Complex regional pain syndromes: Clinical characteristics and pathophysiological factors

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Received 1 March 2011; Accepted 1 May 2011
Available online 5 July 2011

KEYWORDS
CRPS;
TNF;
SSR;
Normetanephrin

Abstract  Aim of the work: To study relationship between clinical pattern of complex regional pain syndromes (CRPS) and inflammatory and sympathetic parameters.

Patients and methods: Twenty one CRPS patients and 15 healthy controls were examined. Clinical data, sympathetic skin response (SSR), TNFα and normetanephrine were evaluated.

Results: Fourteen patients had increased serum TNFα which showed significant relationship with some clinical parameters. Three patients had increased normetanephrine. Mean SSR latency was shortened in patients. No significant relationship between SSR and sweating manifestations and no correlation between serum normetanephrine, SSR, and serum TNFα were found.

Conclusion: Inflammation plays a major role and SSR is enhanced in CRPS.

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1. Introduction

Complex regional pain syndromes (CRPS) describe an array of painful conditions that are characterized by continuous spontaneous regional pain seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor and/or trophic findings [1].

There are two distinct subtypes of CRPS. CRPS type I which occurs typically without a distinct major nerve lesion. It may take place after trauma, stroke or myocardial infarction [2,3]. In CRPS type II there is a major nerve damage, i.e., a partial lesion of a peripheral nerve is necessary for the diagnosis [4].
Several pathophysiological mechanisms have been proposed to explain CRPS. These mechanisms include, facilitated neurogenic inflammation [5], pathological sympatho-afferent coupling [6], neuroplastic changes within the CNS [7,8] and genetic factors [9]. Inflammation has been proposed as a mechanism for CRPS because many clinical symptoms of acute CRPS resemble inflammation [10]. Neurogenic inflammation is mediated by traumatically released nerve growth factor (NGF) and cytokines with consequent nociceptive C fibers sensitization and production of substance P (SP) as well as calcitonin gene-related peptide (CGRP) [11,12]. However, inflammation in CRPS may not always be neurogenic in nature. Regional local inflammation was demonstrated in patients with CRPSI as evidenced by increased TNFα and interleukin 4 without a concomitant increase of neuropeptides [13].

Sympathetic dysfunction in CRPS has been addressed [14–26]. Skin temperature abnormalities have been attributed to either inhibition of norepinephrine-mediated sympathetic control over cutaneous blood vessels [19,20] (as in the acute stage) or their supersensitivity to circulating catecholamines [21–23] (as in the chronic stage with vascular constriction). In addition, abnormal sudomotor function was also found in CRPS patients [24–26]. Patients with sympathetically mediated pain (CRPSII) are suggested to have sympathetic-afferent coupling [18,27,28] triggered by NGF and TNFα in response to peripheral nerve lesion [28–30]. Such coupling may be responsible for the sensitization of the C nociceptive neurons mediated by locally released norepinephrine and epinephrine [29]. In CRPSI, similar coupling may take place [16–18,27] as a result of subclinical traumatic nerve lesions of the cutaneous and deep somatic tissues [31–32]. Moreover, in CRPS type I, sympathetic nerve terminals in peripheral tissues may serve as mediator elements in hyperalgesia and inflammation through a mechanism which is largely independent of activity in the sympathetic neurons. It is triggered by inflammatory mediators as TNFα which lead to synthesis and release of prostaglandin E2 from sympathetic terminal or in association with it leading to sensitization of nociceptive afferents for mechanical stimuli and venular plasma extravasation, i.e., sympathetically mediated neurogenic inflammation [28].

Sympathetic dysfunction [14–26]. TNFα serum or blister [13,33] or soluble TNF receptor [5] levels have been separately investigated. However, the relative contribution of the inflammatory mechanisms and sympathetic dysfunction to the clinical features of the disease is not clearly identified.

The aim of this work was to study the relationship between the clinical pattern of CRPS and the inflammatory factors as well as sympathetic dysfunction. Identifying such a relationship is a prerequisite for a mechanism-oriented therapy [34].

Study design: Case-control cross-sectional study.

