

<http://hdl.handle.net/1765/119916>

# **Clinical course and impact of complex regional pain syndrome confined to the knee**

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*Pain Medicine. 2019 Jun 1;20(6):1178-1184*

## ABSTRACT

**Objective:** Although complex regional pain syndrome (CRPS) of the knee is comparable to CRPS of the ankle/foot at time of diagnosis, no reports are available concerning the course of knee CRPS. Therefore, this study investigated the clinical course in terms of the symptoms and signs, health-related quality of life (HR-QoL), and work status of patients diagnosed with CRPS of the knee.

**Design:** Observational, descriptive study.

**Setting:** Single-center study.

**Subjects:** Patients with CRPS of the knee.

**Methods:** Patients self-reported their past and current CRPS symptoms, HR-QoL and work status; all underwent a physical examination. A comparison was made of changes in symptoms over time between patients with CRPS of the knee and those with CRPS of more distal locations.

**Results:** In total, 32 patients were enrolled. The follow-up time was  $11.5 \pm 6.29$  years since diagnosis, and symptoms and signs showed a significant decrease over time. Twelve patients (37.5%) rated their health as (generally) positive. Patients who were still able to work (31.3%) stated that their physical health gave them at least some problems in the performance of their job. A change in symptoms occurred significantly less often in CRPS of the knee.

**Conclusions:** CRPS of the knee changes in terms of symptoms over time, but significantly less than CRPS of other locations. A change in work status was reported in 82% of the patients due to their CRPS, and in 91% the pain interfered with their daily life. CRPS of the knee is a painful condition with persistent symptoms causing a diminished HR-QoL.

## KEY WORDS

Complex regional pain syndrome, knee, course, quality of life, work status

## INTRODUCTION

Chronic pain due to complex regional pain syndrome (CRPS) is known to adversely affect the life of a patient (1). CRPS is a potentially chronic disease; moreover, continuing pain is the most disabling factor for patients and, unfortunately, pain intensity can increase with disease duration (2-4).

CRPS confined to the knee is less well known in the medical world (5). The most commonly reported initiating trauma for developing CRPS confined to the knee is (arthroscopic) surgery, whereas for CRPS of other locations, fracture is the most reported trauma (6, 7). We concluded from a previous study that, at the time of diagnosis, the clinical picture of CRPS of the ankle/foot (lower limb) is comparable but not identical to that of CRPS confined to the knee. In addition, we found a significantly longer duration of disease of CRPS confined to the knee before receiving the diagnosis, compared to CRPS of the ankle/foot (8).

No reports are available on the outcome of CRPS confined to the knee, whereas multiple studies have investigated the outcome of CRPS of other (more distal) locations. For example, Anderson and Fallat investigated a group of 13 patients with CRPS of a lower limb with an average disease duration of 3.5 years after diagnosis; of this group, 12 (92%) still had continuous pain (9). Others have also found significant pain and impairment in patients with CRPS of the lower limb (10); the same applies for patients with CRPS of an affected upper limb (11). De Mos et al. concluded that, in their CRPS group, although a severe disease outcome was rare, incomplete resolution of all symptoms and signs was common (7).

A study on 656 patients with a duration of CRPS of at least one year showed that 81% of these patients were no longer able to do their work due to pain at some point after diagnosis; of the 81% who stopped working, only 27% resumed their job (4). Others reported a diminished health-related quality of life (HR-QoL) due to disability of the affected extremity (2, 12). As no data are available for CRPS confined to the knee, the present study aimed to investigate the course of symptoms and signs, HR-QoL and work status of patients diagnosed with CRPS confined to the knee. In addition, a comparison was made of symptom presentation between patients with CRPS confined to the knee and patients with CRPS of a more distal location.

## METHODS

### Design

This was a single-center, observational, descriptive study.

## Study Population

All patients included in this study were referred to the outpatient pain clinic of our hospital during the period 2000-2013. For the purpose of an earlier study, we had already performed a manual check of all hospital records of patients with the diagnostic code for CRPS to identify patients with CRPS confined to the knee (8). Every patient was seen by the same physician (FH), or under direct supervision of this pain specialist. Our institutional ethics committee approved a trial we performed at our center (MEC-2014-70) to find patients with CRPS confined to the knee, and all patients consented to participate. If a patient was diagnosed according to the International Association for the Study of Pain (IASP) clinical Budapest diagnostic criteria set (13), they were eligible for inclusion. The IASP clinical Budapest diagnostic criteria were adopted in 2010 as the standard for CRPS diagnosis.

