PAIN® 145 (2009) 52–59

PAIN®

www.elsevier.com/locate/pain

Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review

Annemerle Beerthuizen [a,*], Adriaan van 't Spijker [a], Frank J.P.M. Huygen [b], Jan Klein [b], Rianne de Wit [c,d]

[a] Department of Medical Psychology and Psychotherapy, Erasmus MC, Rotterdam, The Netherlands
[b] Department of Anesthesiology, Erasmus MC, Rotterdam, The Netherlands
[c] Department of Health Care and Nursing Science, Faculty of Health, Medicine and Life Sciences, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands
[d] University Hospital Maastricht, Maastricht, The Netherlands

ARTICLE INFO

Article history:
Received 18 July 2008
Received in revised form 20 April 2009
Accepted 5 May 2009

Keywords:
Complex Regional Pain Syndrome
Systematic review
Psychopathology

ABSTRACT

Complex Regional Pain Syndrome type 1 (CRPS1) is a complication after trauma or surgery. Its pathophysiology is still a matter of debate, and psychological factors have been suggested to play a role, although their influence is unclear. The aim of this study was to investigate the evidence for the influence of psychological factors on the onset and maintenance of CRPS1 in adults. In a systematic review, articles were selected using Cochrane, Pubmed/Medline, Psychinfo, and Cinahl since 1980. Only original articles and empirical studies were included. Based on these selection criteria, 31 articles were identified. Studies were evaluated and weighted using a quality assessment instrument. The few prospective studies do not report a relationship between CRPS1 and depression, anxiety, neuroticism, or anger. The results of the retrospective/cross-sectional studies yield contradictory results regarding psychological problems in patients with CRPS1. A majority show no association, and studies with a higher methodological quality lean to a conclusion of no relationship between psychological factors and CRPS1. The majority of included studies ($N = 24$; 77%) had only a poor to moderate methodological quality. Although many patients with CRPS1 are stigmatized as being psychologically different, this literature review identified no relationship between CRPS1 and several psychological factors. Only life events seemed to be associated with CRPS1: patients who experienced more life events appeared to have a greater chance of developing CRPS1. More studies with greater methodological quality and more participants should be performed on the association between psychological factors and the development and course of CRPS1.

1. Introduction

Complex Regional Pain Syndrome type 1 (CRPS1) is a complication after trauma or surgery, although spontaneous development of the disorder has also been described. There are different sets of criteria for diagnosing CRPS, such as the criteria of Veldman [81], the criteria of the International Association for the study of Pain (IASP) [73], and the criteria of Bruehl [8].

Pain is the symptom most commonly used in these criteria sets; less commonly reported symptoms are allodynia, hyperalgesia, abnormal skin color, temperature change, abnormal sudomotor activity, edema, and motor/trophic disturbances [63,73,81]. The symptoms of CRPS1 patients usually occur in an extremity and are often poorly explained by the presumed cause or known pathology [73].

The pathophysiology of CRPS1 is poorly understood, as reflected in the wide range of explanatory theories, including an unregulated sympathetic nervous system [84], an exaggerated neurogenic inflammation [84], a genetic predisposition, [46,80], and immobilization of the limb (disuse) [11,34]. Apart from these somatically oriented explanations, it has been suggested that "psychologically peculiar" patients have an increased risk of developing CRPS1 [42]. Others, however, refute this influence [21,51]. Hendler [40] stated that doctors use the label "psychogenic pain" when patients do not respond to medical or surgical treatment, or when patients display behavior that doctors find difficult to cope with.

An indication that psychological factors may play a role in the development of CRPS1 is that some case-reports suggest a relationship between conversion neurosis and CRPS1 [23,57,76,78]. Other authors suggest that psychological factors play a role in the course of CRPS1 rather than in its development or suggest that the long-lasting symptoms result in a change in the psychological make-up of patients. Monti et al. [53] stated that the long-lasting, intense pain of a trauma results in an exaggeration of maladaptive personality traits and coping styles. Zucchini et al. [88] concluded that

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

0304-3959/$36.00
doi:10.1016/j.pain.2009.05.003

CRPS1 patients lack motivation to rehabilitate because they profit from secondary gain as a chronic patient.

