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ORIGINAL REPORT

POOR PROGNOSTIC FACTORS IN COMPLEX REGIONAL PAIN SYNDROME 1: A DELPHI SURVEY

Florian Brunner, MD, PhD[1], Mara Nauer, MD[2] and Lucas M. Bachmann, MD, PhD[2]

From the [1]Department of Physical Medicine and Rheumatology, Balgrist University Hospital and [2]Horten Center for Patient Oriented Research and Knowledge Transfer, Department of Internal Medicine, University of Zurich, Zurich, Switzerland

Objective: **A major challenge in the management of patients with complex regional pain syndrome 1 is identifying those individuals who are at risk of developing severe problems. Data from large follow-up studies providing empirical evidence are largely lacking. The goal of this study was to obtain an expert-agreed priority list of parameters that are correlated with a poor prognosis.**

Methods: **In a two-round Delphi survey, experts were asked to list those parameters that they considered to be strongly associated with a poor prognosis (first round) and to weight parameters that they believed to be most relevant for poor prognosis (second round). Median ratings and interquartile ranges were calculated. Rates >7 and interquartile ranges <3 depicted important and expert-agreed parameters.**

Results: **Thirty-nine experts compiled a list of 254 items. Twenty-eight experts reached a consensus on 49 important items associated with poor prognosis. They primarily agreed on clinical manifestations of complex regional pain syndrome 1. Psychosocial factors were considered less important.**

Conclusion: **The findings of this study indicate that poor prognosis for complex regional pain syndrome 1 is primarily dependent on clinical manifestations. While evidence suggests that psychosocial factors may play a role in the development of the condition, their role in poor prognosis appears to be less important.**

Key words: complex regional pain syndrome 1; prognosis; Delphi survey.

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Correspondence address: Florian Brunner, Balgrist University Hospital, Forchstrasse 340, CH-8008 Zurich, Switzerland. E-mail: florian.brunner@balgrist.ch

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a challenging condition with clinical manifestations, including sensory and autonomic disturbances, trophic changes and alterations in motor function (1). Symptoms usually appear after an initiating noxious event, such as trauma or surgery (2, 3). The course varies from mild and self-limiting to chronic disease with a high impact on daily functioning and quality of life.

A major challenge in the management of patients with CRPS 1 is identifying those individuals who are most likely to develop severe problems. Timely identification of these subjects is important, because results from various studies have shown that early and intensified therapy could act against delayed recovery (4–6). However, to date, it remains unclear whether early treatment influences the rate or the degree of recovery or even both. In addition, it is a matter of debate as to what the profile of patients who are susceptible for delayed recovery actually shows. The literature provides a few and quite general factors associated with a poor outcome of CRPS 1, such as duration of complaints, passive coping style and poor response to treatment (5, 7).

Unfortunately, data from large follow-up studies giving clinical guidance are lacking, and the measurement parameters for outcome show great variation and may not be well validated for this population. Because of this lack of empirical evidence the goal of this study was to obtain an expert-agreed priority list of parameters that are correlated with a poor prognosis in CRPS 1. A Delphi survey was performed, approaching experts in the field of CRPS 1, in order to reach a consensus about the most relevant indicators associated with a poor course of CRPS 1. The results of this study should provide initial data on this pertinent problem.

METHODS

We conducted a two-round postal Delphi survey, beginning by generating a list of potential members of an expert panel, a convenience sample of experienced professionals in the field of CRPS 1. We considered clinicians or researchers with a clinical focus from a range of medical specialties with an academic affiliation and least two CRPS-related publications (first or senior author) as experts in the field.

Each nominee was sent a letter including information about the aim of the study and an invitation to participate. We asked the participants to reply to the letter with their approval to participate within 2 weeks. In order to increase the response rate we sent a reminder to all experts. This survey was performed between March and July 2010.

All experts agreeing to participate were sent a subsequent letter requesting them to consider the most important indicators, which they felt were strongly associated with a poor outcome in CRPS 1. All reported parameters were compiled into a list. This list was sent again to the experts, asking them to weight each single parameter, assigning a number between 1 (not important) and 10 (very important).

