Health-related quality of life in 975 patients with complex regional pain syndrome type 1

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ABSTRACT

There are limited data available on health-related quality of life (QoL) in patients with complex regional pain syndrome (CRPS). In the present study we examined QoL in 975 CRPS patients attending 6 different clinics in the Netherlands. QoL was assessed using the MOS 36-Item Short-Form Health Survey (SF-36) with the Mental Health Summary Score (MHS) and the Physical Health Summary Score (PHS) as dependent variables. The influences of gender, type of affected limb, disease duration, pain scores, CRPS severity and set of diagnostic criteria used were investigated. We found the lowest scores of QoL in the physical domains of the SF-36, with lower-limb CRPS patients reporting poorer results than patients with an affected upper limb. Influence of gender on QoL was not observed, and correlations of QoL with disease duration and the CRPS severity score were weak. Pain correlated moderately with QoL. In addition, patients fulfilling stricter diagnostic criteria (ie, the Budapest criteria) had lower QoL scores than patients fulfilling less strict criteria (ie, the Orlando criteria). We conclude that loss of QoL in CRPS patients is due mainly to reduced physical health. A comparison with data available from the literature shows that CRPS patients generally report poorer QoL than patients with other chronic pain conditions, particularly in the physical domains. Pain correlated moderately with QoL and therefore deserves ongoing attention by physicians. Finally, patients meeting the diagnostic Budapest criteria have lower QoL scores than patients meeting the Orlando criteria, highlighting the impact of different sets of criteria on population characteristics.

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1. Introduction

Complex regional pain syndrome (CRPS) is a condition that may have a profound effect on daily life, often rendering patients invalids for many years [7,8]. Typically, CRPS develops after a trauma to 1 of the limbs, but occasionally it progresses to other limbs [17,30,40]. In the acute phase, patients report intense pains accompanied by autonomic, trophic, and motor disturbances of the affected limb [18]. A considerable number of patients develop a chronic course in which autonomic signs are usually less pronounced, and pain, along with sensory and motor disturbances, predominates [34]. The incidence ranges from 5.5 to 26.2 per 100,000 person-years [22,33], with the highest incidence rates occurring between 61 and 70 years and with women being affected 3 to 4 times more often than men [22].

Although, in recent years, considerable progress has been made in the understanding of the pathophysiology of CRPS [18], this has not translated into an effective therapy from which all patients benefit; a large group of patients experience incomplete recovery and are confronted with long-term disability and partial or complete inability to resume their former jobs [4,28].
It is self-evident that such disease consequences may have a grave impact on the lives of CRPS patients. Indeed, previous studies on quality of life (QoL) in CRPS patients reported high levels of disability and continuing pain and motor disturbances. However, these studies were usually performed in small samples [6,14,34,39] or involved patients in trials who had to meet certain eligibility criteria, which affected the generalizability of the findings [29,39]. In the present study, we therefore analysed the QoL data of almost 1000 Dutch patients collected over the past 10 years in 5 major CRPS clinics. Specifically, we studied the influence of gender, type of involved extremity (upper or lower), disease duration, and pain on perceived QoL.

In addition, we studied the influence of diagnostic criteria on QoL, as the profile of signs and symptoms differs according to the diagnostic criteria that the patient fulfils [25], whereas QoL may vary with perceived complaints. Finally, we included the CRPS Severity Score, a recently developed severity index that counts the number of the patient's signs and symptoms, to study the relationship between the number of occurring signs and symptoms and perceived QoL [10].

2. Methods

2.1. Participants

Patients were recruited from 5 pain clinics and 1 department of neurology of university hospitals participating in Trauma RElated Neuronal Dysfunction (TREND), a Dutch knowledge consortium that integrates research on CRPS (www.trendconsortium.nl). All patients were 18 years or older; fulfilled the diagnostic criteria for CRPS adopted at the 1993 consensus conference ('Orlando criteria') [21], the Budapest clinical criteria (Bdp-c), or the Budapest research criteria (Bdp-r) [11], and did not have any other conditions that could account for the signs and symptoms encountered. Exclusion was made based on the presence of dementia, cognitive impairment, or any other factor resulting in an inability to understand and to complete self-assessment questionnaires.