The conclusions of several reviews on the role of psychological factors in CRPS1 are contradictory [4–6,10,24,31,35,42,45,51,54,56,58,65,67,74,89]. Some reviews included (single) case studies, while others reviewed a small number of studies. Therefore, the results are difficult to interpret.

To clarify the role of psychological factors in the onset and maintenance of CRPS1 in adults, we performed a systematic review of the existing literature on the association of these factors with CRPS1 in adult patients. Also, we were interested in how psychological factors have been defined, operationalised, explored, and reported in the existing literature.

2. Methods

2.1. Selection of studies

A computer-assisted search in the Cochrane, Pubmed/Medline, Psychinfo, and Cinahl databases was performed using the keywords "complex regional pain syndrome," "reflex sympathetic dystrophy," "posttraumatic dystrophy," "algodystrophy," and "sudeck" in combination with "psych*". The reference lists of the included articles were also searched for additional references. Only original articles describing empirical studies and written in Dutch or English were included. A further selection was made based on the following criteria: published dates between January 1980 and June 2007; focus on a study population of adults; use of clinical interviews or (validated) questionnaires; and inclusion of data about the influence of psychological factors on the development and/or course of CRPS1. Single case reports, letters, and editorials were excluded. Also, psychological factors that were only studied once were not included in this review.

2.2. Methodological quality assessment

The methodological quality of the studies was assessed using the criteria of de Vet et al. (see Table 1) [82]. The score ranges from 0 to 99 for randomized, controlled trials, and from 0 to 38 for those studies that were not randomized, controlled trials. For individual studies, the percentage of the maximal score obtainable for that study was calculated (e.g., for studies that were not randomized and controlled, a study with 19 points scored 50%). We classified the studies as follows: excellent (75% or higher), good (50–75%), moderate (25–50%), and poor (less than 25%). Two observers assessed the studies independently, blinded to the authors of the study, journal title, and year of publication. Discrepancies were resolved by discussion until consensus was reached.

2.3. Instruments

The instruments used in the included studies have different goals. Table 2 presents an overview of the instruments used in the included studies, classified by probability of psychiatric diagnosis, severity of psychological distress, (pathological levels of) personality traits, psychological distress, and life events (e.g., divorce, death of a spouse, vacation).

2.4. Statistical analyses

Because of the methodological, clinical, and statistical heterogeneity of the studies and a lack of comparable endpoints, pooling of the data was not possible. Thus, the data are qualitatively instead of quantitatively summarized.

3. Results

The included studies evaluated a wide range of psychological factors in relationship to CRPS1. The results for each psychological factor are summarized below. To increase the readability of this review, we present the results in two groups: studies that found no or a limited role of psychological problems in patients with CRPS1 and studies that found a substantial role for psychological factors in patients with CRPS1. Furthermore, when prospective studies are available, prospective and retrospective/cross-sectional studies are summarized separately.

Thirty-one studies fulfilled the inclusion (Supplementary Table 1) criteria. The following psychological factors were included in this review: depression, anxiety, somatization, (psycho)neuroticism, life events, hysteria, hypochondria, obsessive–compulsive behavior, (interpersonal) sensitivity, dependency, hostility/anger, extraversion, introversion, and paranoia. The factors were assigned to the following sections: mood, stress reactions, personality traits, and psychotic tendencies.

3.1. Mood

3.1.1. Depression

3.1.1.1. Prospective studies. In five studies, the relationship between depression and CRPS1 was investigated prospectively. van Spaendonck et al. [70] compared 12 CRPS1 patients with the reference group of the Zung depression questionnaire. They found no significant difference between these two groups. Daviet et al. [15] found that depression did not predict the severity of CRPS1. Puchalski and Zyluk [61] also found no significant differences in depression scores between patients with a distal radius fracture who developed CRPS1 and patients with a distal radius fracture without CRPS1. The mean quality of these three studies is moderate (30%; range: 5–50%).