2. Patients and methods

Twenty one CRPS patients who attended the outpatient clinic of Department of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Alexandria University, were included in the study after signing an informed consent and informed about the details of the procedures. In addition, 15 age matched controls for the electrophysiological study were included. The study was approved by the local ethical commit-

tee of Faculty of Medicine, Alexandria University. Patients were diagnosed according to the revised Budapest criteria (research diagnostic criteria), 2004 [1]. Patients were excluded from the study if one or more of the following were present: hypertension as it affects the level of catecholamines [35], diseases that produce features like CRPS as diabetes mellitus, peripheral neuropathy, vascular disorders as Raynaud’s phenomenon and any concomitant infection or inflammatory disease as it interferes with the level of TNFα, acute phase proteins and blood picture [5], intake of drugs that affect the vascular system, corticosteroids and immunosuppressive drugs [20,33] and delayed bone healing [5]. Moreover, smokers were also excluded from the study [5]. Each patient was subjected to (a) full history taking regarding the etiology of CRPS (whether injury to a major nerve, any painful condition of the limb or immobilization), local symptoms of the affected hand, duration of hand complaints, the causative agent and the prescribed treatment (whether physical or medical). (b) Any medical reports or documents that clarify the etiology of CRPS (electrophysiological study, plain X ray etc) were considered to determine the subtype of CRPS (I or II). (c) Patients were then subjected to local hand examination (where the diagnostic criteria were determined for each case), together with general physical and neurological examination.

Symptoms and signs of CRPS were assessed as follows:

(a) Pain severity was assessed by Visual Analogue Scale (VAS) [36,37] with respect to the hand use in activities of daily living.
(b) Skin temperature asymmetry was detected as follows: the dorsum of the involved and uninvolved hands of the patient were felt by the dorsum of the examiner’s hand and reported as a qualitative data (present or not).
(c) Sweating asymmetry was detected as well, i.e., the palm of the involved and uninvolved hands of the patient were felt by the examiner’s hand and sweating asymmetry was reported as present or not.
(d) The volume of the hand (for quantification of edema) was determined by measuring the volume of the water displaced in milliliters by immersion of the tested hand in a scaled container [33,38] till the level of the unlar styloid process. Then the difference between the involved and uninvolved extremity was calculated.
(e) Motor dysfunction was determined as follows:
  - Grip and pinch strength were measured by a hand-held dynamometer (Preston hand dynamometer and pinch gauge) in kilograms for the involved and uninvolved hands.
  - Active range of motion was measured by a goniometer for the wrist flexion and extension, metacarpo-phalangeal, and interphalangeal joints flexion and extension for the most restricted digit [33] in the standard positions [39] and expressed as an absolute value in degrees.
(f) Electrophysiological study: Sympathetic skin response was performed for the affected hands of the patients as well as the hands of controls [40] as a measure for sympathetic function using NIHON KOHDEN (Neuro-pack) electrophysiological apparatus. The cutoff value of the latency was determined by calculating the mean ± 2SD of the controls. The abnormality of SSR
was judged based on the absence of the response or presence of abnormal latency (shortened or prolonged) because the latency was considered to be a reproducible and effective parameter to detect SSR abnormalities by some authors [41,42].

(g) Laboratory investigations:
- Serum TNFα was detected in patients by chemiluminescence technique using IMMULIT® 1000-Siemens. The normal level was up to 8.1 ng/ml.
- Normetanephrine (NMN) was detected in patients using Metanephrine ELISA Kit, (plasma) from DRG International, Inc. The normal level was < 200 pg/ml.
- CRP and complete blood count with differential leucocytic count were also assessed in patients.

The blood samples were obtained from the venous blood taken from the veins at the dorsum of the affected hands of the patients [20].

Statistics. Description of the sample was expressed as frequencies and percentages. Skewness of the measured variables was assessed to determine normality of distribution. Mann–Whitney test was used for in-between group comparisons. Correlations between quantitative variables were detected by Spearman’s test. The statistical relationships between qualitative variables were detected by Chi square test. SPSS v 11.0 was used to perform the statistical analysis. Cut off values were calculated as the mean ± 2SD of controls for the SSR. Patients who had serum levels of TNFα and NMN exceeding the upper limit of normality were considered abnormal.

