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Spontaneous onset of Complex Regional Pain Syndrome

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ABSTRACT

Complex Regional Pain Syndrome (CRPS) usually develops after a noxious event, but spontaneous onsets have been described in 3–11% of the cases. The existence of spontaneous-onset CRPS is highly debated and the aim of the present study was therefore to compare the phenotypic characteristics of CRPS patients with a spontaneous onset, with those of patients with a trauma-induced onset.

Data of 537 CRPS patients followed up at four departments of anesthesiology were analyzed and comprised 498 (93%) patients with and 39 (7%) patients without a known eliciting event. There where no significant differences between the two groups in gender, or in onset in upper or lower limb or left or right side of the body. Compared to CRPS patients with a trauma-induced onset, spontaneous-onset cases were on average 9 years younger at disease onset and had a 1.4 years longer median disease duration. No significant differences in frequency were found for any of the 34 compared signs and symptoms when the effect of multiple testing was controlled. In conclusion, CRPS may develop both with and without a precipitating noxious event, with both groups exhibiting a largely similar clinical presentation. Spontaneous-onset CRPS patients generally develop the syndrome at a younger age, possibly indicating a susceptibility to develop the condition. The longer disease duration in spontaneous-onset cases may reflect a more gradual disease onset, poorer prognosis, or a delay in diagnosis, possibly as a result of reluctance to make this diagnosis in the absence of a clear initiating event.

1. Introduction

Complex Regional Pain Syndrome (CRPS) is characterized by pain and different combinations of sensory, vasomotor, sudomotor, motor and trophic disturbances (Merskey and Bogduk, 1994). The syndrome develops after a noxious event, such as fracture, sprain or operation, in the vast majority (89–97%) of cases (Veldman et al., 1993; Kurvers et al., 1995; Veldman and Goris, 1996; Geertzen et al., 1998; van der Laan et al., 1998; Allen et al., 1999). This noxious stimulus apparently sets off a complex interplay of different pathogenic mechanisms that may contribute to the development of this syndrome (Birklein, 2005; de Mos et al., 2009b). In the other 3–11% of the cases, however, CRPS develops without a clear causative event (Veldman et al., 1993; Kurvers et al., 1995; Veldman and Goris, 1996; Geertzen et al., 1998; van der Laan et al., 1998; Allen et al., 1999); no apparent trigger could be identified and the syndrome is considered to have developed spontaneously. The question whether CRPS may indeed develop spontaneously has often been a subject of debate among clinicians and researchers.

Interestingly, the diagnostic criteria for CPRS formally accepted by the International Association for the Study of Pain (IASP) do not rule out the possibility of spontaneous onset of CRPS. Although the first criterion describes that CRPS develops after an initiating noxious event, the footnote in the official publication states that this criterion does not have to be fulfilled in order to make the diagnosis (Merskey and Bogduk, 1994). Nevertheless, some authors omit this footnote when reporting the IASP criteria (Stanton-Hicks et al., 1995; Birklein et al., 1998) and the incomplete description of the

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diagnostic criteria may have led to unnecessary restriction to only those patients in whom the condition developed after a causative event (Oakley and Weiner, 1999; Rommel et al., 2001; van Rijn et al., 2009). The different descriptions may result in confusion regarding the acceptability of a spontaneous onset of the syndrome. Other commonly applied diagnostic criteria, like those developed by Harden et al. (1999), Bruehl et al. (1999), and Veldman et al. (1993), also allow for the possibility of spontaneous onset.

Researchers may however have other reasons to exclude non-traumatic onset cases from studies. A potential advantage of excluding these patients could be the supposed improved homogeneity of the study population, though, possibly, at the expense of introducing increased heterogeneity between studies. The question then arises whether differences between trauma-onset cases (tCRPS) and spontaneous-onset cases (sCRPS) indeed justify the exclusion of the latter group from studies.

The objective of the present study is to compare patient characteristics and clinical features of CRPS patients with a spontaneous onset with those of patients with a trauma-induced onset, and to identify any relevant differences between the two groups.

2. Methods

2.1. Patients

Between July 2004 and November 2008, 537 CRPS patients were included from four outpatient pain clinics at departments of anesthesiology that participate in the Trauma RElated Neuronal Dysfunction (TREND) Consortium (http://www.trendconsortium.nl/). In TREND, the acquisition of data concerning the clinical diagnosis and other phenotypic characteristics is performed in a standardized manner, after which this information is stored in a central internet-based database. Information about signs (observed by examiner) and symptoms (reported by patients) were collected using a standard assessment form on which information on pain, sensory impairments, autonomic impairments, trophic changes and motor impairments was recorded. The features were registered as dichotomous variables (i.e., present or absent).