Feldman et al. [27] studied the reciprocal relationship between depression and pain in patients with CRPS1. They found that pain led to an increase in depressed mood and that a depressed mood resulted in an increase in pain. The quality of this study is good (55%). Harden et al. [36] found a non-significant trend for higher preoperative depression scores to be associated with the diagnosis of CRPS1 1 month after the surgery. However, depression scores at baseline did not predict the presence of CRPS1 at 3 and 6 months. The quality of this study is moderate (32%).

3.1.1.2. Retrospective/cross-sectional studies. Nineteen retrospective/cross-sectional studies investigated the influence of depression on CRPS1. Two studies showed that CRPS1 patients are less depressed than headache patients and facial pain patients [16,55]. Eight studies did not find higher depression scores for CRPS1 patients than several control groups (see Supplementary Table 1, for a specification of the control groups) [9,12,28,29,47,48,53,68,70]). Greipp [32] reported that 57% of patients never experienced depression. The mean methodological quality of the 11 studies described above is moderate (39%, range: 8–76%).

In contrast, two other studies found that patients with CRPS1 reported higher depression scores than controls [38,88]. Furthermore, van Houdenhove et al. [43] showed that CRPS1 patients reported higher depression scores than cardiac patients but lower depression scores than psychiatric out-patients. Of the patients with CRPS1, 27% scored in the range of a severe clinical depression. The scores were comparable with those of a group of chronic idiopathic pain patients, significantly higher than those of a group of organic pain patients, and significantly lower than those of two groups of depressed patients. The mean methodological quality of these three studies is poor (20%, range 11–32%).

Table 1
Criteria list for methodological assessment [82].

Criterion		Answer options (weights)*			
A. Selection and restriction	1. Description of inclusion and exclusion criteria	0	?	+(2)	
	2. Restriction to a homogeneous study population	0	?	+(2)	–
B. Treatment allocation	1. Randomization	Yes		No	
	2. Allocation procedure adequate	0	?	+(10)	–
	3. Blinded allocation procedure	0	?	+(5)	–
C. Study size	1. Smallest group >25 participants	0	?	+(4)	
	2. Smallest group >50 participants	0	?	+(4)	
	3. Smallest group >75 participants	0	?	+(4)	
D. Prognostic comparability (9 points total)	1. Duration of the complaint	0	?	+	–
	2. Baseline scores for outcome measures	0	?	+	–
	3. Age	0	?	+	–
	4. Recurrence status (number of relapses) at baseline	0	?	+	–
	5. Radiating pain	0	?	+	–
E. Drop-outs	1. No drop-outs or	0	?	+(12)	–
	2. Number of drop-outs given in each group	0	?	+(2)	
	3. Reasons for withdrawal (of drop-outs) given in each group	0	?	+(2)	
	4. Drop-outs not leading to bias (less than 5%)	0	?	+(8)	–
F. Loss to follow-up	1. Less than 20% loss to follow-up in all groups	0	?	+(2)	
	2. Less than 10% loss to follow-up in all groups	0	?	+(2)	
	3. Loss to follow-up not leading to bias	0	?	+(8)	–
G. Intervention # 1 = experimental(6 point total)	1. Type of intervention	0	?	+	
	2. Intensity of intervention parameters	0	?	+	
	3. Duration of each treatment session	0	?	+	
	4. Treatment frequency	0	?	+	
	5. Number of treatment sessions	0	?	+	
	6. Compliance presented	0	?	+	–
G. Intervention #2 = placebo or other control(6 points total)	1. Type of intervention	0	?	+	
	2. Intensity of intervention parameters	0	?	+	
	3. Duration of each treatment session	0	?	+	
	4. Treatment frequency	0	?	+	
	5. Number of treatment sessions	0	?	+	
	6. Compliance presented	0	?	+	–
H. Extra treatments	1. No co-interventions or	0	?	+(2)	–
	2. Co-interventions comparable between groups	0	?	+(2)	–
I. Blinding of patient	1. Attempt at blinding or naïve patient	0	?	+(2)	–
	2. Blinding evaluated and successful	0	?	+(2)	–
J. Blinding of therapist	1. Attempt at blinding	0	?	+(2)	–
	2. Blinding evaluated and successful	0	?	+(2)	–
K. Blinding of observer	1. Attempt at blinding	0	?	+(2)	–
	2. Blinding evaluated and successful	0	?	+(2)	–
L. Outcome measures (6 points total)	1. Pain	0	?	+	
	2. Global measure of improvement	0	?	+	
	3. Functional status	0	?	+	
	4. Mobility	0	?	+	
	5. Medical consumption	0	?	+	
	6. Life-events	0	?	+	
M. Follow-up period	1. Timing comparable	0	?	+(1)	
	2. Measurement just after the last treatment	0	?	+(1)	
	3. Measurement 3 months or longer	0	?	+(1)	
N. Side effects	1. Description of side effects in each group	0	?	+(1)	
O. Analysis and presentation of data	1. Frequencies or	0	?	+(1)	
	mean/standard deviation or	0	?	+(1)	
	median/quartiles (for most important measurements)	0	?	+(1)	
	2. Intention to treat analysis or	0	?	+(3)	
	3. Adequate corrections for baseline differences or drop-outs	0	?	+(3)	