3. Results

The study included 21 patients with CRPS; 14 patients (66.7%) had type I and seven patients (33.3%) had type II. Type I occurred as a consequence of distal upper limb fractures (12 cases; 57.14%), repaired extensor digitorum tendon and operated ganglion on the dorsal aspect of the wrist (one case each; 9.52%), while type II took place following gross partial nerve injuries including ulnar nerve at the wrist (three cases; 14.29%) and one case for each of the following injuries: superficial radial (seven cases; 33.33%), ulnar nerve apart from the patient with the injured superficial radial nerve whose pain was limited to the dorsum of the hand). Pain usually awakening the patient from sleep (in CRPS type II patients, pain was not restricted to the territory of the injured nerve apart from the patient with the injured superficial radial nerve whose pain was limited to the dorsum of the hand). Pain was expressed as either lancinating, burning, cutting, electric or sawing.

The mean CRP was 6.48 ± 5 mg/L (normally up to 6), while the mean leucocytic count was 8423.8 ± 2576.2 cell/μm (normally up to 11,000). All patients had normal leucocytic count (thus infection was excluded).

There was no statistically significant difference between patients and controls regarding age.

Table 1a and 1b show the clinical features, relevant laboratory data and electrophysiological parameters of the studied CRPS patients. There was a statistically significant decrease of both mean pinch and grip strengths as well as an increase of the mean volume of the affected compared to non-affected hands of CRPS patients. There was also a significant decrease of the mean SSR latency of the affected hands of patients (0.99 ± 0.19 s) compared to controls (1.26 ± 0.18 s) (Z = −3.581, p = 0.001, limits of normality ranged from 0.9 to 1.62 s).

It is to be mentioned that the three patients (14.29%) who had increased serum NMN had also increased serum level of TNFα. Moreover, the seven patients (33.33%) with normal serum level of TNFα had also normal serum level of NMN. Table 2 shows no significant differences between type I and II CRPS regarding hand manifestations, impact of the disease on ADL, laboratory and SSR findings.

Matching between sweating manifestations among the studied patients and the results of their sympathetic skin response (SSR) revealed that seven patients (33.33%) had normal sweating manifestations [six (28.57%), had normal SSR

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Subgroups</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected hand mean ± SD</td>
<td>Non-affected hand mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Pinch strength (kg)</td>
<td>0.75 ± 0.8</td>
<td>4.4 ± 2.18</td>
<td>−3.297</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>1.42 ± 2.5</td>
<td>22.12 ± 10.74</td>
<td>−3.181</td>
</tr>
<tr>
<td>Hand volume (mL)</td>
<td>547.33 ± 161.56</td>
<td>506.67 ± 170.62</td>
<td>−3.19</td>
</tr>
<tr>
<td>Volume difference of both hands (mL)</td>
<td>40.67 ± 30.81</td>
<td>506.67 ± 170.62</td>
<td>−3.19</td>
</tr>
<tr>
<td>VAS for ADL (mm)</td>
<td>64.67 ± 35.23</td>
<td>506.67 ± 170.62</td>
<td>−3.19</td>
</tr>
<tr>
<td>VAS for pain (mm)</td>
<td>58.58 ± 35.46</td>
<td>506.67 ± 170.62</td>
<td>−3.19</td>
</tr>
<tr>
<td>Serum TNFα (ng/mL) (normally up to 8.1)</td>
<td>9.61 ± 5.47</td>
<td>9.61 ± 5.47</td>
<td>0.001*</td>
</tr>
<tr>
<td>Serum normetanephrine (pg/mL) (normally &lt; 200)</td>
<td>149.16 ± 163.1</td>
<td>149.16 ± 163.1</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

VAS = visual analogue scale, mL = millimeter, kg = kilogram, ADL: activity of daily living, SSR = sympathetic skin response, mg/L = milligram/liter, mm = millimeter, ng/mL = nanogram/milliliter, pg/mL = pico gram/milliliter, s = second.

*p is significant if < 0.05.


4. Discussion

Despite of the diagnostic distinction between CRPS type I and II, the lack of significant difference in terms of clinical, laboratory and SSR is suggestive of significant pathophysiologic similarities. This is in agreement with the results of other studies and the proposed existence of a form of triggering nerve trauma in type I CRPS [1,43]. Low density of nociceptive C and Aδ fibers in CRPS I provide further support of such pathophysiologic similarity [31,32].

