Clinical Pain Research

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The challenge of recognizing severe pain and autonomic abnormalities for early diagnosis of CRPS

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Abstract

Objectives: Complex regional pain syndrome (CRPS) is a disabling usually post-traumatic pain condition. International guidelines emphasize early diagnosis for treatment and improved outcome. Early intense and persistent pain along with features of autonomic dysfunction in the first week's post-injury are early warning signs for development of CRPS. We have previously reported a delayed diagnosis of CRPS. The main purpose of the present study was to investigate possible causes of a delayed diagnosis, with a special focus of recognition of risk factors.

Methods: A total of 52 CRPS 1 (without detectable nerve damage) and CRPS 2 (with evidence of nerve lesion) patients were included in the study. When examined at OUS-Rikshospitalet, we retrospectively asked the patients on the development of pain and autonomic abnormalities from the time of the eliciting injury, performed a thorough clinical investigation with an emphasis on signs of autonomic failure and compared symptoms and clinical findings with such information in previous medical records. We also evaluated symptoms and signs according to the type of injury they had suffered.

Results: Of a total of 52 patients (30 women and 22 men, mean age 39.0 years at the time of injury), 34 patients had CRPS type 1 (65.4%) and 18 CRPS type 2 (34.6%), 25 patients with pain in the upper and 27 in the lower extremity. A total of 35 patients (67.3%) were diagnosed with CRPS (following mean 2.1 years) prior to the investigation at OUS-Rikshospitalet (mean 4.86 years following injury). Mean time from injury to diagnosis was 33.5 months (SD 30.6) (2.8 years) for all patients. In retrospect, all 17 patients first diagnosed at OUS met the CRPS diagnosis at an earlier stage. All patients retrospectively reported intense pain (numeric rating scale > 7) from the time of injury with a large discrepancy to previous medical records which only stated intense pain in 29.4% of patients with CRPS type 1 and 44.4% of patients with CRPS type 2 within the first four months. While the patients reported an early onset of autonomic dysfunction, present in 67.3 and 94.2% of the patients within one week and one month, respectively, reports of autonomic abnormalities within the first four months was far less (maximum in 51.7% of patients with CRPS type 1 and in 60% in CRPS 2). In 10 patients with CRPS type 1, no symptom nor sign of autonomic abnormalities was reported.

Conclusions: We still find a significant delay in the diagnosis of CRPS. There is a large discrepancy between both self-reporting of intense, disproportionate pain, as well as symptoms of autonomic abnormalities from the time of injury, and documentation in previous medical records. Our findings suggest a lack of awareness of risk factors for the development of CRPS, such as early intense pain and autonomic abnormalities without recovery, contributing to delayed diagnosis. The present results suggest causes of delayed CRPS-diagnosis. An increased attention to early warning signs/risk factors may improve diagnosis of CRPS.

Keywords: autonomic abnormalities; complex regional pain syndrome; delayed diagnosis; diagnostic criteri; risk factors; severe pain.

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Introduction

Complex regional pain syndrome (CRPS) is a chronic pain condition which usually develops subsequent to trauma [1–4]. It is characterized by disproportionate pain as well as

sensory, motor and autonomic abnormalities, and is further subdivided into CRPS type 1 without detectable nerve damage and CRPS 2 with evidence of a nerve lesion [5, 6]. The pathophysiological mechanisms of CRPS are debated, but there is international consensus that both central and peripheral mechanisms are involved [7–17].

International guidelines emphasize the importance of early diagnosis of CRPS, both to enable treatment and prevent progression [18, 19]. However, there is a major challenge with delayed diagnosis and treatment [18–20]. The question arises as to why diagnosis may be delayed.

Following a trauma to a limb, there will normally be pain, oedema, altered skin temperature, signs of peripheral inflammation [1, 21, 22]. These symptoms will normally be transient. It may be difficult to discriminate between a prolonged healing process and the development of CRPS. Several studies have tried to identify risk factors that predispose to the development of CRPS. Motor nerve injury, immobilization, fractures, and female gender, are all associated risk factors for developing CRPS [23–26]. Different genotypes may also be associated with different risk for developing CRPS [27, 28].

In a prospective study from 2014, Moseley et al. [29] found that early intense pain after wrist fracture was a strong risk factor for developing CRPS. In accordance with these findings [29], severe pain or pain described as "out of proportion" from the eliciting event has been described [30] or also more pain than in patients who did not develop CRPS [1, 5, 21, 31–33]. In a recent large study comparing CRPS 1 with patients with fracture controls (FC) without CRPS, pain > 4 NRS (numeric rating scale 0–10) discriminated patients with CRPS from FC [21].