Using a previously published method (8), we identified the strongest parameter for poor prognosis by calculating the median of attributed

weights and the corresponding 25th to 75th centile range (interquartile range; IQR). We defined an expert agreement if the IQR of a parameter was ≤3. The optimal cut-off value of the median attributed weights for a relevant and agreed parameter was calculated by drawing a receiver operating characteristics (ROC) curve of the medians against an IQR classification of ≤3. Based on this assessment we estimated the optimal cut-off value for a relevant item at a median attributed weight of ≥7.

Statistical analyses were performed using the STATA 11 statistical software package (Stata, College Station, TX, USA).

RESULTS

The invitation letter was sent to 80 experts, 44 of whom agreed to participate in the survey. Thirty-nine experts returned the first questionnaire and 28 completed the second round. The panel consisted of experts from the following medical specialities: neurology $n=7$, anaesthesiology/pain management $n=6$, clinical research $n=5$, rheumatology $n=3$, physical medicine and rehabilitation $n=3$, (hand) surgery $n=3$, and nuclear medicine $n=1$. International experts from the Netherlands ($n=12$), Switzerland ($n=4$), USA ($n=4$), Germany ($n=3$), Australia ($n=1$), Belgium ($n=1$), Japan ($n=1$), Poland ($n=1$), and South Korea ($n=1$) participated in both rounds.

In the first round, the experts listed a total of 254 different items, which, in their opinion, were associated with a poor prognosis in CRPS 1. The complete list of the reported items from the first round and the corresponding medians and IQRs from the second round are shown in Appendix SI (available from https://doi.org/10.2340/16501977-0856).

In the second round, the experts agreed on 49 relevant items (Table I).

Clinical parameters

Consensus was primarily reached on clinical manifestations such as *sensory changes* (median, IQR) (e.g. pain intensity >5 on VAS 8, 7–9; allodynia 8, 5–8; hyperaesthesia 7, 5–8; hypoaesthesia 8, 7–9; hyperalgesia 8, 6–9; hypoalgesia 7, 6–9; spread of pain area 8, 6–9), *motor changes* (e.g. lack of muscle strength 7, 6–8; weakness of the limb 7, 5–7), t*rophic changes* (e.g. joint contractures 8, 5–8; skin lesions 7, 5–8; faster nail growth 7, 6–8) and *autonomic changes* (e.g. vasomotor changes 7, 5–8; sudomotor changes 7, 5–8) followed by *initiating event* (fracture 8, 6–8; spontaneous onset of CRPS 7, 5–8), *localization* of CRPS 1 (e.g. upper limb 8, 7–8), and *duration* (e.g. symptoms between 6 and 12 months 7, 5–8).

Interestingly, some other clinical parameters, for example trauma in history (2, 1–4), contusion (3, 2–5), rapid progression of symptoms (3, 2–5) and cast not tolerated (3, 2–4) were considered less relevant for poor prognosis. For the complete list, see Table I.

Non-clinical parameters

There was also consensus on certain non-clinical factors (e.g. lack of social network 8, 5–8; someone/something caused the problem 7; 5–8; CRPS-related conflict with employer 7, 5–8). However, psychosocial factors were considered much less relevant than clinical factors. For example, predisposing factors (3, 2–5), lack of social support (2, 1–3), work situation (3, 2–5), unemployment (3, 2–5), financial difficulties (3,

Table I. *Set of prognostic factors fulfilling our selection criteria (mean attribute weight of > 7 and interquartile range (IQR) < 3,* n = *49)*