2.2. Assessment methods and measurement instruments

Methods of examining patients were standardised across centres by the use of a universally applied measurement protocol and 3-monthly plenary training sessions. Signs and symptoms were recorded on a standard score sheet. Patients also completed a set of questionnaires. All data were stored in a NEN-7511 certified, central, Web-based data management system (ProMiSe). Written informed consent was obtained from all participants; procedures were performed in accordance with the Declaration of Helsinki; and the protocol was approved by the medical ethical committees of all participating centres.

We classified patients into 3 groups to examine the influence of the involved limb on QoL: 1 upper limb affected, 1 lower limb affected, and more than 1 limb affected. To evaluate the influence of diagnostic criteria on perceived QoL, we allocated patients to the most strict criterion that they met (Orlando < Bdp-c < Bdp-r).

The Dutch version of the MOS 36-Item Short-Form Health Survey (SF-36) was used as outcome measure of QoL in this study [43]. This generic questionnaire consists of 8 health domains: 1) limitations in Physical Functioning; 2) limitations in usual role activities because of physical problems (Role-Physical); 3) Bodily Pain; 4) General Health perceptions; 5) Vitality; 6) limitations in Social Functioning because of physical problems; 7) limitations in usual role activities because of emotional problems (Role-Emotional); and 8) general Mental Health. For the main analysis, the Physical Health sum Score (PHS) (mean of domains 1–4) and the Mental Health sum Score (MHS) (mean of domains 5–8) were used. Scores are presented as percentages (0–100), with higher scores indicating better QoL.

Pain was quantified using the pain rating index of the McGill Pain Questionnaire [20] and the Numeric Rating Scale. The McGill Pain Questionnaire consists of 20 categories of 3 or 4 rank-ordered words that evaluate different aspects of pain (range, 0–63, with higher scores indicating more pain). For the Numeric Rating Scale score, we asked patients to rate the average pain intensity of the previous week on a scale from 0 to 10, with 10 reflecting the worst pain imaginable.

As an indicator of severity of CRPS, we used the CRPS Severity Score, a checklist consisting of 17 CRPS-associated signs and symptoms [10].

The following questionnaires were not used in the primary analyses of this study, but were included to provide a broader perspective on the mental and physical health of patients: The Hospital Anxiety and Depression Scale [44]; the Radboud Skills Questionnaire [24]; and the Questionnaires on Walking and Rising [31,32]. The Hospital Anxiety and Depression Scale measures the presence and severity of mood disorders (range 0–42, with higher scores indicating more severe anxiety or depression); in the present study, the mean Anxiety and Depression scores of this questionnaire were used. The Radboud Skills Questionnaire measures the difficulty that patients with an affected upper limb perceive when performing manual activities of daily life (range, 1–5, with higher scores indicating worse functioning). The Questionnaires on Walking and Rising measures limitations in walking and rising in patients with an affected lower limb (range, 0–30; summary score of ‘walking inside’, ‘walking outside’, and ‘rising’, with higher scores indicating worse functioning: because of the different number of items in these 3 scales, all scores were first transformed to a scale of 0 to 10 and then summed).

2.3. Statistical analyses

All statistical analyses were performed with IBM SPSS Statistics version 20 (IBM Corporation).

Normality of the data was checked by inspecting histograms of frequency distributions, normal probability plots, residual scatter plots, and the Kolmogorov–Smirnov test. Data were considered statistical significant when P values were less than .05 and corrected for multiple comparisons (Bonferroni) when multiple analyses were performed within the same research question.

For the difference in QoL scores between sexes, the independent t test was used, and an analysis of variance (ANOVA) was carried out to examine the influence of type of limb and CRPS criteria on QoL. The Pearson correlation coefficient was calculated to examine the correlation between QoL and age, disease duration, symptom severity, or pain. Coefficients of 0.70 or higher were classified as strong, those 0.30 to 0.69 as moderate, and those less than 0.30 as weak [15]. Data are presented as mean scores ± standard deviations (SD).