A localized inflammatory process (peripheral afferent mechanism) [13,44] as well as autonomic abnormalities (peripheral efferent mechanism) [14–18,45] are among the proposed pathogenic mechanisms of CRPS.

In the present study, TNFα was found elevated in 2/3 of the studied patients. This reflects a significant inflammatory component of the pathogenic mechanism. TNFα is a key cytokine contributing to CRPS features [46,47]. Tissue injury leads to production of TNFα (which also induces other proinflammatory cytokines) [47] by endothelial cells, fibroblasts, lymphocytes and tissue macrophages [48] which can lead to sensitization of nociceptors and amplification of neurogenic inflammation [11]. Proinflammatory cytokines can be operant in CRPS independent of neurogenic inflammation [13]. The increased TNFα level in CRPS patients was proved in many studies whether in patients’ sera [38,49] or locally in blister fluid [13,33]. However, in a study performed by van de Beek et al. [50], serum TNFα was within-normal limits in CRPS patients. This is in agreement of one-third of our patients who had normal serum TNFα indicating that inflammation might not contribute to the pathogenesis of CRPS in those patients. The influence of disease duration is unlikely to explain the normality of TNFα in our study because the range of disease duration was 1–7 months which represents the initial (up to one year) stage of CRPS. Serum TNFα was found elevated in the initial and intermediate stages (up to 40 months) by other researchers [33,38]. Moreover, there was no correlation between serum latency and one (4.76% had enhanced response, i.e., short latency). Moreover, 11 patients (52.38%) had excessive sweating on clinical examination [seven (33.33%) had normal SSR latency and four (19.1%) had enhanced response]. Accordingly, eight patients had a discrepancy between sweating manifestations as detected clinically and the outcome of the SSR. On the other hand, only three patients (14.29%) had impaired sweating (decreased sweating or dry skin) and all had unobtainable SSR. There was no statistically significant association between sweating manifestations and SSR findings (Chi square = 0.101, p = 0.751).

In Table 3, patients with increased serum level of TNFα showed significant increase in the hand volume difference and hence increased edema compared to those with normal TNFα.

In Table 4 increased TNFα in CRPS patients is significantly associated with skin color changes, hand edema, sweating and temperature asymmetries reflecting its probable pathogenic role with respect to these clinical features of such patients while SSR abnormality is not associated with any of them.

No correlation was found between serum normetanephrine level and each of the following: serum TNFα, any of the clinical parameters and SSR parameters.

4. Discussion

Despite of the diagnostic distinction between CRPS type I and II, the lack of significant difference in terms of clinical, laboratory and SSR is suggestive of significant pathophysiologic similarities. This is in agreement with the results of other studies and the proposed existence of a form of triggering nerve trauma in type I CRPS [1,43]. Low density of nociceptive C and Aδ fibers in CRPS I provide further support of such pathophysiologic similarity [31,32].

A localized inflammatory process (peripheral afferent mechanism) [13,44] as well as autonomic abnormalities (peripheral efferent mechanism) [14–18,45] are among the proposed pathogenic mechanisms of CRPS.

Table 3: Frequency of clinical and laboratory findings among the studied patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abnormal TNF (n = 14)</th>
<th>Normal TNF (n = 7)</th>
<th>Abnormal NM (n = 3)</th>
<th>Normal NMN (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (%)</td>
<td>F (%)</td>
<td>F (%)</td>
<td>F (%)</td>
<td>F (%)</td>
</tr>
<tr>
<td>Hand edema</td>
<td>11</td>
<td>100</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Sweating</td>
<td>6</td>
<td>54</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Temperature</td>
<td>9</td>
<td>81</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Color</td>
<td>7</td>
<td>63</td>
<td>3</td>
<td>100</td>
</tr>
</tbody>
</table>

Clin. abn.: clinical abnormalities.
TNFα level and disease duration in our study (this was also proved by Wesseldijk et al. [49]). Also there was no significant difference between patients with elevated serum TNFα and those without regarding disease duration in our study. However, Huygen et al found serum TNFα to be normal in their patients while elevated in suction blister fluid in the affected side representing strictly local inflammation [13]. This may explain the normality of serum TNFα among some of our patients and if so, inflammation can still be considered as an operating mechanism of such patients.