Patients were included if the IASP criteria for the diagnosis of CRPS were fulfilled (Merskey and Bogduk, 1994). Two groups were constructed based on the presence (tCRPS; $N = 498$ [93%]) or absence (sCRPS; $N = 39$ [7%]) of a known noxious event before the development of the syndrome. The reported noxious events of tCRPS patients involved fractures (38%), operations (27%), soft tissue injuries (27%) and miscellaneous causes (8%). The percentage of sCRPS patients in the four different departments of anesthesiology ranged between 5% and 9%. The date of trauma was used to determine disease onset in tCRPS patients; in sCRPS patients, disease onset was determined by the start of the first symptoms as indicated by the patient. Patients' characteristics and frequency of signs and symptoms were compared between the two groups.

2.2. Statistical analysis

Differences in the occurrence of signs and symptoms between the sCRPS and tCRPS patient groups were calculated using Chi-square (χ^2) tests. *P*-values were considered significant if <0.05. To account for the fact that both groups were compared with respect to the presence of 34 signs and symptoms, a Bonferroni-correction was applied (Miller, 1981), resulting in an adjusted *P*-value of 0.00147. Continuous variables were compared with a *t*-test for independent samples or Mann–Whitney U tests as appropriate.

The 95% confidence intervals (CI) for the between-group differences were calculated using Newcombe's method (Newcombe, 1998). Statistical analyses were performed with the Statistical Package for the Social Sciences (version 16) and Confidence Interval Analysis (version 2.1.2).

The study was approved by the Medical Ethical Committee of the involved medical centers. All patients gave written informed consent before participation.

3. Results

Patients' demographics for both groups are summarized in Table 1. There where no statistically significant differences between the sCRPS and tCRPS patients with respect to gender, side of onset and onset in upper or lower extremity. Compared to tCRPS patients, sCRPS patients were on an average 8.6 years younger at disease onset (38.2 versus 46.8; 95% Confidence Interval of the difference [95% $CI_{diff.}$]: 3.4–13.8). The difference in median disease duration between sCRPS and tCRPS patients was 1.4 years (1.8 versus 0.4; 95% $CI_{diff.}$: 0.3–2.5).

Table 2 shows the presence of signs and symptoms in the two groups. The proportion of missing data was low (<8%) in both groups. After correction for multiple testing no significant differences were found between the sCRPS and tCRPS patients. In 62% of the variables the differences in frequency of signs and symptoms was 5% or less and in 91% of the variables the difference was 15% or less. In 65% of the symptoms and 76% of the signs, the percentage was equal or higher among sCRPS patients in comparison to tCRPS patients.

4. Discussion

In the present study, we demonstrated that Complex Regional Pain Syndrome (CRPS) may develop both with and without a precipitating noxious event, with both groups exhibiting a largely similar clinical presentation. We compared the phenotypic

Table 1
Characteristics of spontaneous and trauma CRPS patients.

	Spontaneous	Trauma	*P*-value
Number of patients	39	498	
Percentage of females (*N*)	74% (29)	82% (409)	0.23[a]
Mean (SD) age at onset of CRPS – years	38.2 (15.3)	46.8 (15.8)	0.001[b]
Median (IQR) disease duration – years	1.8 (0.4–4.0)	0.4 (0.2–1.5)	<0.0005[c]
Percentage fulfilling Budapest criteria[e] (*N*)	33% (13)	31% (153)	0.79[a]
Mean (SD) VAS pain score	6.35 (1.7)[d]	6.26 (2.0)[d]	0.20[b]
First affected extremity – percentage (*N*)			0.67[a]
Arm	44% (17)	51% (252)	
Leg	56% (22)	49% (245)	
Both	0% (0)	0% (1)	
First affected side –percentage (*N*)			0.45[a]
Right	56% (22)	48% (237)	
Left	44% (17)	51% (253)	
Both	0% (0)	2% (8)	
Pain medication			
% Paracetamol/NSAID	38%[d]	38%[d]	0.99[a]
% Mild opioids and co-analgetics[f]	38%[d]	32%[d]	0.47[a]
% Strong opioids	3%[d]	7%[d]	0.53[a]

CRPS = Complex Regional Pain Syndrome. *N* = Number. SD = Standard deviation. IQR = Interquartile range. VAS = Visual Analogue Scale. NSAID = Non-Steroidal Anti-Inflammatory Drugs.