* + indicates that the description of this item is informative, and the presence of bias is unlikely for this item. – indicates that the description of this item is informative, but the study is flawed on this item. ? indicates that the description of this item is unclear or incomplete and therefore impossible to interpret. 0, No information about this item is given in the paper.

Four studies reported the prevalence of (chronic) depression in CRPS1 patients. In these studies, prevalence rates ranged from 31% to 96% [41,64,75,77]. It should be noted that in the study of Szeinberg-Arazi et al., for 10 of the 12 participants, the affected limb was amputated [77]. The mean methodological quality of these studies is moderate (29%, range: 5–50%).

3.1.2. Anxiety

3.1.2.1. Prospective studies. Two prospective studies investigated the relationship between anxiety and CRPS1. Feldman et al. [27] studied the reciprocal relationship between anxious mood and pain in patients with CRPS1. Increased pain caused an increase in anxious mood, but increased anxiety did not lead to an increase

Table 2
Categories of instruments used across the included studies.

Category	Instrument	
(Probability of) psychiatric diagnosis	Symptom Checklist [1]	SCL-90
	Symptom Checklist, revised [17]	SCL-90R
	Brief Symptom Inventory [19]	BSI
	Hopkins Symptom Checklist [20]	HSCL
	Beck Depression Inventory [2]	BDI
	Clinical (psychodynamic) interview	
	Montgomery-Asberg Depression Rating Scale [52]	MADRS
	Zung depression scale [22]	
	Yesavage's Geriatric Depression Scale [87]	GDS
Severity of psychological distress	Cognitive – Somatic Anxiety Questionnaire [66]	CSAQ
	State Trait Anxiety Inventory [71]	STAI
	Anger Expression Inventory [72]	AEI
	Survey tool constructed by author of study	
	Affect Balance Scale [18]	ABS
(Pathological levels of) personality traits	Amsterdam Biographic Index [85]	ABV
	Minnesota Multiphasic Personality Inventory – Dutch version [49]	NVM
	Minnesota Multiphasic Personality Inventory [39]	MMPI
	Dutch Personality Questionnaire [50]	DPQ
	Eysenck Personality Questionnaire – revised [26]	EPS
	Personality Diagnostic Questionnaire – revised [44]	PDQRL
Life events	Social Readjustment Rating Scale [62]	SRRS
	Recent Life Change Questionnaire – Dutch version [86]	VRMG
	Investigation of the personal history (life events)	

in pain. The methodological quality of this study is good (55%). Harden et al. [36] found that higher levels of anxiety prior to surgery were associated with the prevalence of CRPS1 at the 1-month follow-up. However, anxiety at baseline did not predict the presence of CRPS1 at 3 and 6 months of follow-up. The methodological quality of this study is moderate (32%).