To investigate the clinical course of CRPS confined to the knee, a pairwise matched analysis was made to compare the course with CRPS of distal locations. Information on the clinical course of CRPS of distal locations was collected earlier by De Mos et al. (7); all results of this latter study were available at our research center.

## Measurements

All patients were asked to visit the department once again to undergo a physical examination to assess the current signs of their CRPS. The physical examination was performed by a physician who has a lot of experience in diagnosing CRPS. Prior to this visit, they were asked to answer questionnaires about: 1) their previous and current symptoms of CRPS, 2) their HR-QoL, 3) their work status, 4) whether they considered their CRPS to be cured or stabilized, and 5) whether they experienced sequelae. The questionnaires were completed by the patients in advance and were discussed during the visit to avoid missing and/or wrong interpretation of their answers. The signs present at the time the patient received the diagnosis of CRPS confined to the knee, were collected by inspection of the hospital records of each patient.

## Statistical analysis

Descriptive statistics were used to determine the frequencies and measures of the central tendency of the demographic and outcome parameters. The Kolmogorov-Smirnov test was used to analyze whether parameters were normally distributed. For parameters with a normal distribution, central tendency and dispersion were described in terms of the mean and standard deviation (SD), and parameters with a non-normal distribution in terms of the median and interquartile range (IQR). The McNemar test was applied to investigate changes that occurred in symptoms and signs.

For all statistics,  $\alpha$  was set at the 0.05 level. Data were analyzed using SPSS Statistics, version 21 (IBM Corp., Armonk, NY, USA).

## RESULTS

A total of 50 patients diagnosed with CRPS confined to the knee were found in the digital patient database of our hospital (8). The research physician (CvB) tried to contact every patient by telephone: five patients were not available, and of the remaining patients, 37 were willing to fill in the questionnaires. Eventually, 32 patients returned their questionnaires to the outpatient clinic and were included in this study. Within this group, 29 patients gave permission to perform a physical examination to assess the current CRPS signs.

### Demographics

The group of patients diagnosed with CRPS confined to the knee consisted of 28 females (88%). At the time of diagnosis, all patients fulfilled the Bruehl and Harden criteria or the IASP clinical Budapest criteria. The mean age at the time of this study was 51.2 (SD 15.33) years. The mean time since receiving the CRPS diagnosis (SD) was 11.5 (6.29) years. The initiating events of the CRPS, as described by the patients, were surgery (44%), some kind of trauma (38%), a fracture (6%), and unknown (12%).

### Course of CRPS confined to the knee

Table 1 shows the current symptoms and those at the time of diagnosis of the CRPS. With the exception of coordination disorder, the relative frequency of all 20 symptoms decreased over time; in nine of these, the decrease was statistically significant. Table 2 shows the CRPS signs at the time of diagnosis and the current signs as measured by physical examination. An increase in relative frequency was found for allodynia, asymmetry in color, hyperalgesia and asymmetry in sweating; however, only the increase in hyperalgesia was significant. The relative frequency of the remaining signs decreased.

Of all 32 patients, 31 (97%) reported temperature asymmetry at the time of diagnosis, and 28 (88%) at follow-up. In 22 (68%) of these patients, the temperature asymmetry remained the same (cold, warm, or alternating hot and cold) and in 10 patients (32%) the temperature asymmetry shifted to another status (Table 3). Furthermore, five patients (16%) considered their CRPS to be cured, six (19%) patients reported their CRPS to be stable, and 27 (84%) experienced sequelae due to CRPS. Of the six patients reporting their CRPS to be stable, all experienced sequelae. Of all patients, 17 (53%) were still on medication and 11 (34%) received physiotherapeutic treatment for the CRPS.

### Current Work Status

Of all patients, 22 (69%) had a job at the time they were diagnosed; of those patients, 18 (82%) reported that their work had changed over time due to the CRPS. Of these 18 patients, 10 (56%) had to stop working, of whom eight patients are still receiving benefits, six (33%) changed their job, and the remaining two (11%) adapted their way of performing their job.

