8 months) from

the time of injury to diagnosing CRPS of the knee has been described by Neuschwander *et al* (15). The retrospective design counts as a limitation of this study. Physicians at our outpatient clinic may not have recognized the complaints of the knee as CRPS, so the symptoms reported and the signs found during clinical examination (and written in the patients' charts) may not give a true picture of the patients' actual condition.

Significant differences in symptoms and signs between the two cohorts were found with regard to four symptoms (hyperesthesia, hyperalgesia, decreased range of motion, and dystonia) and four signs (hypoesthesia, hyperalgesia, color asymmetry, and sweating asymmetry). Although these differences might be due to (not having corrected for) multiple testing, (some of) the differences in signs are plausible. Dystonia of the knee is uncommon and difficult to examine, because decreased range of motion in the knee already influence the flexion and extension of the knee (16). Birklein *et al.* concluded that patients with CRPS have hyperhidrosis in the affected limb, but particularly during the acute phase (<2 months) (17). As this retrospective study shows, patients with CRPS of the knee suffered longer from this condition. Therefore, by the time the CRPS was diagnosed it could already be in a chronic phase. So, an asymmetry in sweating between both knees was hard and probably even impossible to objectify.

Because of the significant difference in duration of the disease, and the possibility that symptoms and signs of CRPS can differ over time (18), we decided to perform post hoc a pairwise matching analysis. We matched the patients based on gender, duration of complaints and age. The range for matching based on duration was within 1 year of complaints and the range for matching on age was within 10 years of age; this resulted in 38 pairs of patients. Re-analysis yielded no significant difference in gender, age or duration ($0.20 \leq p \leq 1.00$). Interestingly, after pairwise matching, the significant differences in symptoms and signs that we found earlier (when comparing the two complete cohorts) were the same. This supports the assumption that CRPS of the knee does differ from CRPS of the ankle/foot in terms of a few symptoms and signs and that the observed phenotypic variation is not due to (possible) inherent changes over time.

The precipitating events differed between both cohorts; patients reported more surgical events before development of CRPS of the knee than before development of CRPS of the ankle/foot. Earlier reports by O'Brien *et al.*, Katz *et al.* and Burns *et al.* confirm this surgical cause of CRPS confined to the knee (10, 19, 20).

In conclusion, the phenotypic variation in terms of symptoms and signs of CRPS of the knee compared to CRPS of the ankle/foot is limited, but the phenotypes are not identical. We found some significant differences between the two cohorts, which probably can be explained by the location of the CRPS. The phenotypic variation might be a reason why CRPS in patients with pain of the knee, that is disproportionate to the initial trauma, is sometimes not recognized. We recommend that physicians add CRPS to their differential diagnosis when encountering a patient with pain of the knee that is disproportionate to the precipitating injury.

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