3.1.2.2. Retrospective/cross-sectional studies. Ten retrospective/cross-sectional studies explored the relationship between anxiety and CRPS1. Eight studies, with moderate mean methodological quality (39%, range: 16–76%), reported no difference in cognitive, somatic, phobic or general anxiety, or in panic disorders between CRPS1 patients and several control groups [9,12,16,28,29,48,53,68]. Two studies reported that CRPS1 patients are more anxious and agoraphobic than other somatic patients, i.e., patients with a hand injury or cardiac patients [38,43]. However, van Houdenhove et al. [43] also found that CRPS1 patients are more anxious than a non-CRPS1 population but less anxious than psychiatric patients. Bruehl et al. [9] found that CRPS1 patients have a higher score on phobic anxiety than patients with low back pain but comparable scores to patients with limb pain. The mean methodological quality of these three studies is moderate (36%, range 18–56%).

3.2. Stress reactions

3.2.1. Life events

Eight studies investigated the influence of life events on CRPS1. Two studies, with poor (8%) [70] and moderate (29%) [53] methodological quality, found no differences in reported life events before the development of CRPS1. Three studies, with moderate mean methodological quality (29%, range 18–39%), reported that CRPS1 patients had experienced more stressful life events than the controls [28,29,43]. Three studies, with poor mean methodological quality (22%, range: 5–42%), found high percentages of patients with CRPS1 reporting adverse life events preceding the disease. The percentages ranged from 49% to 100% [25,30,41].

3.2.2. Somatization

Nine studies explored the effect of somatization on CRPS1. Three studies found that CRPS1 patients show less somatization than controls [12,16,48]. Four studies did not find a difference between CRPS1 patients and controls regarding somatization [12,28,29,48]. The mean methodological quality of these five studies is moderate (42%, range: 18–76%). However, three studies reported that CRPS1 patients more often express psychological problems as somatic complaints than other patient groups [9,38,43]. The methodological quality of these studies is moderate (29%, range: 18–58%). de Vilder [83] reported a somatization prevalence rate of 64% in patients with CRPS1. The methodological quality of this study is poor (21%).

3.2.3. Hostility/anger

3.2.3.1. Prospective studies. One prospective study investigated the reciprocal relationship between anger and pain. Feldman et al. [27] found that "a high-pain day" was predictive for an increase in anger. An increase in anger was not predictive of an increase in pain. The methodological quality of this study is good (55%).

3.2.3.2. Retrospective/cross-sectional studies. Seven retrospective/cross-sectional studies investigated the influence of hostility/anger on CRPS1. Two studies found that CRPS1 patients had a significantly lower score on hostility than the control groups [16,43]. Four studies reported that there was no difference in hostility between patients with CRPS and controls [9,16,28,48]. The mean methodological quality of these five studies is moderate (45%, range: 18–76%). van Houdenhove et al. [43] however, stated that CRPS1 patients reported significantly more hostility symptoms than cardiac patients. The methodological quality of this study is moderate (32%).

One study investigated the relationship between anger and pain. Bruehl et al. [7] found an interaction effect of anger expression and diagnostic group: in patients with CRPS1, greater expression of anger was related to a higher intensity of pain, while in non-CRPS1 limb-pain patients, greater expression of anger was related to a lower intensity of pain. The methodological quality of this study is moderate (34%).

van Houdenhove [41] reported that 13% of the CRPS1 patients showed passive-aggressive personality traits. The methodological quality of this study is poor (18%).

3.2.4. Obsessive–compulsive behavior

Seven studies reported on the influence of obsessive–compulsive behavior on CRPS1. DeGood et al. [16] concluded that CRPS1 patients show less obsessive–compulsive behavior than headache patients. Also, van Houdenhove et al. [43] found that CRPS1 patients show less obsessive–compulsive behavior than psychiatric patients (difference not significant). In four studies, no difference was found between CRPS1 patients and several groups of control patients [9,38,48,53]. The mean methodological quality of these six studies is moderate (42%, range: 18–76%). van Houdenhove [41] reported histrionic traits in 12.5% of the CRPS1 patients (poor methodological quality: 18%).

3.2.5. Insomnia

Five studies involved the relationship between insomnia and CRPS1. Two studies, with moderate mean methodological quality (47%), found no significant difference in insomnia between CRPS1 patients and controls [16,28]. On the other hand, two studies, also with moderate methodological quality (34%), found more sleeping problems in CRPS1 patients than in controls [43,48].