**Table 1.** Symptoms at time of diagnosis and current symptoms in 32 patients with CRPS confined to the knee

Symptom	At diagnosis n = 32	At follow-up n = 32	Change n = 32		p
			Yes → No	No → Yes	
	n (%)	n (%)	n	n	
Continuous pain	32 (100)	21 (66)	11	0	-
Weakness	32 (100)	27 (84)	5	0	-
Increase after exercise	32 (100)	25 (78)	7	0	-
Hyperesthesia	31 (97)	24 (75)	8	1	0.04*
Decreased range of motion	31 (97)	26 (81)	6	1	0.13
Hyperalgesia	30 (94)	28 (88)	2	0	0.50
Asymmetry in temperature	30 (94)	22 (69)	8	0	0.008*
Asymmetry in color	29 (91)	20 (63)	9	0	0.004*
Swelling	28 (88)	22 (69)	6	0	0.03*
Allodynia	27 (84)	17 (53)	12	2	0.01*
Stiffness	27 (84)	20 (63)	7	0	0.02*
Hypoesthesia	22 (69)	18 (56)	5	1	0.22
Cramp	18 (56)	17 (53)	2	1	1.00
Tingling	17 (53)	12 (38)	5	0	0.06
Involuntary movements	17 (53)	11 (34)	6	0	0.03*
Asymmetry in sweating	15 (49)	8 (25)	7	0	0.02*
Tremor	14 (44)	8 (25)	6	0	0.03*
Asymmetry in hair	14 (44)	11 (34)	3	0	0.25
Asymmetry in nails	11 (34)	10 (31)	3	2	1.00
Coordination disorder	10 (31)	10 (31)	2	2	1.00

\*, significant proportional decrease; CRPS, complex regional pain syndr

**Table 2.** Signs at time of diagnosis and current signs in 29 patients with CRPS confined to the knee

	Signs at diagnosis n = 29	Current signs n = 29	Change of signs n = 29		p
			Yes → No	No → Yes	
	n (%)	n (%)	n	n	
Asymmetry in temperature	22 (76)	15 (52)	10	3	0.09
Swelling	19 (66)	17 (59)	8	6	0.79
Decreased range of motion	19 (66)	18 (62)	7	6	1.00
Allodynia	16 (55)	19 (66)	5	8	0.58
Asymmetry in color	10 (34)	13 (45)	4	7	0.55
Motor changes (tremor, dystonia, weakness)	10 (34)	3 (10)	10	3	0.09
Trophic changes (hair, nails)	9 (31)	5 (17)	8	4	0.39
Hyperalgesia	3 (10)	14 (48)	2	13	0.007*
Asymmetry in sweating	0 (0)	1 (3)	0	1	-

\*, significant increase; CRPS, complex regional pain syndrome

**Table 3.** Patients with CRPS confined to the knee (n=32) who did/did not show change in type of temperature asymmetry

	Change in temperature asymmetry over time				
	Warm	Cold	Variable	No difference	Temperature at time of diagnosis
	n (%)	n (%)	n (%)	n (%)	n (%)
Warm	9 (28)	5 (16)	1 (3)	2 (6)	17 (53)
Cold	0	9 (28)	0	1 (3)	10 (31)
Variable	0	1 (3)	3 (9)	0	4 (13)
No difference	0	0	0	1 (3)	1 (3)
Current temperature asymmetry	9 (28)	15 (47)	4 (12.5)	4 (12.5)	32 (100)

CRPS, complex regional pain syndrome

Six patients have filed a claim for a work-related injury with their employer. Of those, one claim has been settled, whereas the others are pending. At the time of this study, the 10 patients that had a job were asked additional questions about their ability to perform their job. Eight reported that their physical health gave some, or major, problems in performing their job due to CRPS. The most frequently reported reason for this was decreased range of motion of the knee.

### Current Quality of Life

All 32 patients with CRPS confined to the knee were asked to rate their health; six (19%) rated their health as poor, 14 (44%) as fair, nine (28%) as good, and three (9%) as very good. Of all patients, 28 (88%) reported that their health status caused limitations in performing moderate or more demanding activities (e.g. moving a table) and 29 patients (91%) reported that the pain interfered with their daily life. In addition, almost 50% of the patients stated that, as a result of emotional problems, they experienced difficulties with their work or (other) regular daily activities (Table 4).

### Comparison of knee CRPS and other CRPS

Patients with CRPS confined to the knee were pairwise matched (based on disease duration) with patients with CRPS of distal locations (hand/wrist/ankle/foot) to compare changes in the relative frequency of symptoms over time between the groups. For this analysis, we matched 24 patients from each group. The results show that, in terms of the defined symptoms, CRPS confined to the knee showed less change over time compared to CRPS of distal locations: that is, of the 20 symptoms, only four showed a significant change in patients with CRPS confined to the knee, compared with 11 in patients with CRPS of distal locations (Table 5).