### Table 2
Comparison between patients with type I and type II CRPS regarding selected clinical characteristics, laboratory findings and SSR parameters (Mann–Whitney test).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRPS type I (n = 14) Mean ± SD</th>
<th>CRPS type II (n = 7) Mean ± SD</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.36 ± 14.38</td>
<td>34.29 ± 13.63</td>
<td>−2.057</td>
<td>0.04*</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>3.71 ± 2.3</td>
<td>3.83 ± 2.23</td>
<td>−0.286</td>
<td>0.775</td>
</tr>
<tr>
<td>VAS for pain.</td>
<td>62.92 ± 36</td>
<td>51.14 ± 36</td>
<td>−0.552</td>
<td>0.581</td>
</tr>
<tr>
<td>Affected hand volume (mL)</td>
<td>538.18 ± 159.86</td>
<td>572.5 ± 188.39</td>
<td>−0.396</td>
<td>0.692</td>
</tr>
<tr>
<td>Hands volume difference (mL)</td>
<td>40.91 ± 28.1</td>
<td>40 ± 42.43</td>
<td>0.000</td>
<td>1</td>
</tr>
<tr>
<td>Affected pinch strength (kg)</td>
<td>0.97 ± 0.84</td>
<td>0.2 ± 0.28</td>
<td>−1.853</td>
<td>0.064</td>
</tr>
<tr>
<td>Affected grip strength (kg)</td>
<td>1.83 ± 2.92</td>
<td>0.5 ± 1</td>
<td>−1.008</td>
<td>0.313</td>
</tr>
<tr>
<td>VAS for ADL</td>
<td>77.5 ± 26.3</td>
<td>54.4 ± 40.83</td>
<td>−1.246</td>
<td>0.213</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>5.57 ± 4.32</td>
<td>7.96 ± 6.26</td>
<td>−0.784</td>
<td>0.433</td>
</tr>
<tr>
<td>Leucocytic count</td>
<td>7607.14 ± 2144.57</td>
<td>10057.14 ± 2736.7</td>
<td>−1.791</td>
<td>0.073</td>
</tr>
<tr>
<td>TNFα (ng/mL)</td>
<td>10.62 ± 6.45</td>
<td>7.6 ± 1.52</td>
<td>−1.493</td>
<td>0.136</td>
</tr>
<tr>
<td>Normetanephrine (pg/mL)</td>
<td>166.62 ± 193.6</td>
<td>111.33 ± 57.21</td>
<td>−0.132</td>
<td>0.895</td>
</tr>
<tr>
<td><strong>SSR (affected hand)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (s)</td>
<td>0.98 ± 0.19</td>
<td>0.99 ± 0.21</td>
<td>−0.422</td>
<td>0.673</td>
</tr>
</tbody>
</table>

VAS = visual analogue scale, ADL = activity of daily living, SSR = sympathetic skin response, mg/L = milligram/liter, mm = millimeter, ng/mL = nano gram/milliliter, pg/mL = pico gram/milliliter, s = second, µV = microvolt.

* p is significant if < 0.05.

### Table 3
Comparison between patients with increased (†) and normal TNFα regarding selected clinical characteristics, laboratory findings and SSR parameters (Mann–Whitney test).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with † TNFα (n = 14) Mean ± SD</th>
<th>Patients with normal TNFα (n = 7) Mean ± SD</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.93 ± 15.1</td>
<td>43.14 ± 16.51</td>
<td>0.000</td>
<td>1</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>3.21 ± 2.25</td>
<td>4 ± 1.63</td>
<td>−0.736</td>
<td>0.462</td>
</tr>
<tr>
<td>VAS for pain.</td>
<td>65.83 ± 38.41</td>
<td>46.14 ± 28</td>
<td>−1.273</td>
<td>0.203</td>
</tr>
<tr>
<td>Affected hand volume (mL)</td>
<td>529.17 ± 155.59</td>
<td>620 ± 199.25</td>
<td>−1.093</td>
<td>0.274</td>
</tr>
<tr>
<td>Hands volume difference (mL)</td>
<td>48.33 ± 28.87</td>
<td>10 ± 17.32</td>
<td>−2.041</td>
<td>0.041*</td>
</tr>
<tr>
<td>Affected pinch strength (kg)</td>
<td>0.77 ± 0.88</td>
<td>0.67 ± 0.5</td>
<td>−0.314</td>
<td>0.754</td>
</tr>
<tr>
<td>Affected grip strength (kg)</td>
<td>1.35 ± 2.81</td>
<td>1.67 ± 1.53</td>
<td>−0.920</td>
<td>0.357</td>
</tr>
<tr>
<td>VAS for ADL</td>
<td>62.86 ± 36.84</td>
<td>71 ± 41</td>
<td>−0.298</td>
<td>0.766</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>6.43 ± 5.57</td>
<td>6.6 ± 4</td>
<td>−0.56</td>
<td>0.576</td>
</tr>
<tr>
<td>Leucocytic count (cell/ cumm)</td>
<td>8150 ± 2835.15</td>
<td>8971.43 ± 2045.1</td>
<td>−0.672</td>
<td>0.502</td>
</tr>
<tr>
<td>Normetanephrine (pg/mL)</td>
<td>166.46 ± 193.6</td>
<td>111.67 ± 57.15</td>
<td>−0.044</td>
<td>0.965</td>
</tr>
<tr>
<td><strong>SSR (affected hand)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (s)</td>
<td>1 ± 0.21</td>
<td>0.93 ± 0.15</td>
<td>−0.609</td>
<td>0.542</td>
</tr>
</tbody>
</table>