Greipp [32] concluded that insomnia was never a problem in 43% of the CRPS1 patients, occasionally a problem in 43%, and a severe problem for 14%. The methodological quality of this study is poor (14%).

3.3. Personality traits

3.3.1. Neuroticism

3.3.1.1. Prospective studies. Two prospective studies evaluated the role of neuroticism in the development of CRPS1. Puchalski and Zyluk [61] found no significant differences in neuroticism between CRPS1 patients and controls. The methodological quality of this study is moderate (34%). van Spaendonck et al. [70] concluded that patients who did develop CRPS1 after a wrist fracture are not more neurotic than patients with a wrist fracture without CRPS1. Both patients with CRPS1 and patients without CRPS1 showed an increased score on neuroticism than the general population, and similar scores as psychiatric patients. The methodological quality of this study is poor (5%).

3.3.1.2. Retrospective/cross-sectional studies. Six retrospective/cross-sectional studies reported on the influence of neuroticism on CRPS1. Four studies, with moderate methodological quality (38%, range: 18–58%), found no differences in neuroticism between CRPS1 patients and controls [9,28,29,48]. However, van Spaendonck et al. [70] concluded that CRPS1 patients showed fewer neurotic characteristics than psychiatric patients but more than the normal population. In the same study, female patients with CRPS1 showed fewer neurotic characteristics than female patients with functional complaints. In a study by van Houdenhove et al. [43], CRPS1 patients had a significantly higher score for psychoneuroticism than a reference group of cardiac patients. Furthermore, in two studies that overall found no differences between CRPS1 patients and the control group, female CRPS1 patients showed higher scores on neuroticism [29] and were more unstable than female hand pathology patients waiting for elective hand surgery [28]. The mean methodological quality of these four studies was poor (24%, range: 8–39%).

3.3.2. (Interpersonal) Sensitivity

Six studies explored the effect of (interpersonal) sensitivity on CRPS1. Two studies found that CRPS1 patients report fewer symptoms of interpersonal sensitivity than the control groups [16,43]. No differences were found in three studies concerning sensitivity between CRPS1 patients and the controls [9,28,48]. The mean methodological quality of these five studies is moderate (45%, range: 18–76%).

However, two studies, with a moderate mean methodological quality (39%), reported that CRPS1 patients have a higher score on the (interpersonal) sensitivity subscale than the control groups of patients with a hand injury without CRPS1, and low back pain patients, respectively [9,38].

3.3.3. Dependency

Two studies addressed the prevalence of dependent behavior in patients with CRPS1. van Houdenhove [41] found that in 28% of CRPS1 patients, a dependent personality was observed. The methodological quality of this study is poor (18%). However, Monti et al. [53] found dependent behavior in only 4% of patients with CRPS1 (compared with 8% of the control group with chronic low back pain). The methodological quality of this study is moderate (29%).

3.3.4. Extraversion/introversion

3.3.4.1. Prospective studies. Two prospective studies explored the effect of extraversion/introversion on CRPS1. Puchalski and Zyluk [61] found no difference in extraversion between CRPS1 patients and control groups, with moderate methodological quality (34%). In contrast, van Spaendonck et al. [70] concluded that patients with CRPS1 after a wrist fracture have a higher score on extraversion than the general population (quality: 5%, poor).

3.3.4.2. Retrospective/cross-sectional studies. A study by van Spaendonck et al. [70] with poor methodological quality (8%) found no statistically significant difference in extraversion/introversion between patients with CRPS1 and both control groups.

de Vilder [83] concluded that 19% of CRPS1 patients scored higher than average on the extraversion scale. The methodological quality of this study is poor (21%).