Category	Item	Median	IQR
Initiating event	Fracture	8	6–8
	Spontaneous onset of CRPS	7	5–8
Localization	Upper limb	8	7–8
	Hand	8	7–8
	Third metacarpal bone	7	7–8
	Dominant hand	7	5–8
	Wrist	7	5–8
Duration	Past the acute stage	8	7–9
	Prolonged duration of symptoms	8	7–9
	Symptoms between 3 and 6 months	8	7–9
	Symptoms between 6 and 12 months	7	5–8
Sensory changes	Pain intensity >5 on VAS	8	7–9
	Pain at rest, worsening when moving	8	7–9
	Hypoaesthesia	8	7–9
	Any movement is very painful	8	6–8
	Spread of symptoms to uninjured mirror-image or remote sites	8	6–8
	Pain scores is high	8	6–8
	Hyperalgesia	8	6–9
	Pain intensity >8 on VAS	8	6–9
	Spread of pain area	8	6–9
	Severe, excruciating pain	8	5–8
	Allodynia	8	5–8
	Spontaneous pain	7	6–8
	Hypoalgesia	7	6–9
	Hyperaesthesia	7	5–8
	Pain at rest	7	5–8
	Non-anatomical spread of the self-reported symptoms or behavioural display[a]	7	5–8
	Pain gets progressively worse	7	5–8
Motor changes	It is impossible to resume previous level of daily activities and work	8	7–8
	Lack of muscle strength	7	6–8
	Weakness of the limb	7	5–7
	Reduced strength	7	5–8
Trophic changes	Joint contractures	8	5–8
	Glossy skin	7	6–8
	Faster nail growth	7	6–8
	Loss of skin integrity	7	6–8
	Blister	7	6–8
	Trophic changes	7	5–8
	Ulceration	7	5–8
	Skin lesion (ulcers, or ischaemic lesions)	7	5–8
Autonomic changes	Vasomotor changes	7	5–8
	Sudomotor changes	7	5–8
	Livid skin discoloration	7	6–8
	Warm skin	7	6–8
Treatment	Unsuccessful response to treatment[a]	7	5–7
Environmental factors	It is impossible to resume previous level of daily activities and work	8	7–8
	Lack social network	8	5–8
	Someone/something caused the problem	7	5–8
	CRPS-related conflict with employer	7	5–8

[a]These items were edited slightly for conceptual reasons.
CRPS: complex regional pain syndrome; VAS: visual analogue scale.

1–4), and evidence of malingering (2, 1–3) received markedly lower ratings.

DISCUSSION

In this Delphi survey, experts first compiled a list of more than 250 items associated with poor prognosis in CRPS 1 (first round) and then reached a consensus on 49 of those items being relevant (second round). These items comprised various clinical manifestations, followed by localization of CRPS 1 on the upper extremity, spontaneous onset or initiation by a fracture and disease duration of more than 3 months. Clinical manifestations primarily included sensory changes, but also contained autonomic, motor and trophic features. Psychosocial factors were considered less important to predict poor prognosis.

To our knowledge this is the first Delphi survey attempting to obtain an expert-agreed priority list of parameters that are correlated with a poor prognosis in CRPS 1. The Delphi method has advantages over other consensus methods. Theory suggests that it allows agreement to be achieved in a given area of uncertainty or lack of empirical evidence (9). Moreover, it can be performed rapidly, is inexpensive, and allows the anonymous aggregation of expert opinion (10). Informal methods of reaching a consensus, such as committees, are recognized to be prone to domination by powerful individuals, the biasing effects of personality traits, seniority, and the fact that only 1 person can speak at a time (9). In group consensus meetings, the presence and actions of others may inhibit creativity and the possibility of resolving ambiguous and conflicting issues (11). However, it has been noted that expert opinion does not necessarily reflect reality in clinical practice. As stated above, in the absence of empirical evidence, expert consensus reflects the best available information (12). We believe that the findings of our study contribute to a better understanding of the course of CRPS 1 and are useful in a situation in which data from large follow-up studies providing empirical evidence are largely lacking. Our findings could also be used to evaluate the content validity of existing tools for the measurement of CRPS.