CRPS is characterized by autonomic abnormalities. Clinical experience suggested that symptoms and signs of autonomic dysfunction in patients with verified CRPS occurred early following the actual trauma. Persisting pain together with signs of autonomic failure from 1 to 3 weeks post-injury may be early warning signs of CRPS [30, 34]. Complaints of both pain and various autonomic symptoms like oedema, discoloring of skin, skin temperature differences have also been reported within one day by 75% of 829 patients [35].

In the present study we wanted to investigate possible reasons for a delayed diagnosis of both CRPS type 1 and 2 [20]. We wanted to compare how pain and autonomic abnormalities from time of injury as retrospectively reported by the patients (including symptoms and findings at a clinical examination at OUS-Rikshospitalet) corresponded with the documentation in the patients' written medical reports. We further evaluated the impact of different trauma on different signs of autonomic changes.

Materials and methods

Patient material

A large number of patients were referred to the Department of Neurology, Section of Clinical Neurophysiology, Oslo University Hospital (OUS), Rikshospitalet in the period 2004 to present (2019), as part of an assessment of a chronic pain condition secondary to trauma or primary surgical treatment and for determination of degree of medical disability (insurance cases). Of these, a total of 52 patients diagnosed with CRPS (34 patients with type 1 and 18 patients with type 2) were selected for participation in this study. Current information is based on **1**. a retrospective report from the patients on the development of pain and autonomic abnormalities from the time of the precipitating injury (interviews with the patients when examined at OUS-Rikshospitalet) **2**. Reports of pain and autonomic changes from review of previous medical records, specialist statements from the time of the injury and **3**. results from examination at OUS-Rikshospitalet (symptoms and clinical findings).

The patient material in this study is to some degree overlapping, but not entirely identical with the patient material reported previously, where patients were examined up to 2015 [20]. We have excluded patients from our previous material where we did not have accurate information of intensity of pain from time of injury, and we have included more new patients, investigated as late as in 2019.

Ethical considerations

The publication of results was considered by the Regional Ethical Committee as part of a quality improvement of a clinical material with no actual necessity of an ethical approval. We chose anyhow to obtain informed consent from the patients. All patients were investigated according to ethical guidelines and the Helsinki declaration and are anonymous in the present study.

Diagnosis of CRPS

When examined at OUS-Rikshospitalet, CRPS was diagnosed using two different guidelines/diagnostic criteria, depending on the time period of examination. Patients examined in the period 2004–2010 were diagnosed according to the IASP criteria Table 1 [6]. After 2010,

Table 1: The IASP-criteria for CRPS.

IASP-criteria for CRPS
1. The presence of an initiating noxious event, or a cause of immobilization
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event
3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Table 2: The Budapest diagnostic criteria for CRPS.

Budapest criteria for CRPS
1. Continuing pain, which is disproportionate to any eliciting event
2. Must report at least one symptom in three of the four following categories:
– ***Sensory:*** reports of hyperesthesia and/or allodynia
– ***Vasomotor:*** reports om temperature asymmetry and/or skin color changes and/or skin color asymmetry
– ***Sudomotor/oedema:*** reports of oedema and/or sweating changes and/or sweating asymmetry
– ***Motor/trophic:*** reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
– ***Sensory:*** evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
– ***Vasomotor:*** evidence of temperature asymmetry and/or skin color changes and/or asymmetry
– ***Sudomotor/oedema:*** evidence of oedema and/or sweating changes and/or sweating asymmetry
– ***Motor/trophic:*** evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

new and current criteria were used, the so-called Budapest criteria [5] which are described in detail in Table 2 above

Patients' retrospective reports of pain and autonomic abnormalities, when examined at OUS-Rikshospitalet

The patients were asked about both pain and symptoms of autonomic abnormalities (oedema, vasomotor and sudomotor changes, and trophic changes in the injured extremity), from the debut after the actual injury as well as the development of such symptoms. It was explicitly asked for the debut of pain and its intensity on a numeric rating scale (NRS) from 0 to 10, where 0 represents no pain and 10 worst imaginable pain.

Regarding the time course of autonomic dysfunction, we (retrospectively) explicitly asked for the onset and development over time of oedema, discoloration of skin, altered skin temperature, altered sweat pattern and trophic changes.

The onset/debut of autonomic abnormalities was classified as follows; (1) immediately after primary injury, (2) within one week, (3) within 2–4 weeks and (4) after one month.

We further defined the time period for development of autonomic changes as the time from onset/debut until a stable clinical picture was achieved. The distribution of type of autonomic signs and symptoms at both onset and at the time of a stable clinical picture was evaluated.

We also obtained a detailed description of both loss and/or addition of the type of signs and symptoms of autonomic dysfunction over time.