3.3.5. Hysteria/hypochondria

Eight studies investigated the influence of hysteria and/or hypochondria on CRPS1. Nelson and Novy [55] (methodological quality: 74%) found that CRPS1 patients score was lower on both the hysteria and hypochondria scales of the Minnesota Multiphasic Personality Inventory (MMPI) than patients with fascial pain. Shiri et al. [68] (quality: 16%) found no differences in the hysteria or the hypochondriasis subscales of the MMPI between conversion disorder patients and CRPS1 patients. The mean methodological quality of these two studies is moderate (45%). Zucchini et al. [88] reported that CRPS1 patients scored higher on both the hysteria and hypochondria scales of the MMPI than controls with brachial plexus lesions (methodological quality: 11%). van Hilten et al. [79] found an elevated score for both the hysteria and hypochondria subscales of the MMPI in patients with CRPS1-related dystonia (quality: 13%). The mean methodological quality of these two studies is poor (12%).

Two studies reported only prevalence rates in CRPS1 patients, without comparing these rates with other populations. Subbarao and Stillwell [75] and Grunert et al. [33] reported prevalences of hysteria and hypochondria in patients with CRPS1 of 42% and 90%, respectively. van Houdenhove [41] found histrionic traits in 44% of the CRPS1 patients, while the diagnosis "conversion hysteria" was made in 40% of these patients. Finally, Szeinberg-Arazi et al. [77] reported that CRPS1 patients showed hysterical behavior, without providing percentages. The mean methodological quality of these four studies is moderate (26%, range: 5–50%).

3.4. Psychotic tendencies: Paranoia

Five studies explored the effect of paranoia on CRPS1. Four studies found no significant difference in paranoia between CRPS1 patients and the control groups [9,16,55,68]. Monti et al. [53] made the diagnosis paranoia once (4%) in the control group of chronic low back pain patients and in none of the CRPS1 patients. The mean methodological quality of these five studies is good (50%, range: 16–76%).

3.4.1. Insomnia

Five studies involved the relationship between insomnia and CRPS1. Two studies, with moderate mean methodological quality (47%), found no significant difference in insomnia between CRPS1 patients and controls [16,28]. On the other hand, two studies, also with moderate methodological quality (34%), found more sleeping problems in CRPS1 patients than in controls [43,48].

Greipp [32] concluded that insomnia was never a problem in 43% of the CRPS1 patients, occasionally a problem in 43%, and a severe problem for 14%. The methodological quality of this study is poor (14%).

4. Discussion

The objective of the present study was to review the literature on the influence of psychological factors on the onset and course

of CRPS1 in adults. Also, we were interested in how psychological factors have been defined, operationalised, explored and reported on in the existing literature. The majority of included studies ($n = 24$, 77%) have only a poor to moderate methodological quality.

Two main results emerge from this review. First, most prospective studies found no relationship between a diagnosis of CRPS1 and depression, anxiety, neuroticism, hostility/anger, or extraversion/introversion. Second, the results of the retrospective/cross-sectional studies seem to yield contradictory results regarding psychological problems in patients with CRPS1. A majority of studies found no association between psychological factors and CRPS1. For nine out of the 13 psychological factors in this review (paranoia, hysteria/hypochondria, obsessive–compulsive behavior, somatization, insomnia, hostility/anger, interpersonal sensitivity, neuroticism, and dependency), studies with a relatively high methodological quality found no association with CRPS1. For three other factors (depression, anxiety, and extraversion/introversion), the majority of studies also found no association, but the methodological quality of these studies was equal to or worse than the quality of the studies that found an association with CRPS1.

For life events, the evidence seems to indicate a relationship with the development of CRPS1. Life events may lead to CRPS1 because a repeatedly triggered sympathetic system develops an altered local catecholamine responsiveness resulting in a prolonged increased autonomic arousal [6,24,28,36,37]. Furthermore, the somewhat more obscure results regarding insomnia may partly be explained by the fact that CRPS1 may lead to sleeping problems (leading to increased scores on the insomnia subscale).

It can be concluded that there is no evidence for a relationship between CRPS1 and depression, anxiety, neuroticism, anger, obsessive–compulsive behavior, somatization, hostility/anger, interpersonal sensitivity, extraversion/introversion, or paranoia. This conclusion finds further confirmation from the fact that several studies included only patients attending a specialized pain clinic.[9,12,16] As Covington [13] stated, pain clinic patients represent a biased sample because these patients report more intense pain that is more constant and associated with greater functional impairment. They also have a higher chance of experiencing depression, withdrawal, and substance abuse [14]. Therefore, any existing relationship between psychological factors and CRPS1 is expected to be clearly present in this biased population. Moreover, when no relationship is found in this biased population, it is even more probable that no relationship exists. This does not preclude that psychological factors are associated with the maintenance of CRPS1.