3. Results

3.1. Study participants

A total of 975 patients (age, 46.8 ± 14.3 years; 817 female) were included in the analysis, of whom 374 (38.4%) had an affected upper limb and 408 (41.8%) had an affected lower limb (Table 1). In 193 patients (19.8%), more than 1 limb was affected: 28 patients (2.8%) had 2 affected upper limbs, 25 (2.6%) had 2 affected lower limbs, and the remaining 140 (14.4%) had a combination of an affected upper and lower limb (n = 53; 5.4%) or more than 2 affected
Table 1
Demographic and clinical characteristics of study patients.

<table>
<thead>
<tr>
<th></th>
<th>N (% female)</th>
<th>975 (83.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, year</td>
<td>46.8 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age at onset, year</td>
<td>42.1 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) disease duration, year</td>
<td>1.8 (0.4–6.7)</td>
<td></td>
</tr>
<tr>
<td>Employed/unemployed/retired/missing, %</td>
<td>51/28/9/12</td>
<td></td>
</tr>
<tr>
<td>N 1 arm/1 leg/1 limb</td>
<td>374/408/193</td>
<td></td>
</tr>
<tr>
<td>Fulfilling only Orlando criteria (%)</td>
<td>975 (100)</td>
<td></td>
</tr>
<tr>
<td>Fulfilling Bdp-c criteria (%)</td>
<td>697 (71.5)</td>
<td></td>
</tr>
<tr>
<td>Fulfilling Bdp-r criteria (%)</td>
<td>447 (45.8)</td>
<td></td>
</tr>
<tr>
<td>CRPS Severity Score, median (IQR)</td>
<td>11.0 (8–13)</td>
<td></td>
</tr>
</tbody>
</table>

| Hospital Anxiety and Depression Scale, mean (SD) | 6.17 (3.8) |
| Depression | 4.93 (3.8) |
| McGill Pain Questionnaire, mean (SD) | 25.50 (11.7) |
| Walking and Rising Questionnaire, mean (SD) | 18.73 (7.7) |
| Radboud Skills Questionnaire SQ, mean (SD) | 3.05 (0.9) |

| SF-36 | Physical Health Summary score, mean (SD) | 34.9 (18.0) |
|       | Physical Functioning, mean (SD) | 41.4 (26.1) |
|       | Role-Physical, mean (SD) | 18.1 (30.7) |
|       | Bodily Pain, mean (SD) | 27.5 (20.5) |
|       | General Health, mean (SD) | 52.1 (21.7) |
|       | Mental Health Summary score, mean (SD) | 58.4 (21.1) |
|       | Vitality, mean (SD) | 47.3 (19.9) |
|       | Social Functioning, mean (SD) | 58.9 (26.8) |
|       | Role-Emotional, mean (SD) | 60.2 (44.3) |
|       | Mental Health, mean (SD) | 67.1 (18.4) |

Bdp-c = Budapest clinical criteria; Bdp-r = Budapest research criteria; IQR = inter-quartile range; SD = standard deviation; SF-36 = MOS 36-Item Short-Form Health Survey.

3.5. QoL, disease duration, and age

Correlations of disease duration and age with the various summary and domain scores were all weak (Table 4). When we divided the patients into 3 approximately equal age groups, namely 40.0 or less, 40.1 to 55.0, and 55.1 or more years, it was apparent that the oldest CRPS patients had the highest PHS scores (32.73 ± 16.53, 33.99 ± 17.62, and 38.33 ± 19.47, respectively) (F2,974 = 8.24, P < .001) and the highest MHS scores (57.17 ± 20.24, 56.68 ± 21.77, and 61.80 ± 20.74, respectively) (F2,974 = 5.56, P = .004). Post hoc analysis showed that only Bodily Pain (from the PHS) and Vitality (from the MHS) were significantly related to age.

3.6. QoL and pain

Correlations with the numeric rating scale or McGill Pain Questionnaire were generally higher for the physical domain scores than for the mental domain scores, with the physical domain scores mostly showing moderate correlations with pain ratings. The highest correlations were found with the Bodily Pain scale (Table 4).

3.7. QoL and symptom severity

The CRPS severity score for patients affected in 1 limb significantly correlated with the PHS (r = −0.16, P < .001) but not with the MHS (r = −0.06, P = .13) (Table 4). Post hoc analysis showed that the strongest correlations were found for Physical Functioning, Role-Physical, and Bodily Pain. However, when the patient group was divided in subgroups based on the set of CRPS criteria that they fulfilled, correlations were no longer significant.