Clinical examination at Oslo University Hospital

Clinical examination was performed of all patients at OUS-Rikshospitalet, including a thorough neurological examination. An evaluation of anamnestic details of both symptoms and signs of autonomic abnormalities was performed in all patients. The following symptoms and signs were asked for: swelling/oedema, discoloration of the skin, altered skin temperature, trophic changes (changes in hair and nail growth, as well as thin and/or gleaming skin) and altered sweat production (increased/decreased).

Furthermore, a detailed patient history of the intensity of pain in the days following the actual injury as well as a detailed assessment of later pain profile was obtained, with description of the following variables; pain character, localization, spontaneous ongoing pain, paroxysmal pain and provoked pain (hyperalgesia and/or allodynia).

All patients were clinically examined for possible motor dysfunction in terms of possible palsy, as well as dystonia and tremor (results not reported here). A clinical assessment of sensory profile, including the presence of hyposensitivity and hypersensitivity, was performed for different modalities. Allodynia to light touch was tested with a cotton swab and hyperalgesia to pin-prick/pressure. EMG/neurography with Dantec counterpoint or Keypoint was performed in most patients (not possible in all patients due to pain) in order to ascertain the diagnosis of CRPS 1 vs. 2. Quantitative sensory testing (assessment of thermal thresholds) was also performed in all patients, but the results are not presented here and the methods not described.

Detailed examination of autonomic dysfunction: A thorough evaluation of the presence of autonomic dysfunction was performed in all patients at OUS-Rikshospitalet. The following signs were looked for, identified and compared to the healthy/unaffected side; oedema/swelling, discoloration, trophic changes (changes in hair and nail growth, as well as thin and/or gleaming skin), altered sweat patterns and any temperature differences. Skin temperature was measured by a handheld measuring device (Somedics Tempett, Hőrby, Sweden) at the site of injury, and in the same area in the contralateral limb. A temperature difference of >1 °C (degrees Celsius) was considered significant [18].

Patient history as obtained from medical records

We obtained detailed information regarding past medical history from the time of the actual injury and until examination at OUS-Rikshospitalet from a complete overview of the patients' medical records sent to the principal investigator (Dr. Jorum) (from primary care physicians as well as specialists (orthopedic surgeons, specialists in pain medicine, specialists in "physical medicine", neurologists) before examination at OUS-Rikshospitalet). All information about pain (debut and development of pain, eventual intensity of pain) as well as the description of autonomic abnormalities from the time of the injury until examination at OUS-Rikshospitalet was noted.

Comparison of reports of symptoms and actual signs of autonomic abnormalities

Diagnosis of CRPS is based on a total clinical picture, requiring a combination of both symptoms and clinical signs. We wanted to evaluate if the clinical signs during examination at OUS-Rikshospitalet coincided with the patient's reported symptoms on the day of investigation, or if there existed a discrepancy.

Autonomic dysfunction according to eliciting events

For all patients the mechanism of injury/eliciting event was noted. The following groups were described and classified; (1) Soft tissue damage without fracture, (2) Fractures and (3) Primary surgery. Soft tissue injury (gr. 1) was composed of patients with contusions, squeeze injuries, crushing injuries, stretch injuries and cut/penetrating injuries.

We also included patients with soft tissue injuries and fractures, who had also undergone secondary surgery with exacerbation of pain and often with development of additional signs and symptoms. Group 4 (tissue injuries) and 5 (fractures) therefore represent patients with a secondary triggering event (i.e., secondary surgery).

The distribution of symptoms and signs of autonomic dysfunction at examination at OUS-Rikshospitalet was evaluated for these five groups of eliciting events. We investigated for possible correlations between type of autonomic dysfunction and type of eliciting events. Analyzes were performed only for CRPS 1 and 2 merged, as the numerical data for CRPS 1 and 2 separately were too small, and could have resulted in unreliable results.

Statistical analyses

In this study, we investigated for significant differences between CRPS type 1 and 2. A student Mann–Whitney *U*-test was used to compare the following variables: (1) mean time for development of a stable clinical picture, (2) mean difference in skin temperature between healthy and affected side and (3) mean pain intensity (numeric rating scale-NRS).

Furthermore, we used a two-sided chi-square test (non-parametric test) to compare (1) debut/onset of autonomic dysfunction, (2) distribution of the type of signs and symptoms of autonomic dysfunction at examination at OUS-Rikshospitalet and (3) distribution of allodynia, hyperalgesia and paroxysmal pain.

We also investigated for significant differences (using a two-sided chi-square test) between the defined groups of eliciting events and the distribution of autonomic dysfunction at examination at OUS-Rikshospitalet, but it was not possible to conduct a more detailed analysis separately for CRPS 1 and 2 due to an insufficient number of patients in each group. For all described analyzes a p-value of less than 0.05 (5%) was defined as being statistically significant.

Limitations of the study

We include retrospective reports of the patients' intensity of pain from the time following the injury as well as reports of time debut and development of autonomic abnormalities. A retrospective analysis will always be encumbered with possible errors.