When we compare our results with those of previous reviews, our findings are more robust and therefore of enhanced value for a few reasons [4–6,10,24,31,35,42,45,51,54,56,58,65,67,74,89]. First, we focused solely on psychological factors. In addition, we included more studies, and we weighted those studies based on their methodological quality.

However, several limitations also must be considered. First, because in several studies psychological variables are poorly defined, it may be that they are used to trying to identify patients as having primarily a psychological disorder, rather than understanding their disease.

Second, the evidence is limited or inconclusive because of a lack of high-quality studies; studies with a higher quality mainly included more patients, described the methods and results more extensively, and included controls. The evidence is also limited because of inconsistent outcomes, restricted follow-up, and non-comparable study designs [69]. Therefore, our conclusions should be interpreted with some caution.

Third, the criteria of de Vet [82] were used because of the absence of a validated methodological quality instrument for studies that are not randomized, controlled trials, at the time this article was written.

Fourth, there are approximately 72 names for CRPS described in the literature and although we used the most common terms for this syndrome in our literature search, we cannot rule out that relevant articles were left out in this review.

An explanation for the inconclusive results found in the included studies could be the use of different diagnostic criteria for CRPS1. For instance, the criteria sets of the International Association for the Study of Pain [73], Bruehl [8], and Veldman [81] yield different prevalence rates in the same study group [59]. In addition, existing criteria sets originate from different medical disciplines and/or countries, emphasizing different symptoms in the diagnosis [3]. An obvious recommendation based on this difference is to improve diagnostic rigor by using criteria that have proven discriminative power [60].

The same concern applies to the diagnosis of psychological problems: several slightly different definitions are used across diagnostic instruments in the included studies. This difference implies that it is difficult to make comparisons across studies of the prevalence of psychological problems and their influence on the development of CRPS1.

A fourth point of concern is that the time since diagnosis of CRPS1 varies largely across the studies, from weeks [43] to more than 6 years [27]. The same is true for the duration of psychological problems and the duration of pain. Bruehl and colleagues [9] suggested that patients who have pain for a longer period either adapt well or suffer from increased distress. Measuring psychological problems in such a group may lead to an overestimation (or an underestimation) of the prevalence of these problems. Because of the variance in duration of complaints, the nature, number, and duration of medical and/or psychological treatments presumably also differ across the studies.

A fifth point of concern is the possible effect of medication on the association between psychological factors and CRPS1. It is possible that the number of patients in the studies on psychiatric medications may have resulted in less evidence of certain psychological characteristics. Due to a lack of data no conclusion can be drawn on this possible effect of medication.

A fifth point of concern might be the differences in the initiating event varying across studies, such as fractures or surgery. In the literature, it is unclear whether the type of trauma leading to CRPS1 influences the role of psychological factors. However, the overall finding across studies of no relationship between psychological factors and CRPS1 makes it unlikely that this issue is of concern.

A final point is that no psychological theory or framework was used in the included articles, and in some studies, only a portion of the included patients participated in the psychological study, which may have led to a selection bias.

In summary, studies with a higher methodological quality suggest no relationship between psychological factors and CRPS1 in adults. More prospective studies with high-quality methodology should be performed on the association between psychological factors and the development or maintenance of CRPS1. To gain further insight in this association, consensus in terms of diagnostic criteria is essential.

No firm conclusion can be drawn from the literature on the association between psychological factors and the maintenance of CRPS, and our review identified no direct relationship between psychological factors and the development of CRPS1, with the possible exception of life events. Research showed that there is no justification for stigmatizing adult patients with CRPS1 as being psychologically different from other patients.

Acknowledgement

The authors do not have any conflicts of interest related to this work.

The authors thank J. Beerthuizen, M.Sc., for his valuable contribution to the quality assessment of the articles included in this review.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2009.05.003.

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