[a] Chi-square test.
[b] *T*-test for independent samples.
[c] Mann–Whitney U test.
[d] Percentages were calculated from non-missing data.
[e] Harden et al. (2007).
[f] Co-analgetics include tricyclic antidepressants and anticonvulsive medication.

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Table 2
Signs and symptoms in spontaneous CRPS patients and trauma CRPS patients.

	Symptoms (subjective)					Signs (objective)				
	Spontaneous ($N = 39$)		Trauma ($N = 498$)		P-value*	Spontaneous ($N = 39$)		Trauma ($N = 498$)		P-value*
	N	%	N	%		N	%	N	%	
Allodynia	21	54	241	49	0.52	24	62	321	65	0.69
Hyperesthesia	13	33	153	31	0.78	14	36	171	35	0.89
Hypoesthesia	6	16	91	19	0.69	15	41	138	29	0.13
Hyperalgesia	16	41	232	47	0.46	20	51	239	49	0.75
Hypoalgesia	3	8	33	7	0.79	14	38	83	18	0.002
Asymmetry in color	29	74	368	74	1.00	27	69	329	67	0.72
Asymmetry in temperature	30	81	368	76	0.47	23	62	299	62	0.95
Edema	27	69	359	73	0.63	18	46	302	61	0.06
Asymmetry in sweating	23	59	230	46	0.13	10	26	101	20	0.43
Trophic disturbances	21	54	292	59	0.56	15	39	261	52	0.09
Muscle atrophy	6	16	79	16	0.97	10	27	84	18	0.15
Decreased range of motion	24	63	319	66	0.78	29	76	369	76	0.96
Weakness	22	56	285	60	0.64	25	64	224	47	0.04
Dystonia	17	44	169	34	0.24	3	8	37	8	0.97
Tremor	15	39	126	26	0.08	3	8	28	6	0.61
Myoclonus	14	38	97	20	0.01	1	3	8	2	0.64
Bradykinesia	11	31	111	24	0.36	18	50	239	51	0.90

Percentages were calculated using non-missing data. CRPS = Complex Regional Pain Syndrome. N = Number.
* Three signs and symptoms were significant at the 0.05 level, though none reached Bonferroni-adjusted significance ($P < 0.00147$).

characteristics of patients with a spontaneous onset (sCRPS) with those of patients with a trauma-induced onset (tCRPS). No significant differences were found between sCRPS and tCRPS patients in gender, or in onset in upper or lower limb, or left or right side of the body. Compared to tCRPS patients, sCRPS patients were on average 9 years younger at disease onset. A similar observation, that is, younger age at onset in combination with a more frequent spontaneous onset, has previously been reported in other comparative studies. De Rooij et al. (2009) found that in comparison with sporadic (i.e., non-familial) CRPS patients, familial CRPS patients had a 8 year younger age at onset (33.9 years versus 41.9 years) while familial patients also more often developed the syndrome spontaneously (26% versus 16%). Veldman and Goris (1996) reported that CRPS patients in whom the disease recurred in the same or another extremity, showed a younger median age at onset (35 years versus 41 years) in combination with a more frequent spontaneous onset (16% versus 10%). Together these observations may hint at an increased susceptibility to develop this condition, possibly on the basis of genetic vulnerability.

There may be three explanations for the longer disease duration of sCRPS patients in comparison with tCRPS patients. Firstly, this may reflect reluctance among physicians to consider the diagnosis of CRPS in the absence of a clear initiating event, which may lead to a delay in referral to CRPS specialist centers for further diagnostics. It is important to prevent this delay in view of the fact that early and adequate treatment of CRPS may improve disease course and outcome (Perez et al., 2003; Quisel et al., 2005). Secondly, the longer disease duration may reflect the previously reported poorer prognosis of patients who develop the syndrome after a less severe trauma (or, in this case, no trauma at all). Sandroni et al. (2003) and de Mos et al. (2009a) found that injuries other than fracture (which generally are less severe) had a poorer outcome. It would seem plausible that patients who develop CRPS after a less severe trauma or no trauma at all have an increased vulnerability to develop the syndrome, which likely will have consequences for prognosis and duration of recovery. Finally, the longer disease duration could be a consequence of a slower disease progression in sCRPS patients, which could lead to a delay in referral to CRPS specialist centers.

None of the 34 signs and symptoms that were compared between the sCRPS and tCRPS patients differed significantly after correction for multiple testing. If there were doubt regarding the validity of the diagnosis of sCRPS, one might expect that there would be marked discrepancies between the reported symptoms and the observed signs, with signs occurring more frequently among tCRPS patients and symptoms occurring more frequently among sCRPS patients, but this was not the case. In 76% of the signs, they were either distributed equally or more often present in sCRPS. Additionally, there is a large similarity between both groups; in 62% of the variables the differences in frequency of signs and symptoms was 5% or less.