Furthermore, we removed five patients with CRPS type 1 and three patients with CRPS type 2 in an analysis of data from previous medical reports, because it was uncertain whether we had the complete set of medical records for evaluation of autonomic abnormalities.

Results

A total of 52 patients with CRPS were included in the study. Of these, 30 were women (57.7%) and 22 men (42.3%). 34 patients had CRPS type 1 (65.4%) and 18 CRPS type 2 (34.6%). By gender, 22 women had CRPS 1 and 8 CRPS 2. There were 12 men with CRPS 1 and 10 with CRPS 2. The mean age at the time of injury was 37.8 years for women, 40.7 years for men and 39.0 years overall for both genders. All patients had developed CRPS following trauma to an extremity, 25 patients in the upper and 27 in the lower extremity. No patients in the present study suffered from spread of pain to the contralateral extremity (or to other regions) [36].

The mean time from injury/eliciting event to examination at OUS-Rikshospitalet was 4.86 years overall, with 5.2 and 4.18 years for CRPS 1 and 2, respectively. A total of 35 patients (67.3%) were diagnosed with CRPS prior to this investigation; 26 (76.5%) with CRPS 1 and nine patients (50%) with CRPS 2. The mean time from injury to diagnosis for all patients (n=52) was overall 33.5 months (SD 30.6, min 1, max 139) = 2.8 years, 34.8 (SD 35.1, min 2 max 139) months for CRPS 1 and 30.9 months (SD 20.34, min 2 max 65) for CRPS type 2. Diagnosis prior to investigation at OUS- Rikshospitalet, was 22.9 months (1.91 years) for CRPS 1 and 19.2 months (1.6 years) for CRPS 2, respectively, and 2.1 years overall. CRPS type 1 patients (n=8) diagnosed at OUS-Rikshospitalet were diagnosed as late as after 73.6 months, 6.1 years and CRPS type 2 patients (n=9) after 42.7 months, 3.6 years. Although 17 patients were not diagnosed with CRPS before examination at OUS-Rikshospitalet, it was clear from the patients' own reports as well as from the actual symptoms and findings at the examination that they fulfilled the diagnostic criteria, evidence of a late diagnosis, as also described previously [20].

Pain profile

All patients reported spontaneous pain immediately or within the first days of the eliciting event. Mean pain intensity was 7.27 (SD 1.7) (CRPS1 and 2) 7.2 (SD 1.8) (CRPS1) and 7.3 (SD 1.6) (CRPS2).

A detailed presentation of stimulus dependent and independent pain from the investigation at OUS-Rikshospitalet is presented in Table 3.

We found no significant differences between CRPS1 and 2. Correlation analysis between pain variables (Table 3) and autonomic symptoms was not possible to perform.

Report of early pain (less than four months following injury) in medical reports

For patients with verified CRPS type 1 (n=34), there were reports of intense pain (described as strong, intense,

Table 3: Distribution of pain variables at time of investigation at Oslo University Hospital.

	Stimulus independent pain (spontaneous pain)		Stimulus dependent pain (evoked pain)				Migration of pain localization
	Spontaneous ongoing pain	Paroxysmal pain	Allodynia for light touch	Hyperalgesia (mechanical)	Thermal allodynia	No evoked pain	
CRPS 1	52	28	40	24	39	5	34
and 2	100%	53.8%	76.9%	46.2%	75.0%	9.6%	65.4%
CRPS 1	34	18	24	14	26	5	21
	100%	52.9%	70.6%	77.8%	76.5%	14.7%	61.8%
CRPS 2	18	10	16	10	13	0	13
	100%	55.5%	88.9%	55.5%	72.2%	0%	72.2%

increasing) in at total of 10 patients (29.4%). In the remaining patients, there were either no notifications of pain or only pain, with no evaluation of intensity. Pain in the early phase was not assessed by VAS (visual analogue scale) nor NRS (numeric rating scale). For patients with CRPS type 2 (n=18), intense pain (described as strong, intense, unbearable) was reported in a total of 8 patients (44.4%).

Early onset of autonomic dysfunction, as reported retrospectively by the patients

Of a total of 52 patients, merged for CRPS 1 and 2, we found the following distribution of onset of autonomic dysfunction: 16 patients (30.8%) with immediate onset, 19 (36.5%) with onset within 1 week, 13 (25%) within 2–4 weeks and three patients (5.8%) with onset after one month. Subsequent to the eliciting event/injury, we found that autonomic dysfunction was present in 67.3 and 94.2% of the patients within 1 week and 1 month, respectively. We found similar figures separately for CRPS type 1 and 2, without any significant differences. The distribution of various autonomic failures within the first month is presented in Table 4A.