To date, only a small number of generic factors have been linked with a poor outcome of CRPS 1, such as duration of complaints, passive coping style and poor response to treatment (5, 7). In terms of clinical parameters, our expert panel reached consensus on several factors that are in line with previous research. For example, in the past, several studies have concluded that sensory changes are correlated with poor prognosis in CRPS 1 (13–15). In 2004, Rommel et al. (14) found that the presence of generalized sensory impairment was correlated with significantly longer duration of illness. Moreover, Vaneker et al. (15) concluded in their study that pain measures, in combination with measuring active range of motion, appear to be the most useful factors for CRPS 1 diagnosis and prognosis. Also, in agreement with the literature, our expert consensus associated CRPS 1 of the upper extremity with a poor prognosis. For example, in a case series from Thevenon et al. (16) patients with CRPS 1 of the upper extremity had a longer treatment duration and a longer work absence than patients with CRPS 1 of the lower extremity. In accordance with the conflicting evidence in research, our expert panel did not consider a lower skin temperature of the affected extremity at symptom onset as a factor for poor prognosis (primary cold CRPS 1) (4, 15, 17).

Our expert panel endorsed only a few prognostic factors, which are in conflict with the findings in the literature. For example, our experts considered the initiation of CRPS 1 by a fracture and a spontaneous onset as relevant parameters for poor prognosis. However, in their study Veldman et al. (18) concluded that the type or severity of the primary trauma does not seem to be of a prognostic value.

In terms of non-clinical parameters, the findings of our survey are partly discordant with the results in the literature. The participating experts agreed that psychosocial factors are less important in predicting poor outcome in CRPS 1, while the literature states that CRPS 1 represents a complex biopsychosocial disorder (19–21). Treatment guidelines therefore recommend an equal target for medical and psychosocial components in a multidisciplinary setting (19, 22). However, to date the benefit of a multidisciplinary approach has not been investigated in clinical trials. Nevertheless, thoughtful communication among all members of the treatment team is essential for identifying patients at risk for delayed recovery.

A strength of this study is the participation of a multidisciplinary and international expert panel. The limitations of this paper are two-fold. First, it may be argued that the conclusions of the Delphi experiment are based on the opinion of only 28 experts and therefore, they are somewhat limited. We agree that a larger group of panellists might have derived another set of agreed parameters. Secondly, another potential limitation represents the Delphi method itself. The method has been criticized because it may suppress individual differences, and the statements are those from a selected group. Furthermore, the Delphi method does not explore disagreement, and consequently an artificial consensus may be generated. Arguably performing only two rounds might be insufficient to reach a robust consensus. However, there are also theoretical considerations and practical reasons to limit the survey to two rounds. Evidence suggests the loss of accuracy is not substantial (12) and two rounds can be justifiably applied in such a survey. We cannot completely exclude that a third round would have changed our overall findings. However, we are confident that this was not a large problem in our study.

Future research should aim at investigating prognostic aspects of CRPS 1 in large prospective cohort studies. The Swiss cohort study aims in this direction by following patients with suspected CRPS 1 of the hand or the foot in a strictly observational design over a period of 1–2 years (23). The authors hope to identify those prognostic factors that are associated with an unfavourable course of CRPS 1, so that patients at risk may be spotted at an early stage and a timely treatment can be initiated. However, whereas these patients may be identified early, there still is a relative lack of evidence about which modalities the patients must be treated with. Recently, a multidisciplinary task force from the Netherlands published treatment guidelines for CRPS 1 after carefully reviewing the evidence of various treatment effects (24). The authors concluded that further research

is needed on this topic.

In clinical practice, practitioners often have to make diagnostic or therapeutic decisions in situations in which there is contradictory or insufficient information. Consensus methods, such as the Delphi technique, may help guide the clinician through the decision process. However, it is still consensus based on an expert opinion and might not reflect the practical realities. The results of this Delphi survey may help the clinician to identify patients with CRPS 1 who have a risk of delayed recovery, by focusing primarily on clinical manifestations of the condition.

Our findings indicate that the prognosis of CRPS 1 is primarily dependent on the clinical manifestations. While evidence suggests that psychosocial factors may play a role in development of the condition, their role in guiding prognosis appears to be less important. For clinicians this finding might be useful, because poor prognosis and the need for intensified treatment measures can be predicted using reliably and easily accessible signs and symptoms.

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