**Table 4.** Frequency of answers of patients diagnosed with CRPS confined to the knee (n=32) regarding their quality of life (QoL)

Current quality of life (QoL)	Frequency (n)					
	Excellent	Very good	Good	Fair	Poor	
Health in general	0	3	9	14	6	
	Yes, a lot		Yes, a little		No, not at all	
Health limits in:						
Moderate activities	21		7		4	
Climbing flights of stairs	20		9		3	
	Yes			No		
Physical health:						
Accomplished less		26		6		
Limited in activities		27		5		
Emotional problems:						
Accomplished less		15		17		
Limited in activities		13		19		
	Not at all	A little bit	Moderately	Quite a bit	Extremely	
How much did pain interfere	3	6	6	8	9	
	All of the time	Most of the time	A good bit of the time	Some of the times	A little of the time	None of the time
Felt calm and peaceful	1	7	7	14	3	0
Had a lot of energy	1	4	6	14	6	1
Felt downhearted and blue	0	3	3	10	8	8
Interference with social activities	5	12	0	9	1	5

## DISCUSSION

The aim of this study was to investigate the course of CRPS confined to the knee in terms of symptoms and signs, self-reported HR-QoL, and the work status of patients diagnosed with this disorder. This study was performed due to the absence of earlier reports on this specific topic.

In our patients, a self-reported recovery rate of 16% was found after a mean follow-up of 11.5 years, compared with the 29% reported by de Mos et al. (7). However, in the latter study, follow-up was only 5.8 years and, in contrast to our sample, their 102 patients were diagnosed with lower/upper limb CRPS. Although spontaneous resolution did not occur in our patients with knee CRPS, this has been described previously (14-16); however, in these latter studies, most patients had CRPS of the upper extremity. In our group, only one patient was free of symptoms and signs, but this was after extensive treatment. Some significant changes in symptoms were found in our patients at follow-up, mostly based on a decrease in presentation. Regarding possible changes in signs, we found a significant increase in presentation only for hyperalgesia. Therefore, although our patients experi-

**Table 5.** Changes in symptom presentation in both groups after matching duration of disease

Symptom	Change in Knee CRPS group n = 24		Change in Distal CRPS group n = 24	
	n (%)	p	n (%)	p
Continuous pain	9 (38)	-	15 (63)	<0.001*
Allodynia	8 (33)	0.02*	14 (58)	<0.001*
Asymmetry in color	7 (29)	0.02*	15 (63)	<0.001*
Hyperesthesia	7 (29)	-	6 (25)	0.07
Asymmetry in temperature	6 (25)	0.03*	11 (46)	0.001*
Asymmetry in sweating	5 (21)	0.06*	7 (29)	0.02*
Increase after exercise	5 (21)	-	4 (17)	0.22
Stiffness	5 (21)	0.06	3 (13)	0.38
Decreased range of motion	4 (17)	0.22	9 (38)	0.004*
Swelling	4 (17)	0.25	15 (63)	<0.001*
Tremor	4 (17)	0.13	1 (4)	1.00
Weakness	4 (17)	-	6 (25)	0.07*
Hypoesthesia	3 (13)	0.25	4 (17)	0.22
Tingling	3 (13)	0.25	4 (17)	0.13
Involuntary movements	3 (13)	0.25	1 (4)	1.00
Asymmetry in hair	1 (4)	1.00	7 (29)	0.02*
Asymmetry in nails	1 (4)	1.00	7 (29)	0.02*
Hyperalgesia	1 (4)	1.00	8 (33)	0.01*
Cramp	0 (0)	1.00	3 (13)	0.25
Coordination disorder	0 (0)	1.00	2 (8)	0.50

\*, significant difference; CRPS, complex regional pain syndrome

enced a subjective recovery of CRPS or a reduction in symptoms, the objective signs did not show a significant decrease, that is, the subjectively experienced improvement could not be objectified. As there are no earlier reports on the clinical course of CRPS confined to the knee in terms of symptoms and signs, no comparison could be made between our results and other studies.

Currently, the diagnosis of CRPS is still based on symptoms and clinical signs, and no additional measurements are needed. So, a physician needs a significant amount of experience in diagnosing CRPS. The clinical examination in our patients was done by an experienced physician. Still, we figure this to be a limitation of diagnosing patients with CRPS and also a limitation of this study. The CRPS Severity Score (CSS) may be a helpful tool for monitoring the course of CRPS and outcomes research (17). We did use the CSS at the time of the study, but unfortunately, it was not used at the time the patients received their diagnosis of CRPS. We would like to add the CSS in future research at our center.