VAS = visual analogue scale, ADL = activity of daily living, SSR = sympathetic skin response, mg/L = milligram/litre, mm = millimeter, pg/mL = pico gram/milliliter, s = second, µV = microvolt.

* p is significant if < 0.05.
Comparison between patients with normal and increased serum TNFα revealed significant increase in hand edema in the latter group. Moreover, elevated serum TNFα showed significant association with changed skin color, temperature, sweating asymmetry and nail changes as well as hand edema in contrast to another set of features including pain severity, hand weakness and movements and impact on daily activities; all of which showed no significant relation to elevated serum TNFα. Accordingly, while inflammation in general could explain some major disease features, TNFα as a marker may not explain other features. In the present study markers of neurogenic inflammation were not assessed. Neurogenic inflammation may account for these features not explained by the elevated TNFα as well as those explained by elevated TNFα [50,51]. One should note that TNFα itself is a triggering factor of neurogenic inflammatory pathway. Neurogenic inflammation was found to play a role in sweating abnormalities in CRPS patients as concluded by Kumazawa et al through CGRP and SP [52].

Normetanephrine provides a monitor of norepinephrine (NE) release during regional sympathetic nervous system activation, as it depends on NE spillover (not under resting conditions) [53–55]. Unlike several studies which demonstrated lowered serum NE [14,15,20], the majority of our patients (18) had normal serum NMN level denoting normal secretion of NE (about 80% of which by sympathetic postganglionic vasoconstrictor terminals to muscles and skin) [20] and lack of sympathetic overactivity. Rather, this reflects adaptive supersensitivity due to disruption of efferent sympathetic modulation [14,20,56]. However, only 3 of our patients (all of type I CRPS) had increased plasma NMN level denoting NE spillover due to sympathetic over activity. None of the available literature found increased NE or its metabolite in CRPS patients apart from Wasner et al [15] who had one patient with CRPS I with increased serum NE in the affected limb compared to unaffected one. Our 3 patients had also increased plasma TNFα. This might suggest combined inflammatory process and sympathetic overactivity as underlying mechanisms for CRPS. Collectively, the overall clinical features were common among those patients with increased serum NMN and those without and some of their features can not be explained by sympathetic overactivity as local increase of temperature, edema and redness of the skin implying that the inflammatory factors might have an upper hand in the clinical manifestations of those patients.

Seven patients (4 with type II and 3 with type I CRPS) had normal serum levels of TNFα and NMN. The likelihood of inflammation to be the underlying mechanism is decreased unless its presence was restricted to the blister fluid [13,33] or the inflammation in such patients is neurogenic in origin with normal profile of classic innate inflammatory cytokines as TNFα [50] a condition which may be associated with the release of neuropeptides from primary afferents into peripheral tissue [57]. The normality of NMN does not exclude entirely the role of sympathetic dysfunction in CRPS because following nerve trauma (whether overt in type II or subtle in type I) adrenergic receptors are expressed on nociceptive fibers [6,58], and contribute to sympatho-afferent coupling through which sympathetic activity can increase spontaneous pain and the spatial extent of hyperalgesia, i.e., sympathetically mediated pain [18]. Finally, the laboratory profile of the single patient (type II) who presented by the “cold” CRPS revealed normal serum NMN as well as increased serum TNFα. This may be explained in terms of alpha adrenergic denervation supersensitivity of sweat glands (SG) and cutaneous blood vessels to circulating catecholamines (released in response to life stress or pain itself) leading to excessive sweating and vasoconstriction [23]. Neurogenic inflammation can also account for this presentation as increased TNFα tends to stimulate the release of a potent vasoconstrictor neuropeptide, endothelin-1 in patients with CRPS [59].