Development of autonomic symptoms and signs over time, as reported retrospectively by the patients

Mean time from onset until a stable clinical picture (symptoms and signs of autonomic dysfunction) was achieved were 1.02 years for CRPS 1 and 2 merged, 1.05 for CRPS 1 and 0.96 years for CRPS 2 (no significant difference).

The distribution of symptoms and signs of autonomic failure changed over time (Table 4B). The main trend was that over time, patients developed additional symptoms and signs of autonomic abnormalities. The exception was a continuous reduction in both self-reported and objective detection of oedema, from 86.5% (88.2 and 83.3% of patients with CRPS type 1 and 2, respectively), to 73.1% (82.3 and 55.5% for CRPS 1 and 2, respectively). For all other variables of autonomic dysfunction, an increase was seen over time (Table 4B).

Skin discoloration was the most common type of autonomic dysfunction, present in 46 patients (88.5%), followed by alteration in skin temperature, oedema, and altered sweat patterns, while trophic change was least frequent (Table 4B) (no significant difference between CRPS1 and 2).

Table 4: Initial presentation of signs/symptoms of autonomic failure (A) and changes over time (B).

	Oedema	Discoloration of skin	Altered skin temperature	Trophical changes	Altered sweat pattern
CRPS 1 and 2 (n=52)					
Within one-month post-injury (early phase) (A)	45	26	15	1	7
	86.5 %	50.0 %	28.8 %	1.9 %	13.5 %
Actual symptoms and signs at examination at	38	46	44	23	26
OUS (B)	73.1 %	88.5 %	84.6 %	44.2 %	50.0 %

Table 5: Addition of signs and symptoms of autonomic dysfunction.

	Oedema	Discoloration of skin	Altered skin temperature	Trophical changes	Altered sweat pattern
CRPS 1 (n=34)	2	15	21	18	19
	(5.9%)	(44.1%)	(61.8%)	(52.9%)	(55.9%)
CRPS 2 (n=18)	0	8	9	4	3
		(4.4%)	(50.0%)	(22.2%)	(16.7%)
CRPS 1 and 2 (n=52)	2	23	30	22	22
	(3.8%)	(44.2%)	(57.7%)	(42.3%)	(42.3%)

A total of 92.3% of the patients experienced a change (loss or addition of symptoms and signs), 88.5% of patients (CRPS 1 and 2) experienced an overall increase in symptoms and signs, while only 3.8% (CRPS 1 and 2 merged) experienced an overall loss of symptoms and signs. Alteration in skin temperature was the most frequent additional symptom/sign, accounting for 57.7% for CRPS 1 and 2 merged. Oedema very rarely developed over time, only in 3.8%. The remaining symptoms and signs were evenly distributed and present in just under 50% of the patients. We tested for possible statistical differences between CRPS 1 and 2 and found that the development of both trophic changes (p-value = 0.032) and altered sweat patterns (p-value = 0.006) was significantly higher in patients with CRPS 1 (Table 5).

Of the various autonomic changes, we found that oedema was the most frequent feature that lapsed over time, both for CRPS overall (19.2%) and for types 1 and 2 separately.

Apart from oedema, loss of autonomic changes was relatively rare over time. For the other variables, we found the following distribution for loss of autonomic dysfunction, merged for CRPS 1 and 2, 7.7% of patients with skin discoloration, 1.9% of altered skin temperature, 1.9% of trophic changes and 3.8% of altered sweat pattern. We found similar patterns for CRPS 1 and 2 separately, without any statistical differences between CRPS 1 and 2.

Assessment of autonomic symptoms and signs from medical records

We report from 29 (of 34) patients with CRPS 1 and 15 (of 18) patients with CRPS 2. It was not possible to evaluate presentation of autonomic dysfunction from the first week post-injury, so we chose to present reports of symptoms/signs of autonomic abnormalities within the first four months following injury, and then symptoms and signs in the following months and years. The results are presented in Table 6, separately for CRPS 1 (Table 6A) and CRPS 2 (Table 6B). As apparent from the results, descriptions of autonomic abnormalities were far inferior to what

Table 6: Reports of early (less than months post-injury) and late (greater than four months post-injury) autonomic abnormalities from medical records in (**A**) CRPS1 and (**B**) CRPS 2.

(A)

CRPS 1 (n=29)	Oedema	Discoloration of skin	Altered skin temperature	Trophical changes	Altered sweat patterns
Early reports (within four months from injury	15	9	4	1	3
	51.7%	31.0%	13.8%	3.4%	10.3%
Late reports (up to several years)	15	9	9	5	9
	51.7%	31.0%	31.0%	17%	31%

(B)

CRPS 2 (n=15)	Oedema	Discoloration of skin	Altered skin temperature	Trophical changes	Altered sweat patterns
Early reports (within four months from injury	9	5	3	0	2
	60%	33.3%	20%		13.3%
Late reports (up to several years)	9	4	6	1	3
	60%	26.7%	40%	6.7%	20%

reported by the patients. In a total of 10 patients with CRPS 1, no symptom or sign of autonomic abnormalities was reported.