3.8. QoL and CRPS criteria

Table 5 shows data from the MHS and PHS for patients meeting the different sets of diagnostic criteria. A significant difference between the groups emerged for MHS (F2,972 = 10.4, P < .001) and PHS (F2,972 = 29.6, P < .001), with the post hoc analysis showing a significantly higher MHS and PHS for the Orlando group than for the
PHS and MHS of the SF-36 in CRPS; 5) correlations affected upper limb; 4) pain intensity is moderately associated affected lower limb have worse PHS scores than patients with an
patients was mostly determined by the loss of physical capabilities, and less so by mental complaints; 2) no gender differences in QoL of patients with CRPS were found; 3) CRPS patients with an affected lower limb have worse QoL as compared to patients with an affected upper limb, which was largely due to the lower scores in the Physical Functioning domain. This finding is likely explained by a bias of this domain towards lower

4. Discussion

This study examined QoL in a large group of almost 1000 Dutch patients with CRPS. We observed the following: 1) QoL in CRPS patients was mostly determined by the loss of physical capabilities, and less so by mental complaints; 2) no gender differences in QoL of patients with CRPS were found; 3) CRPS patients with an affected lower limb have worse PHS scores than patients with an affected upper limb; 4) pain intensity is moderately associated with both the PHS and MHS of the SF-36 in CRPS; 5) correlations between QoL and symptom severity were weak for the PHS, and absent for the MHS; and 6) patients meeting the Budapest diagnostic criteria have worse QoL as compared to patients meeting the Orlando criteria, underscoring the impact of different sets of criteria on sample characteristics.

4.1. QoL, type of affected limb, and physical functioning

Although, in CRPS patients, both PHS and MHS are lower than in the general population [5], our findings indicate that patients are burdened mainly by the physical consequences of CRPS.

Bdp-c or Bdp-r group, while no difference was found between the 2 Budapest criteria groups.
limb functions: 9 of 10 Physical Functioning items apply to lower limb function, whereas only 4 of 10 apply to upper limb function. Nevertheless, as illustrated by the scores of the Radboud Skills Questionnaire and questionnaires on Walking and Rising, CRPS is associated with severe disability, which corresponds to findings of others showing that a large proportion of CRPS patients experience partial or complete inability to resume their former jobs [4,28].

Clear explanations for the poor physical functioning of CRPS patients cannot be inferred from this study and are still a major question in CRPS research. The small but significant negative correlation between disease duration and Physical Functioning shows at least that long-term CRPS can have a negative effect on physical function. A role for kinesiophobia, often hypothesised to have a strong negative influence on physical function in CRPS, could not be confirmed in 2 recent studies [12,19]; instead, a negative association of functional limitations with perceived harmfulness of activities and “resting” as a pain coping strategy was found. This seems to point out that patients’ attitudes and behaviour towards pain is a very important aspect in the physical impairments that they experience. In line with these findings, new therapies for CRPS patients are being developed with a focus on improvement of physical function rather than pain reduction [3,13]. The question, however, remains why precisely CRPS patients show these low Physical Functioning and Role-Physical scores, which are lower than scores in other musculoskeletal or neuropathic pain conditions in patients with conditions such as rheumatoid arthritis [15] or neuralgic amyotrophy [2], and in lower limb amputees with or without phantom limb pain [2,15,35,37]. Only fibromyalgia patients have been found to exhibit worse scores in many domains [41]; however, in contrast to fibromyalgia, in which the condition also greatly affects mental health [41], QoL of CRPS patients is best explained by the impact of the condition on physical health. This is further substantiated by the fact that the Hospital Anxiety and Depression Scale scores in this cohort were considerably better than in a large group of fibromyalgia patients [26].

In previous studies, it has often been assumed that physical complaints experienced by CRPS patients start off initially with an aberrant host response to tissue damage that triggers a cascade of reactions leading to peripheral and central sensitization, which may have a profound and prolonged influence on pain and function, although the precise mechanisms are not clear [36]. In addition, CRPS is associated with central changes in sensorimotor cortical networks [16], which may further add to functional limitations.