Based on the pairwise matched analysis, the symptoms of CRPS confined to the knee were more stable over time compared to CRPS of more distal locations, and recovery was less common. However, due to multiple testing, our study may have been at increased risk of a type 2 error; this implies that some statistical tests may have incorrectly resulted in significance. Nevertheless, as reported earlier, the diagnosis of CRPS confined to the knee seems problematic; for example, it took longer (possibly due to phenotypic variation) before a diagnosis of CRPS was made (8). This can lead to a potential delay in starting the appropriate treatment and, subsequently, to a more stable course in terms of symptoms (i.e. a significantly reduced decrease in reported symptoms). This corresponds to earlier reports stating that earlier recognition and treatment result in potentially better outcome in patients with CRPS (18).

Patients with cold CRPS at the time of diagnosis are reported to have a poorer clinical pain outcome (19). In our patients diagnosed with CRPS confined to the knee, 11 (34%) started with cold CRPS, of whom five reported that their continuous pain resolved over time. On the other hand, 17 patients (53%) started with warm CRPS, and at the time of this study, five reported that they no longer had continuous pain. Therefore, for this patient group, we cannot confirm the poorer clinical pain outcome based on the temperature at diagnosis. A possible explanation for this could be that, as shown in this study, CRPS confined to the knee has a limited change in symptoms over time compared to other more distal locations. In 10 of our patients, the temperature asymmetry changed based on the symptoms. This self-reported temperature shift could imply that physicians should change their treatment strategy based on the possible underlying mechanisms, to achieve a better outcome for patients diagnosed with CRPS (20, 21).

Patients with CRPS confined to the knee appear to have reduced HR-QoL, similar to patients with CRPS in more distal locations. For example, van Velzen et al. described patients with lower limb CRPS who reported poor HR-QoL; they also found a negative correlation between disease duration and physical functioning. In line with this finding, they reported that the HR-QoL of patients is best explained by the impact of CRPS on their physical health (12). Kemler and de Vet reported that the HR-QoL of patients with chronic reflex sympathetic dystrophy (RSD, a term earlier used to describe CRPS) of the leg was affected due to CRPS (10). In addition, Galer et al. concluded that persistent CRPS symptoms after a mean disease duration of 3.3 years substantially interfered with patients' health-related quality of life and daily functioning (22).

In the present study, there was a change in the work status of 82% of our patients diagnosed with CRPS confined to the knee. This is in line with Kemler and Furnee, who found that in 72% of their patients, the work status changed due to the CRPS (1). Dumas et al. found that lower limb involvement was significantly negatively correlated with return to work (23). In contrast, Duman et al. reported a return to work ability of 72% (24); surprisingly, this latter group consisted solely of male patients, whilst mostly female patients are

diagnosed with CRPS (15, 25). In our group of patients, 80% reported that their physical health gave them problems in performing their job. This is in line by other reports that CRPS interferes with functional activity and the ability to (resume) work (22). In contrast, two studies reported that 68% and 72% of their patients with CRPS of the upper limb resumed their work (23, 24). Also, CRPS of the lower limb led to difficulties in social activities and work compared with patients with an affected upper limb (10).

Furthermore, Thevenon et al. described that patients with CRPS affecting an upper limb needed longer treatment and had longer work absence than patients with CRPS affecting a lower limb (26). A study on 656 patients (after a duration of CRPS of at least one year) showed that 81% of these patients were no longer able to do their work due to pain at some point after diagnosis; of the 81% who stopped working, only 27% resumed their job (4).

In conclusion, this study was performed to investigate the course of CRPS confined to the knee. Since this is the first study to provide information on the clinical course of this specific CRPS location, no comparison can be made with other studies. Despite a decrease in symptom presentation, most of our patients had persistent symptoms and signs at a mean of 11.5 years after initial diagnosis, and only a minority returned to their original work. Compared to CRPS of more distal locations, CRPS confined to the knee shows significantly less change in terms of symptoms. Most of our patients reported to have sequelae, and only five (16%) considered themselves to be cured. Also, the pain continued to interfere with their daily activities.

In summary, CRPS confined to the knee is a painful condition with a less favorable clinical course than CRPS of more distal locations, including an adverse impact on work status and a diminished HR-QoL, which could potentially lead to high socioeconomic costs.

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