Diagnosis of CRPS prior to or during examination at OUS-Rikshospitalet

CRPS was diagnosed in 35 patients prior to investigation at OUS-Rikshospitalet and only by specialists, primarily specialists in orthopedic surgery or in pain medicine, and by no primary care physician (although autonomic abnormalities were described by some physicians). A total of 20 patients were diagnosed in the time period of IASP criteria and 32 patients by Budapest criteria. However, the exact criteria were seldom mentioned, it was noted "diagnosis according to criteria" or also with no mentioning of any criteria. Budapest criteria was mentioned in the case of three patients. When the diagnosis of CRPS was decided, also in the time period of Budapest criteria, there was seldom mentioning of more than one or two types of autonomic abnormalities, see next section. Diagnosis in the time period of Budapest criteria, was seldom based on a combination of both symptoms and clinical findings (as required).

For the whole material (n=52): in a total of 10 patients with CRPS type 1, there was no report of any autonomic abnormalities during the first four months following injury, seven patients with injury after 2010 (time period of Budapest criteria with more specific demands of autonomic failures) and three patients in the time period of former IASP-criteria. Four of these patients were diagnosed from 13 to 21 months post-injury. The remaining six (as also included in section below) from 51 to 126 months after injury. There was no significant difference in delay of diagnosis from the use of Budapest (38.2 months [SD 37.9 min 2 max 139]) or IASP (28.2 months [SD 22.7 min three max 75]) criteria.

A total of 10 patients (six patients also from section above) were diagnosed with CRPS type 1 as late as greater than four years (range 50–139 months), two patients with injuries before 2010 and eight patients after 2010 (Budapest-criteria). Intense pain was only reported in one patient, and autonomic changes only for two patients (oedema in one case, discolored skin in one patient). On the other hand. a total of eight patients, six with CRPS type 1 and two patients with CRPS 2, were diagnosed by specialists (orthopedic surgeons and pain specialists) within four months following injury. In these patients, intense pain was described in four patients with CRPS type 1 and in both patients with CRPS type 2 (recognizing the risk factor of intense pain). Autonomic abnormalities were also described in more detail. Details of time intervals for diagnosis are presented in Table 7.

Table 7: Number of patients with CRPS 1 and 2 diagnosed within different time intervals.

	<4 months	4–12 months	1–2 years	2–4 years	>4 years
CRPS 1 (n=34)	6	2	12	4	10
CRPS 2 (n=18)	2	2	3	7	4

Distribution and correlation of clinical signs and self-reported symptoms of autonomic dysfunction during investigation at OUS

At examination at OUS-Rikshospitalet, we assessed whether symptoms of autonomic failure coincided with the actual clinical findings. We found an equal distribution only for altered skin temperature in the affected limb (Table 8, around 85% of the patients). For all other modalities, there was a higher degree of self-reported symptoms compared to what was objectively found (Table 8). This discrepancy was most prominent for oedema, which was reported by 38 (73.1%) and demonstrated in 17 (32.7%), a difference of 40.4% ($p<0.001$) and for alteration in sweating (primarily hyperhidrosis) reported in 26 (50% and demonstrated only in 3 (5.8%) ($p<0.001$) (and with no significant difference between CRPS 1 and 2). Also, with regard to discoloration of skin and trophic changes, there were larger percentages of reported symptoms than clinically shown, but with lesser differences.

Changes in skin temperature

Altered skin temperature was found in as many as 86.5% of patients, 10 patients (19.2%) had elevated skin temperature in the affected area with an average difference of 1.8 °C (1.0–2.5 °C increase), and the majority, as many as 35 patients (67.3%) had decreased skin temperature in the affected area with an average temperature difference of 1.98 °C (1.0–6.5 °C.) (no significant differences CRPS 1 and 2)

The eliciting injuries/events

Isolated soft tissue injuries were the most frequent eliciting cause in our patient material, both overall (38.5%) (CRPS 1

Table 8: Comparison of distribution between symptoms and signs of autonomic dysfunction at examination at Oslo University Hospital.