In the present study NMN had no correlation or association with any of the disease parameters. It did not show difference between patients with normal and increased TNFα or patients with type I or II CRPS. This makes the contribution of sympathetic over activity via the cutaneous and muscular blood vessels to the pathogenesis of CRPS [20] in our study a far possibility.

In the context of assessment of autonomic dysfunction, the studied patients significantly differed from control in having shorter SSR. Similar findings have been shown by Drory et al justifying their recommendation of SSR as a useful complementary method in diagnosing reflex sympathetic dystrophy [60]. Shortening of SSR latency has been considered to reflect enhanced SSR [24]. In our study the latency of SSR was used for interpretation because it depends on the integrity of the innervation of the SG and even if potentials of very few axones were recorded they would be enough to reflect the latency of response [42] while several factors may render the amplitude difficult to interpret [61,62] especially in CRPS.

Several studies assessed SSR in CRPS [24,26,63–66]. It was found to be increased in acute disease [24,65,66], normalized after therapy [24,66] while in the chronic conditions it was decreased or unobtainable [63]. The lack of consistency or significant association between sweating manifestation and SSR among the studied patients raised the possibility that the mechanism(s) controlling clinical sweating may differ from those responsible for the SSR in CRPS. Abnormal local sweating in CRPS may be attributed to several mechanisms [23,52,67] including non-sympathetically mediated ones as inflammation. The latter may involve CGRP which is found in the SG themselves or co-localized with acetycholine in sudomotor axons [68]. CGRP per se does not induce sweating [52] but induces a stronger sweat response as it enhances sweat production in single SG [52,69]. Substance P is another inflammatory product that potentially may contribute to decreased sweating through non-sympathetically mediated mechanism [52,70]. However, in the present study, the relationship between abnormal SSR and abnormal sweating is still well recognized as observed in those patients with dry hands or with decreased sweating who showed associated un-obtainable SSR that is.
possibly relevant to nerve injury as in CRPS II or an initial nerve trauma in CRPS I with injury of the un-myelinated C-fibers. Both inflammatory and sympathetically mediated factors, thus, seem to interplay, resulting into abnormal sweating manifestations in CRPS patients.

In the present study, the studied parameters of sympathetic function (SSR and serum NMN) varied differently among the studied patients with no mutual significant association, a finding that is probably explained by differential involvement of the cholinergic and adrenergic sympathetic components in CRPS [71]. Thus detection of sympathetic dysfunction in CRPS may necessitate investigating both systems.

Taken together, analysis of the clinical as well as the laboratory findings of the studied sample reveals a general trend favoring inflammation as a pathogenic mechanism (based on increased TNFα, normal NMN and relevant clinical presentation). However, in some patients with normal laboratory findings no solid conclusions could be derived and all mechanisms could be employed equivocally to explain the clinical findings. This imposes a great challenge in managing such patients and requires too many laboratory markers to search for. In such impractical puzzling situation the physician may be obliged to treat the patient empirically.

From this study it may be concluded that inflammation plays a major role in the pathogenesis of CRPS while the role of sympathetic dysfunction could not be clearly defined probably because the different mechanisms [15,19,20,25,71] of sympathetic dysfunction in CRPS were not tested in this study. This can be accepted if CRPS is considered as a dynamic process affecting multiple parts of the nervous system rather than to be a static, single-factor disease [12]. However, based on the results of this study, TNFα is recommended as a marker of inflammation in CRPS and SSR as a marker for sympathetic dysfunction combined with meticulous analysis of the clinical manifestations in a trial to find a cause-effect relationship and hence there may be a place for the mechanism-oriented treatment of CRPS.

References


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