Using three different diagnostic criteria sets for CRPS, Perez et al. found that the features that best discriminated between patients who fulfilled all or none of these sets were reported hyperesthesia and allodynia, along with observed color asymmetry, hyperesthesia, temperature asymmetry and edema (Perez et al., 2007). However, we found that the percentage of all these signs and symptoms were not significantly different between sCRPS and tCRPS patients, which again underlines the similarity of the two groups.

One may question whether psychological stress could play a role in the onset of CRPS in cases with a spontaneous onset. The "fight or flight" reaction in stress causes a release of pro-inflammatory cytokines independent of endotoxemia, tissue injury, or inflammation (LeMay et al., 1990; Garcia-Bueno et al., 2008). The same cytokines are suggested to play a major role in the acute phase of CRPS (Huygen et al., 2002; Birklein and Schmelz, 2008) and one could therefore argue that psychological stress primes the body for an immune response, thereby reducing the threshold for the aberrant inflammation reaction seen in CRPS. Unfortunately, we have no information on the presence or severity of psychological stress in the period before onset of CRPS of our patient group. There is, however, increasing evidence that, at least at the group level, the role of psychological factors in the onset of the condition is negligible (de Mos et al., 2008). In a large, recently published population-based case-control study in which patients who developed CRPS were compared with age and sex matched controls who did not develop CRPS after a similar trauma, no significant differences in psychological factors were found in the period before onset in the medical records of subjects of both groups (de Mos et al., 2008). This does not rule out the possibility that the role of psychological stress would be different in cases with a spontaneous onset, but unfortunately the number of sCRPS patients in that study was too low ($n = 15$; 8%) to draw any conclusions. Nevertheless, if psychological stressors would indeed play an impor-

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tant role in the onset of sCRPS, one would expect to find at least some influence in the onset tCRPS as well, which, as mentioned, was not the case which makes this explanation less probable.

One of the strengths of the present study is the large number of patients collected, which lends support to the credibility of the findings. Although the information on signs and symptoms was collected by different examiners, which may have led to an increase in variability in the evaluation of signs and symptoms, there is little reason to assume that this variability affected both groups differentially and would have led to bias in any direction. Additionally, to reduce variability, uniform guidelines for data collection were provided and methods of examining patients were standardized across centers.

Another point that should be considered is the certainty that there was no noxious event before the onset of the syndrome in sCRPS patients. This depends first of all on the memory of the patient. It is known that even a very minor trauma can trigger the onset of CRPS (Merritt, 2005), which raises the possibility that patients do not relate this minor trauma to the ensuing development of CRPS, especially after a long disease duration. Another possibility is that symptoms may not have developed directly after the noxious event, but after a certain amount of time, which also would make it more difficult to recognize the association between trauma and CRPS. It is, on the other hand, also possible that the number of spontaneous CRPS patients is underestimated because the first signs of a spontaneous CRPS may have faultily been attributed to questionable causes, such as, for instance, overuse.

Taken together, the present study shows that CRPS may develop spontaneously with somatic features that are very similar to those of patients in whom the syndrome developed after a trauma. This underlines that a noxious event is a likely though not necessary component in the causal pie model of CRPS; in stead, the onset of the syndrome may be considered multifactorial in nature, with extrinsic (i.e., environmental) and intrinsic (i.e., genetic) factors interacting. It is important that only one set of IASP criteria is used in future studies. The current study shows that there is little reason to deviate from the originally agreed IASP criteria as presented by Merskey and Bogduk. We also found that CRPS patients with a spontaneous onset contract the condition at a younger age, possibly indicating a predisposition to develop the disease. The longer disease duration found in patients with a spontaneous onset may reflect a delay in diagnosis, possibly as a result of the reluctance to make the diagnosis in the absence of trauma, a situation that should be avoided given the better chances of success if treatment is initiated early.

Conflict of interest

All authors declare that they have no conflict of interest with respect to the subject of this study.

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This study is part of Trauma RElated Neuronal Dysfunction (TREND), a consortium that integrates research on epidemiology, assessment technology, pharmacotherapeutics, biomarkers and genetics on Complex Regional Pain Syndrome type 1. The consortium aims to develop concepts on disease mechanisms that occur in response to tissue injury, its assessment and treatment. TREND is supported by a government Grant (BSIK03016).

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