	Oedema	Discoloration of skin	Altered skin temperature	Trophical changes	Altered sweat pattern
CRPS 1 and 2 (n=52)					
Actual symptoms at examination at OUS	38	46	44	23	26
	73.1%	88.5%	84.6%	44.2%	50.0%
Isolated clinical signs at examination at	17	32	45	14	3
OUS	32.7%	61.5%	86.5 %	26.9 %	5.8%

[41.2%] and CRPS 2 [33.3%]), followed by fractures/skeletal injury 23.1% (26.5% in CRPS 1, 16.7% CRPS 2), primary surgery 7.7% (8.8% CRPS1 and 5.6% CRPS 2). Merged for CRPS 1 and 2, exacerbation after subsequent surgery was seen in 19.2% of patients with primary soft tissue injury, and in 11.5% of patients with primary skeletal injury (fractures). In our patient material we found that 30.7% of patients (CRPS 1 and 2 merged) experienced exacerbation after subsequent surgery. These figures are presented in Table 9.

Possible correlations between eliciting events and type of autonomic dysfunction

We found a significant difference in the incidence of skin discoloration between group 2) fractures/skeletal damage (and without worsening after secondary surgery), and patients with primary surgery (group 3) (p=0.0088). Similarly, we also found a significant incidence of skin discoloration between patients with soft tissue injury (without worsening after secondary surgery) and patients with primary surgery (p=0.0157). Our results show that discoloration of the skin was significantly more prevalent in patients with soft tissue injury and with fractures. We found no other correlations.

Discussion and conclusions

The results of this study show that whereas all patients with CRPS type 1 or 2 reported (retrospectively) an intense pain from the time of the injury (NRS > 7), intense pain was only noted in medical records of 29.4% of the patients within the first four months (described as intense, abnormally high, increasing). Although a retrospective analysis must be treated with caution, the trauma resulting in the development of CRPS represented a dramatic event in the life of the patients, an event which they claimed to remember in great detail.

Diagnosis of CRPS may be considered after the time course of an expected recovery for a trauma, i.e. 4–8 weeks after a fracture [37], or even as early as 1–2 weeks post trauma, if the patients have persisting symptoms, with no signs of decrease [34]. In the follow up of patients after an injury, a difficult task for primary care clinicians or specialists will be to discriminate between a prolonged healing and to recognize patients at risk for CRPS [19, 21]. There is so far no gold standard for diagnosing CRPS and physicians must rely on clinically derived diagnostic criteria [21, 22, 38]. The importance of an out of proportion pain as an important warning factor for a possible development of the CRPS has been emphasized [1, 5, 21, 29–33]. A lack of

Table 9: Distribution of groups of eliciting events according to the type of CRPS, and respective signs and symptoms of autonomic dysfunction at the time of investigation at Oslo University Hospital.

	Oedema	Discoloration of skin	Altered skin temperature	Trophical changes	Altered sweat pattern
Groups of eliciting events (CRPS 1 and 2)					
(1) Soft tissue injury 38.5% (n=20)	14	16	17	9	12
(2) Fractures/skeletal damage 23.1% (n=12)	9	12	11	7	6
(3) primary surgery 7.7% (n=4)	2	2	4	2	3
(4) Soft tissue injury with exacerbation after subsequent surgery 19.2% (n=10)	9	10	8	3	3
(5) Fractures/skeletal damage with exacerbation after subsequent surgery 11.5% (n=6)	4	6	4	2	2

awareness of the presence of intense pain within the first weeks (in addition to autonomic abnormalities as described below) may jeopardize a correct early diagnosis of CRPS, as we see in the present study. These patients will thereby miss the possible benefits of an early treatment.

Typical symptoms and findings of CRPS are various kinds of autonomic abnormalities which are now (compared to previous IASP-criteria) specifically referred to in the present Budapest CRPS criteria. The majority of our patients (94.2%) presented autonomic abnormalities within 1 month of the triggering event, and as many as 67.3% within 1 week, corresponding to previous reports [14, 35]. With the presence of autonomic changes within 1-month past-injury (in addition to intense pain), and with exclusion of other causes, a correct diagnosis of CRPS should be feasible within one month, which is in accordance with the UK Guidelines [18, 22].

The early autonomic changes (within 1-month post-injury) as reported by the patients (Table 4) included oedema (86.5%, discoloration of skin (50%), altered skin temperature (28.8%), trophic changes (1.9%) and altered sweat patterns (13.5%). Comparing these data with the previous reported findings in the medical records of the patients (Table 6), there is an apparent mismatch and a far lower rate of descriptions of autonomic abnormalities in the records. We assume the lack of recognition and reporting of autonomic abnormalities to be an additional important reason for a delayed diagnosis. In as many as 10 patients with a later verified CRPS 1, there was no mentioning of autonomic changes in the first four months post injury, resulting in a late (13–21 months) and very late (greater than four years) diagnosis. It is encouraging, however, to note that in a few patients with reports of both early intense pain as well as accurate description of autonomic changes, the diagnosis was made early, within the first 4 months. Most of these patients were injured after 2010, after the introduction of Budapest criteria, bringing hope that these criteria have become more widely recognized, as also indicated by the decrease in delay of diagnosis from 3.9 years [20] to our present study (2.9 years). The delay is still unacceptable. The problem is that although the rate of incidence of CRPS varies from 5.46 per 100,000 a year [39] up to as high as 26.2 per 100,000 a year [40], many physicians will rarely see these patients, and thereby gain little experience. It may therefore not be surprising that CRPS most commonly is diagnosed by experienced specialists, in particular orthopedic surgeons, who treat a large percentage of patients with CRPS due to fractures, in addition to pain specialists.