4.2. QoL and gender

We found no difference in QoL between male and female CRPS patients. This is in contrast to the somewhat worse scores found for women in the general Dutch population [1] and with the results of many studies on QoL in chronically ill patients (see Sprangers et al. [38] for a review on QoL in patients with a range of chronic conditions). The pain scores of men and women were also similar, which again is quite remarkable if one considers that women generally have less efficient pain inhibitory controls than men [27]. Hypothetically this might indicate that, once men are affected by CRPS, the characteristics of CRPS have the same impact on QoL as in women.

4.3. QoL and age

In this study, younger CRPS patients exhibited lower QoL scores than older CRPS patients. Given that we found no difference in the CRPS severity score between age groups (<40 years, 10.6 ± 3.57; 40.1–55.0 years, 10.6 ± 3.52; and ≥55.1 years, 10.1 ± 3.45; P = .24, one may speculate that this could be due to the more demanding societal activities with which younger people tend to be confronted (e.g. work, family duties), which can be severely hindered by CRPS. However, conclusions drawn from these results must be interpreted with caution, given the cross-sectional nature of this study and the facts that absolute differences were small and correlations between the SF-36 domains and age were weak.

4.4. QoL and pain

Pain scores correlated moderately with the PHS and MHS. Although one might have expected these correlations to be stronger, it is known that pain intensity is a moderate predictor of disability [23] and that pain reduction per se does not necessarily result in a significant increase in Physical Functioning [42], the domain with 1 of the lowest scores in our patient group. In our data, the correlation between the numeric rating scale or the McGill Pain Questionnaire and Physical Functioning or Role-Physical likewise was not strong.

4.5. QoL and CRPS criteria and severity

It is again noteworthy that of all patients who fulfilled the Orlando criteria, only two-thirds fulfilled the Bdp-c criteria, whereas less than one-half met the Bdp-r criteria. It is obvious that criteria matter. The main difference between the Orlando criteria (the former IASP criteria) and the Bdp-c and Bdp-r criteria is, besides the inclusion of signs, the addition of motor symptoms and signs to the Budapest criteria [9]. Therefore it is not surprising that patients who fulfilled the Budapest criteria had lower QoL scores and, in particular, lower PHS scores, than patients who fulfilled the Orlando criteria.

CRPS severity measured with the number of signs and symptoms showed only weak correlations with the PHS. These correlations were lower than those in a study that found significant correlations between all SF-36 domains (except General Health) and the CRPS Severity Score [10]. We have no clear explanation for this difference, especially as scores on the PHS domains were remarkably similar to those in our study. Still, the reported correlations in that study were generally weak as well. This once more underlines that relations between impairments and disabilities are not as direct and strong as one might expect. The physical consequences of having a complex pain syndrome are apparently much more complicated than can be inferred from a simple summation of the associated signs and symptoms.

4.6. Study limitations

Several aspects should be taken into account when interpreting the results of this study. First, the institutions that participated in this study are nearly all specialised academic centres, and generalization of the results is therefore limited. However, because of the complexity of the diagnosis and treatment of the condition, CRPS patients are generally referred to specialised clinics, which, in the case of The Netherlands, are often academic centres, which makes selection towards more severely affected cases in the present study less likely. Nevertheless, an earlier study in the Netherlands found that about 25% of patients were not seen by a medical specialist but only by their general practitioner [22], and therefore selection bias cannot be ruled out completely. In addition, different specialists were involved in the collection of information on signs and symptoms, and although measures to reduce variability in assessment were imposed, this may have led to some residual inaccuracy.

To summarize, this is, to our knowledge, the largest report on QoL in patients with CRPS. The study shows that CRPS patients...
generally report a poorer QoL than patients with other chronic pain conditions, particularly in the physical domains. Gender and the type of affected limb do not influence QoL. In contrast, the diagnostic criteria used do matter: patients fulfilling stricter criteria (ie, the Budapest criteria) had lower QoL scores than patient's fulfilling less strict criteria (ie, the Orlando). Finally, pain scores correlated moderately with QoL, underscoring the need for further studies aimed at improving pain management in CRPS.

Conflict of interest statement

The authors report no conflicts of interest that pertain to the subject of this study.

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