Our findings of symptoms/signs of autonomic failure/when examined at OUS-Rikshospitalet) (Table 4), correspond to previously published findings, with presence of oedema in 55–89% of the cases, with skin abnormalities in 71–97% of the cases, and temperature differences in 79–98% to results of previous studies [12, 35, 41]. These results confirm the legitimacy of the patients' own reports.

It has been argued that CRPS may be overdiagnosed [21, 32, 42] and that use of IASP-criteria has contributed to overdiagnosis [43]. We may not compare these findings directly with our results. Our findings of an over-all late diagnosis will anyhow suggest that CRPS is under and not-overdiagnosed, as also suggested previously [38].

Symptoms and signs of autonomic abnormalities will alter over time, as also shown in the present study. Oedema usually becomes less frequent and/or less severe [12]. The transition from an acute "warm" phase (oedema, redness, warmth" to a more chronic "cold" phase (cold, cyanotic) [13, 44, 45] involve complex mechanism such as early posttraumatic immune activation [46], involvement of inflammatory mechanisms, also neurogenic inflammation [10, 45], and release of proinflammatory cytokines [2], whereas a "cold" phase may be related to an alteration of underlying pathophysiological mechanisms, from a previous state of vasodilation to increased vasoconstriction [15, 45], involving hypersensitivity to vasoconstricting substances and attenuation of neurogenic inflammation [10, 13, 15, 16, 47, 48]. In our study, alteration in skin temperature was found in 86.5% of the patients and 67.5% of the experienced a decreased and in some cases a severe drop in temperature. We emphasize the importance of accurate and objective measurement of skin temperatures. Due to a gradual change in the clinical expression of CRPS, some patients will after some time no longer fulfill the Budapest criteria, which is described in the term CRPS-NOS [18, 19]. This implies that when the diagnosis is not made after reasonable time, there is also an increased chance of a failed diagnosis.

It is important to be aware that not all signs may be present at an actual investigation as we also see in the present study, because of variation throughout the day [46] and depending on the level of activity [22, 46, 49–51]. It has been argued that the number of patients fulfilling the CRPS criteria one year post trauma is relatively low, due to the decline of several symptoms [43]. But it has also been reported that none of the CRPS 1 patients were free of symptoms at 1 year after trauma, confirming that CRPS 1 is a disabling, long-lasting condition [43]. This is supported by the findings in a prospective study of 59 patients with fracture showing that only 5.4% were free of symptoms following one year [52]. This seems to be in contrast to the claim that most cases resolve within one year [22]. It has

been argued that a CRPS diagnosis made after several years (as we report here) should be questioned [37]. Our patients may have experienced an alteration of their conditions over time, but they still fulfilled the criteria for the disease. Although oedema was no longer permanent in a majority, they still could report a reappearing oedema upon use of the injured extremity, corresponding to the disposition for swelling reported even after 15 years of CRPS [12].

It was surprising that CRPS 2 was not diagnosed in 50% of the patients before investigation at OUS-Rikshospitalet. These patients were however diagnosed with post-traumatic neuralgia based on the finding of a nerve injury. A diagnosis of CRPS was probably missed due to the lack of description of autonomic abnormalities located in the whole region of the extremity (which was found) and not only within the innervation territory of the actual nerve [37].

We did not see any difference in the symptoms and findings between CRPS 1 and 2, the reason for why we have presented findings for both groups together, supporting results of previous studies [10, 12, 38]. Also, pathophysiological mechanisms seem to be similar, including inflammation, altered sympathetic activity as well as peripheral and central sensitization [7, 9, 10, 12–17]. This is of relevance to the ongoing discussion on whether CRPS type 1 is a neuropathic pain condition ("pain arising as a direct consequence of a lesion or disease affecting the somatosensory system") [53]. Even CRPS type 2 may not fulfil the criteria [54]. The findings of no significant differences in various variables of pain (Table 3) may suggest from a clinical point of view that CRPS type 1 also to be a neuropathic pain disorder, in some cases possibly due to an affection of small nerve fibers [11, 55, 56]. However, since pathophysiological mechanism still may be different from a strict neuropathic pain disorder, it is recommended to consider CRPS (both type 1 and 2) as a separate entity [54, 57].

In conclusion, we report lack of report and awareness of early severe pain and autonomic abnormalities as a probable cause of delayed diagnosis of CRPS.

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